M.A. Rekhter and B.A. Rekhter

The complementary principle in chemical reactions and methods of analysis.

Collection of articles.

Introduction

M.A. Rekhter, B.A. Rekhter

We have developed a completely new process for formation of a pair of opposites in course of expanding the complementarity principle to chemistry. This has been achieved by including the most specific features of a studied reaction (the model) as the content of the first opposite, along with the directly opposed specific features of an undescribed reaction (the anti-model) as the content of the second opposite. Such a tight connection between the reaction mechanism and the opposite has enabled to reveal some reaction mechanisms, which are hard to discover by another approach. In the field of synthesis, the equation and the mechanism of a reaction are predicted, before conducting any experiments. The indolinedione-indole and quinolone-indole rearrangements have been described. The intermolecular electrophile, nucleophile and radical substitution reaction mechanisms have been complemented by an intermolecular mechanism, the decay of which is not accompanied by breaking of the bonds at the radioactive atom, whereas the atom itself is substituted in the same Position by another radioactive or stable atom. The cooperative method of structure determination for several substances at once has been introduced into praxis. For this purpose a pair of opposites is analyzed, one opposite is an individual complex, for which the elemental composition and the structure determination by physicochemical means is conducted while steadily experimenting with the substance; the second opposite is a chain of radioactive complexes, the structure determination for which begins with the structure determination for the first relatively long-living link and the last long- living (stable) link, and, when their identical structure is discovered, every intermediate link is also provided with the same structure without proving its structure

and without experimenting with it directly. Taking into account the complexity and danger of conducting a radioactive decay it has been proposed to use, along with the solids, their Solutions under low temperatures. In case of alpha decay tetrathiafulvalenium (TTV) is taken into work, a π-donor that gives out an electron. The solvents are liquid electron donors with heteroatoms (O, S, P, N etc.) in possession of free electron pairs, such as pyridine, tetrahydrofuran, as well as water, glycerin. They can easily give out the electron, which is taken over by an alpha particle, thus transforming it into helium cation He^+. After that, helium is formed: $He^+ + e = He$. But the basic role of the solvents is to reduce energy and speed, and the alpha particle is taken over very easily, as the π-donor tetrathiafulvalene (TTV) is used in excess. In case of ß-decay solvents and other substances with partly positive carbon atoms are used. They decelerate the beta particle thus reducing its energy and speed: chloroform, fluoroform, esters of trifluoroacetic acid. The main role in the taking over of the beta particle plays a π-acceptor - tetracyanoquinodimethane (TCNQ) and its analogues. The structure of the obtained products can be easily found in publications.

Far analogue approach

After getting to know about the existence of the method of particle acceleration discovered by academician V.l. Veksler there was made a conclusion about existence of a cooperative method for substance analysis. There is no such factor as mutual complementarity here. For the present, we can only suppose, that the term "cooperative" has a deeper meaning than the one we attach to it. Nevertheless, the physics of the phenomenon remains unrevealed. In particular, what is substituted by the opposites, what do the restrictive peculiarities consist in? A great amount of scientific and popular science publications on physics, biology and other sciences needs to be studied

THE COMPLEMENTARY PRINCIPLE IN CHEMICAL REACTIONS

M.A. Rekhter* and B.A. Rekhter

An alternative method for the creating the pairs of opposites

It was managed to expand the complementarity principle to chemistry [1, 2].

All common reactions in the organic chemistry are divided into type 1 (not numerous most common reactions) and type 2 (more numerous less common reactions) based on the abilities if two reactions in each group to complement each other.

It is appeared only in group of type 2, which is the research area by means of the complementarity principle, based on the analysis of the pair of opposites. N. Bohr formulated the pairs of opposites in comparison of the classical physics and the quantum mechanics taking into consideration the dualism of electron-wave and electron-particle.

An alternative method for the creating the pairs of opposites is based on the fact that the most specific features of the studied and detected reaction are directly opposed to each other. The research begins with the selection of the already studied reaction and with the determination of its most specific features. The combination of these features makes up the content of the first opposite. Then each specific feature of the studied reaction gets the directly opposite features. These features together constitute the content of the second opposite, as a rule, it complements the first one. Thus the most specific features of the detectable reaction are known before generation of the equation

of this reaction. The features, which are the base of the equation, form the mechanism and the probable structure of the final product, usually confirmed by the mass spectrometry or the X–ray analysis.

Application of the studied reaction to determine the most specific features of the detectable reaction and the alternative method of creating pairs of opposites end up with the same results, which is quite natural. But the alternative method demonstrates the need to pay attention not only to the reaction itself, but also to the pair of opposites, which appeared on the basis of its analyses.

The minimum number of common reactions in organic chemistry

The minimum number of common reactions in the organic chemistry is not known, however, data concerning a major part of them can be obtained from the huge amount of reactions known at the time being. Without solving this problem it will not be possible to formulate adequate theories and to study the interrelation between the structure and the characteristics of a substance, as well as its biological activity.

We have formulated a hypothesis according to which a small group of very common reactions being widely applied in practice is fully contained in the mentioned minimum, the others have to be included individually.

Examples: The Grignard reaction, diene synthesis, carbohydrate oxidation by periodic acid and its salts, the Wittig reaction, the Michael reaction, the Fischer indole and Knorr pyrrole synthesis, charge transfer complexes obtained from tetrathiafulvalene (TTF) and tetracyanoquinomethane (TCNQ) of the formula TTF • TCNQ and their analogues, Arbuzov rearrangement…

The minimum of common reactions tend to be supplemented by new examples up to a certain limit, after which there follows a sharp decrease for a long time.

After that a group of less common reactions not so often applied in practice is analyzed. As a criteria the citation index has been chosen, which is the number of references in literature reference lists at the end of reviews or book chapters dedicated to a single reaction:

200 to 100 for the first group, 20 to 120 for the second, 120 to 200 for the first group reduction and/or the second group increase. In the course of study these randomly assumed growths will be replaced by specific ones.

Consolidation of the two groups will provide determination for a minimum number of reactions which form the basis for the organic chemistry. They shall be the subject of the study in the first place.

From the rest of reactions the ones having high citation indices are selected, compared with the ones chosen in accordance with the above statements, and in the case nothing in common is found, the reasons for their existence are examined. Both themes maybe closely related.

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DISCUSSION

THE COMPLEMENTARITY PRINCIPLE IN CHEMICAL REACTIONS

M. A. Rekhter[1]* and B. A. Rekhter[1]

New reactions are usually discovered in the course of experiments. On the other hand, there is another "method" for discovering new reactions to be discussed below, in which the course and mechanism of a reaction can be predicted and the predicted structure as though known in advance is confirmed by physicochemical methods of analysis.

The theoretical basis for such prediction is the complementarity principle proposed by Niels Bohr. "When viewpoints differ to the point of inconsistency, it may be that such viewpoints give a true picture of things only when taken together". "Contradictions do not contradict each other but only supplement each other". [1]. The principle of complementarity was discovered in 1927 but the argument between Joseph Proust and Claude Berthollet on the law of definite proportions (1801-1807) may be considered a manifestation of this principle in chemistry. We first encountered this principle relative to chemical reactions and the experimental discovery of reactions.

We will take below different viewpoints as an already studied reaction and a still unknown reaction. In the former (A), the most characteristic features are determined in order to distinguish the latter (B) by directly opposite features. Hence, concepts are formed about the still unknown reaction and the number of possible pathways for its accomplishment is reduced to a minimum and sometimes to a single pathway. If the known reaction A is general, then new reaction B is most likely the same. The special nature of reaction A is reflected in limitations in syntheses according to scheme B. These are examined together for a more complete description of the properties of compounds and, primarily, of reactants, while in the case of identical structure of reactants, they combine into a single common reaction. An important role is given to orienters – indicators. We shall illustrate the manifestation and use of the complementarity principle by two "pairs" of reactions, in which type-B are described by us for the first time.

1. Reduction of isatins to give indoles (A) and the indolinedione-indole rearrangement (B) [2, 3] (Scheme 1). The most characteristic features of the reduction of isatins **1** to give indoles **2** are that isatins and the reducing agents B_2H_6, $NaBH_4$, and $LiAlH_4$ are the reactants. The reduction of both CO groups proceeds without opening of the five-membered ring. The orienter for prediction and discovery of the indolinedione-indole rearrangement was the well-known method for the purification of isatins: the impure preparation

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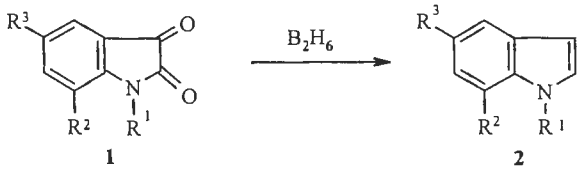
is dissolved in an aqueous solution of an equimolar amount of NaOH, the five-membered ring immediately opens to give the sodium salt of isatinic acid, the insoluble impurities are filtered off, and purified isatin is precipitated from the aqueous layer upon acidification

In the case of the indolinedione-indole rearrangement, the five-membered ring of the key N-acylmethylisatin **3** obtained from isatins and halomethyl ketones is readily opened upon dissolution in aqueous alkali (NaOH) and alcoholic solutions of sodium alcoholate (BuONa in BuOH). The sodium salt of isatinic acid and its incomplete orthoester have the same arrangement of functional groups so that cyclization to give 2-acylindole-3-carboxylic acid through aldol and ester condensation mechanisms is unavoidable. Thus, isomerization is used instead of reducing agents.

Scheme 1

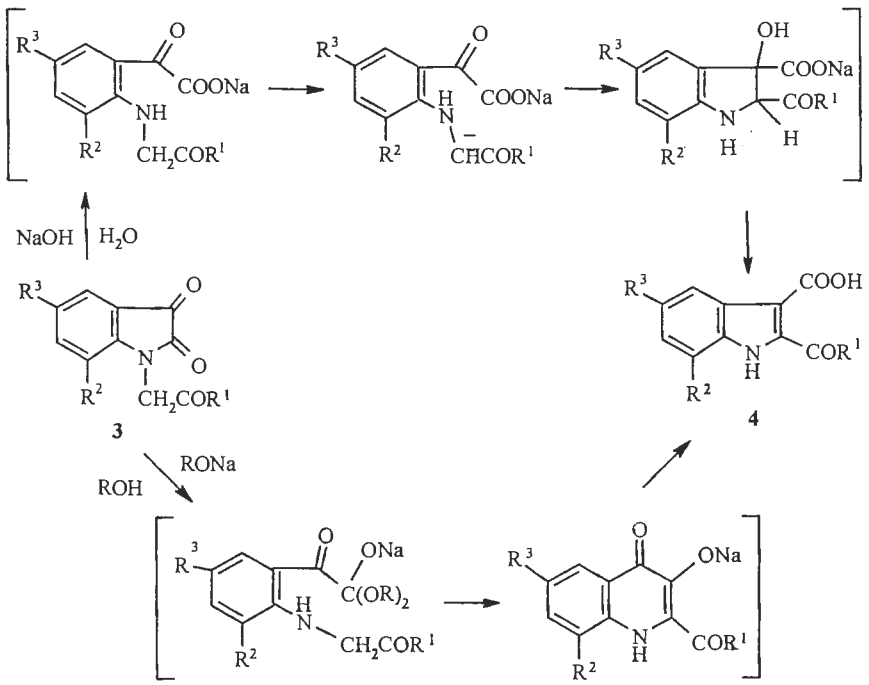
Reaction A:



1 **2**

$R^1 = R^2 = R^3 = H$; $R^1 = Me$, $R^2 = R^3 = H$; $R^1 = R^3 = H$; $R^2 = F$, Br, I, NO_2; $R^1 = H$, $R^2 = R^3 = Br$

Reaction B:



3 **4**

R^1 = Me, Et, Pr, CHMe–CH_2Me, CH_2CHMe_2, $CHEt_2$, Ph, 4-BrC_6H_4, 4-Cl; R^2 = H, Me;
R^3 = H, Me, MeO, Cl, Br

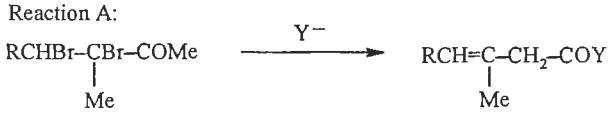
Both reactions are general and are considered together in describing the transformations of the oxidized form of indole into the reduced form. In this case, we may also note limitations of each of the reactions. The limitation in the first reaction is the impossibility of synthesizing indoles with aldehyde and ketone groups in the benzene ring. The limitation in the second reaction is the impossibility of synthesizing acids such as **4** with alkyl or aryl substituents at the nitrogen atom.

2. Favorsky Rearrangement (A) and Synthesis of Enamines of β-Diketones (B) [4, 5] (Scheme 2). The successive loss of the α- and β-halogen atoms as HBr is one of the characteristic features of the Favorsky rearrangement of α,β-dibromo ketones. The final product is a β,γ-unsaturated carboxylic acid. The orienter for the development of reaction B is the mechanism of the Favorsky rearrangement.

The most characteristic features of enamine synthesis are as follows. Even in the case of a 10-fold excess of amine (imidazole, 1,2,4-triazole, piperidine, diethylamine), which serves both as a reacta and base, the β-bromine atom is the first to be lost at temperatures from -20 to 110-120°C followed by the α-bromine atom. The final product is an enamine of a β-diketone. The rearrangement and enamine synthesis are general in nature. Taken together, these reactions give a more general concept of the properties of α,β-dibromo ketones than when examined separately.

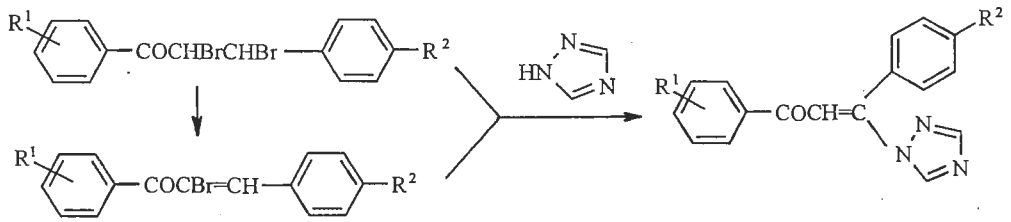
Scheme 2

Reaction A:



R = Alk, Ar; Y = OH, AlkO, NH_2, NR^1_2; R^1 = H, Alk

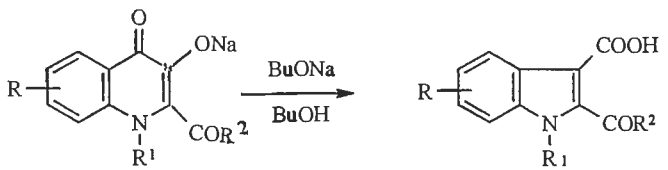
Reaction B:



$R^1 = R^2 = H$; R^1 = 4-Cl, $R^2 = H$; R^1 = 4-Cl, R^2 = Cl; R^1 = 2,4-Cl_2, $R_2 = NO_2$;
R^1 = H, R^2 = OMe; R^1 = 4-Cl, R^2 = OMe; R^1 = 4-Cl, $R^2 = NO_2$

3. Modification of the indolinedione-indole rearrangement. In light of their role in chemical transformations, reacta and intermediates are seen as opposites. This is the basis for a conclusion concerning modifications in the indolinedione-indole rearrangement.

The one-step isomerization of 1-alkyl-, 1-aryl-, or 1-H-2-acyl-3-hydroxy-4-quinolones to give 1-alkyl-, 1-aryl-, or 1-H-2-acylindole-3-carboxylic acids is called the quinolone-indole rearrangement.



R – substituents at C(5)–C(8); R^1 = H, alkyl, aryl

The same quinolones but without a substituent at the nitrogen atom preceded as intermediates the formation of the final products in Scheme 2 and, thus, this reaction is already confirmed experimentally. The original and modified rearrangements proceed through a single mechanism under identical conditions, while the final products differ only by the substituents at the nitrogen atom. We should note significantly that the N-alkyl derivatives of the acids are obtained in a multistep synthesis. Thus, the most important limitation in the first of these reactions is removed.

Other examples of application of the complementarity principle in chemical reactions are devoted to various areas of chemistry. Such examples are not treated in this communication.

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TOPICS FOR DISCUSSION

THE COMPLEMENTARITY PRINCIPLE IN CHEMICAL REACTIONS. MODIFICATIONS OF THE INDOLINEDIONE-INDOLE REARRANGEMENT AND ENAMINE SYNTHESIS

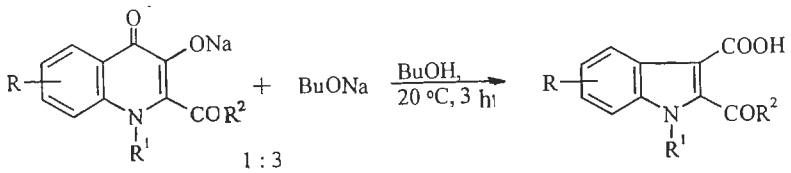
M. A. Rekhter[1]* and B. A. Rekhter[1]

The experimental discovery of a significant modification of a chemical reaction has always been considered a noteworthy achievement. As shown below, four modifications of the indolinedione-indole rearrangement and three modifications of the synthesis of β-diketones provide evidence for the usefulness of the complementarity principle [1] for the discovery of such specific reactions.

MODIFICATION OF THE INDOLINEDIONE-INDOLE REARRANGEMENT

Quinolone-indole rearrangement. As noted in our previous work [1], 2-acyl-3-hydroxy-4-quinolones are intermediates in the indolinedione-indole rearrangement, which provides the possibility of the quinolone-indole rearrangement (Scheme 1). This one-step rearrangement has special significance for obtaining 2-acyl-1-alkyl- indole-3-carboxylic acids; the usual syntheses of these carboxylic acids involve multiple steps.

Scheme 1



The quinolone-indole rearrangement proceeds under conditions described for the indolinedione-indole rearrangement [2]. The use of quinolone as an intermediate in the latter rearrangement opens the possibility of carrying out the rearrangement of quinolones synthesized by various methods. Thus, *N*-alkylation of 2-acyl-3-chloro- and 2-acyl-3-bromo-4-quinolones by methyl iodide, benzyl chloride, allyl bromide, and propargyl bromide in DMF in the presence of K_2CO_3 [3] yields the corresponding *N*-alkylquinolones.

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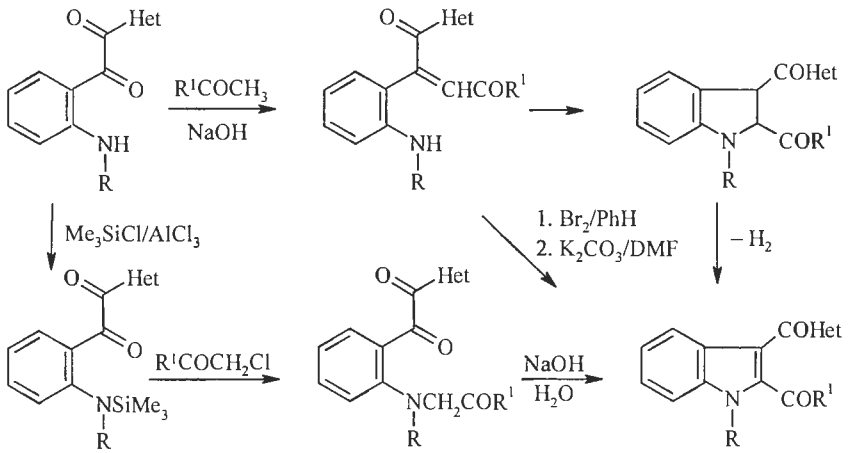
Subsequently, heating with anhydrous CF_3CO_2K leads to the replacement of the halogen atom by a trifluoroacetyl group, which is saponified already during dilution of the reaction mixture by 5% aqueous sodium bicarbonate. The indole yields are about 80% when the quinolone-*n*-BuOK ratio is 1:3. The yields become quantitative when this ratio is increased to 1:6.

Syntheses of 2-acyl-1-alkylindole-3-carboxylic Acids and their Derivatives from *N*-Alkylisatinic acids. Salts, esters, and amides of isatinic acid are commonly available. These compounds act as intermediates in the reaction of isatins with halomethyl ketones. If, on the other hand, these compounds are used as reagents, we may consider the reaction as a new modification of the indolinedione-indole rearrangement leading to the synthesis of amides and esters of 2-acylindole-3-carboxylic acids (Schemes 2 and 3) similar to the quinolone-indole rearrangement.

N-Substituted isatins are readily synthesized from isatins without a substituent at the nitrogen atom by reactions with halogen compounds. Salts of isatinic acids are obtained by the action of an equimolar amount of alkali at temperatures below 40°C. If the reaction is carried out in 9:1 DMF–H_2O in the presence of 3-5% NaOH and an alkyl halide is added after formation of the salt, esters of isatinic acid are obtained. Amides are synthesized using a 1:1 ratio of the isatin and a secondary amine.

Schemes 2

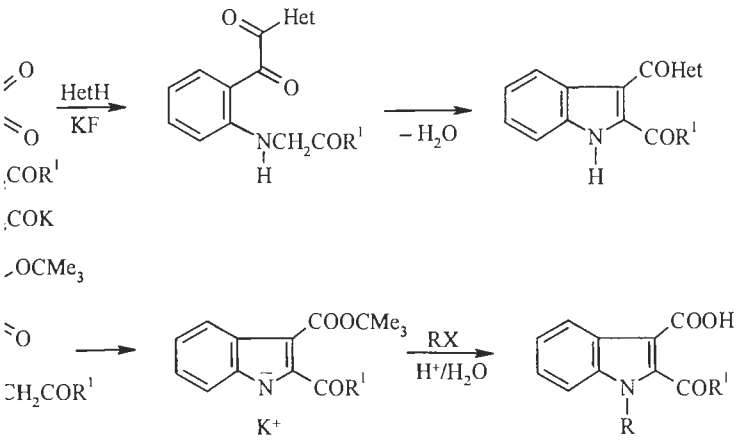


Het = imidazol-1-yl, pyrazol-1-yl, 1,2,4-triazol-1-yl, piperidin-1-yl;
R = H, Alk; R^1 = Ph, pyridyl

Modification of the synthesis of esters of 2-acylindole-3-carboxylic acids, which were previously obtained from salts of the acids and alkyl halides in aprotic solvents such as DMF and DMSO, is based on replacement of sodium *n*-butylate with potassium *tert*-butylate in *tert*-butyl alcohol or DMF. Scheme 3 shows that the steric hindrance created by the *tert*-butyl group prevents formation of the orthoester and leads to formation of the *tert*-butyl ester of isatinic acid, which cyclizes to give the *tert*-butyl ester of 2-acylindole-3-carboxylic acid through the aldol condensation mechanism instead of the expected ester condensation. The mole ratio of the key compound and potassium *tert*-butylate was 1:3, and the reaction time was 3 h at 20°C. The large excess of the base facilitates formation of the *N*-potassium salt, which is capable of undergoing alkylation at the nitrogen atom by means of halides.

Modification of the synthesis of acid amides (Scheme 3) is based on the use of indolinediones as the reactants, the replacement of alkali as the base by potassium fluoride, and the introduction of an additional reagent, namely, a secondary or primary amine; α-, β-, and γ-amino acids may act as a primary amine. This is the most efficient method for introducing functional groups in the search for biologically active compounds.

Scheme 3



Het = 1,2,4-triazol-1-yl, residues of α-, β-, and γ-amino acids;
R = H, Alk; X = Cl, Br, I; R^1 = Ph, pyridyl

alkali, facilitating opening of the five-membered ring at the N–C(2) bond and clization of the isatinic acid amide to give the amide of 2-acylindole-3-carboxylic ısation method. The salt effect of potassium fluoride results from the formation of a ın with the carbon atom of the reactive isatin β-CO group bearing partial positive duced tendency of the β-CO group to form aminals and Schiff bases such that the heme 3. The indolinedione–amine–KF mole ratio is 1:1:2 or 1:1:3, and the reaction

ıns do not alter the reaction mechanisms of the rearrangement or the structure of the uch more common in nature for the acids themselves as well as for their esters and

ENAMINE SYNTHESIS

α,β-dibromo ketones by α,β-dibromoaldehydes and α,β-dibromocarboxylic acids nines of β-ketoaldehydes and β-ketocarboxylic acids, respectively. The use of a tional reagent leads to a fundamental modification, namely, formation of ıes (Scheme 4).

Scheme 4

the catalyst. The reaction is carried out for 12-18 h at 10-20°C. The resultant product of the aldol condensation is dehydrated without isolation in the same flask. In the one-step process, an α,β-dibromoaldehyde is mixed with a ketone and amine in 1:3:20 mol ratio in DMSO. The mixture is maintained at from -15 to -10°C for 72 h [4].

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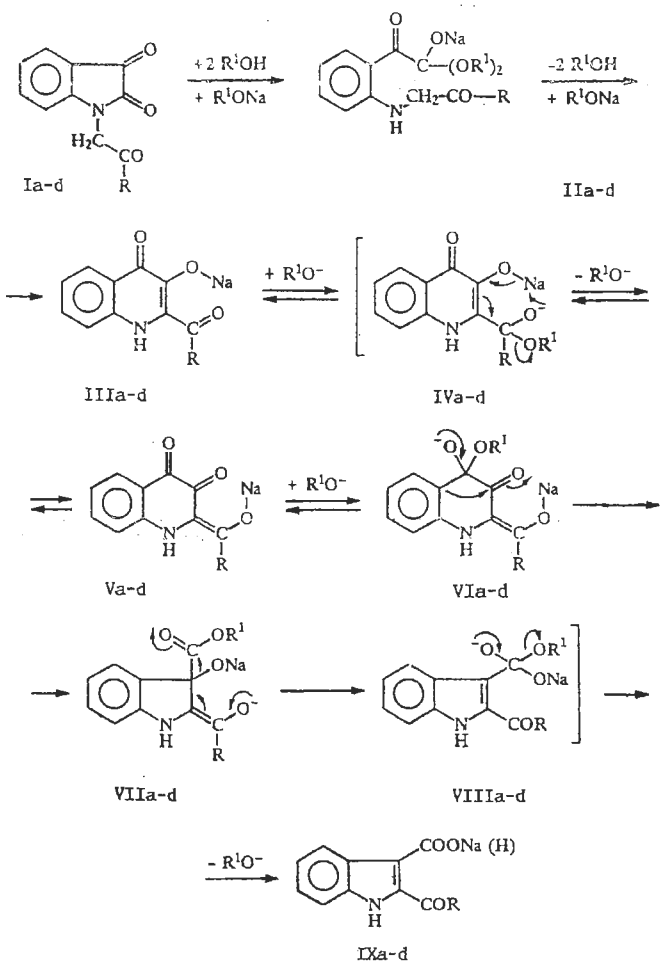
REARRANGEMENT OF 1-[2-OXOALKYL(ARYL)]INDOLE-2,3-DIONE TO FORM 2-ACYLINDOLYL-3-CARBOXYLIC ACID

M. A. Rekhter

It has been shown that 1-[2-oxoalkyl(aryl)]indole-2,3-diones are recyclized under the influence of sodium alcoholate to form 2-acylindolyl-3-carboxylic acids. A reaction scheme is proposed for this rearrangement.

It was shown previously [1] that the ethyl ester of isatin-1-acetic acid (I) is recyclized under the influence of sodium methylate in boiling methanol to form the ethyl ester of 3,4-dihydroxyquinaldinic acid (III, R = OC_2H_5). An intermediate in this reaction is the partial orthoester II ($R^1 = CH_3$), which was isolated successfully.

We have shown that when the ester group is replaced by a keto group in compound I, the reaction proceeds with a further contraction of the pyridine ring of the quinoline III to a pyrrole ring. The final product is the sodium salt of the acid



I—IXa R = C_2H_5, R = P-C_3H_7, R = —$CH(CH_3)$—CH_2CH_3, R = $CH_2CH(CH_3)_2$, R = 4-Cl—C_6H_4, R = 4-Br—C_6H_4

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0009-3122/93/2905-0548$12.50

TABLE 1. Characteristics of Compounds I and IX

Compound	Empirical formula	mp, °C	PMR spectra, δ, ppm,	J, Hz
Ia	$C_{12}H_{11}NO_3$	159...161	1,13 (3H, t, J=7,3, CH_3), 2,60 (2H, q, J=7,3, CH_2), 4,55 (2H, s, CH_2N), 6,63...7,66 (4H, m, H_{arom})	77
Ib	$C_{13}H_{13}NO_3$	108...109	0,97 (3H, t, J=6,4, CH_3), 1,64 (2H, m, CH_2), 2,53 (2H, t, J=7,1, CH_2CO), 4,52 (2H, s., CH_2N), 6,59...7,68 (4H, m, H_{arom})	75
Ic	$C_{14}H_{15}NO_3$	95...96	0,95 (3H, t, J=7,2, CH_2CH_3), 1,19 (3H, d, J=6,9, $CHCH_3$), 1,78 (2H, m, CH_2CH_3), 2,66 (1H, m, CH), 4,59 (2H, s, CH_2N), 6,57...7,65 (4H, m, H_{arom})	75
Id	$C_{14}H_{15}NO_3$	141...142	0,97 (6H, d, J=6,4, $2CH_3$), 2,30 (2H, m, CH), 2,43 (2H, d, J=5,5 CH_2), 4,50 (2H, s, CH_2N), 6,57...7,66 (4H, m, H_{arom})	79
IXa	$C_{12}H_{11}NO_3$	215...222*	1,13 (3H, t, J=7,2, CH_3), 3,19 (2H, q, J=7,2, CH_2), 7,16...8,11 (4H, m, H_{arom})	100
IXb	$C_{13}H_{13}NO_3$	210...220*	0,93 (3H, t, J=7,3, CH_3), 1,62 (2H, m, CH_2), 3,13 (2H, , J=7,3, $COCH_2$), 7,19...8,12 (4H, m, H_{arom})	100
IXc	$C_{14}H_{15}NO_3$	204...210*	0,86, (3H, t, J=7,3, CH_2CH_3), 1,06 (3H, d, J=7,3, $CHCH_3$), 1,78 (2H, m, CH_2CH_3), 3,60 (1H, m CH), 7,09...8,10 (4H, m. H_{arom})	84
IXd	$C_{14}H_{15}NO_3$	204...205	0,94 (6H, d, J=6,6, $2CH_3$), 2,17 (1H, m, CH), 3,06 (2H, d, J=6,8, CH_2), 7,12...8,11 (4H, m, H_{arom})	79

*Decarboxylation temperature.

**Owing to a typographical error in the Russian original, no heading is given for this column; the numbers in this column probably represent percentage yields — Translator.

IX. The rearrangement goes forward at 20°C, but under these conditions requires a large quantity of sodium alcoholate. With an equimolar ratio of the ketone I and R^1ONa, the conversion of the original ketone is very low; but with a ratio of 2.5/1 to 3/1, the reaction proceeds with a high yield.

The role of the sodium alcoholate apparently comes down to conversion of the intermediate quinoline III to its tautomeric form V, which has the structure of a cyclic 1,2-diketone and, like other compounds of this type, can undergo ring contraction — a benzyl type rearrangement to an ester of benzylic acid. Subsequent aromatization of the indole ring proceeds via migration of the ONa from the C_3 atom to the carbon atom of the ester group in the intermediate VII, leading to the formation of the structure VIII with subsequent detachment of the alkoxide ion.

It is obvious that the acid IX could also be formed by intramolecular crotonaldehyde condensation of compound II, followed by cleavage of the orthoester group by acid treatment of the reaction mixture. However, this possibility can be eliminated on the basis of the evidence that has been obtained. After completing the rearrangement of 1-phenacylindole-2,3-dione in CD_3OD-CD_3ONa, we obtained the ^{13}C NMR spectrum of the reaction mixture before it had been treated and acidified. In addition to the signals of the carbon atoms of the benzene and pyrrole rings, we observed two more signals at 176 and 197 ppm, indicating the presence of two carbonyl groups. If, after completing the reaction in a methanol solution of sodium methylate, the reaction mixture is treated with the calculated quantity of water, and the methanol is replaced by a 9:1 mixture of DMF and water, and then an excess of methyl iodide is added, the main product of the conversion is the methyl ester of 2-benzoylindolyl-3-carboxylic acid, along with a small admixture of its 1-methyl derivative. From this we conclude that in the reaction mixture before acidification, there was no orthoester of the acid IX, and the signal in the ^{13}C NMR spectrum are assigned to two CO groups of its sodium salt.

We had previously worked out in detail the recyclization of the ketone I in 1-5% aqueous caustic solution at 20°C. This reaction proceeds through a stage of formation of n-2-oxoalkyl(aryl)-ortho-aminophenylglyoxylic acid (X), which, through an intermolecular crotonaldehyde condensation, is converted to the acid IX [2, 3]. Thus, when the acid IX is obtained from the ketone I, we observe two different mechanisms of formation of its pyrrole ring. In an aqueous caustic solution, the blockage of the carboxyl group of the acid X in the form of the salt presupposes the crotonaldehyde mechanism of its cyclization and direct closure of this ring. Activation of the carboxyl group in the form of the partial orthoester II leads to

inclusion of its carbon atom in the new pyridine ring through an ester condensation mechanism. Here the pyrrole ring is formed as a result of a second process: contraction of the pyridine ring of the quinoline III under the influence of sodium alcoholate.

The structure of the compounds IXa-d that we obtained was proven by countersynthesis from the corresponding ketones I in an aqueous caustic solution. The acids IXe,f are identical to those described above; dissociative ionization is characteristic for 2-benzoylindolyl-3-carboxylic acid [3]. Unambiguous proof of the structure of the acid IX was also obtained by means of ^{13}C NMR data, which we will publish subsequently. The indicated contraction of the pyridine ring of the quinoline is described here for the first time; and this sort of recyclization is known [4] only for previously quaternized 4-nitro-3-hydroxyquinoline; other examples are concerned with the formation of the oxidized form of the pyrrole ring — indole-2,3-diones [5].

An extremely promising method for obtaining the halomethylketones that are required for the synthesis of the compounds I is a method described in [6], which gives a mixture of bromomethyl- and methylbromoalkylketones with a predominance of the former. Upon bromination of 2-butanone, 2-pentanone, or 3- or 4-methyl-2-pentanone, a mixture of bromoketones containing 75% of the bromomethylketone was obtained. Without separating the isomers, this was used for the N-alkylation of the 3-ethyleneacetal of indole-2,3-dione in a K_2CO_3/DMF system [7]. Under the conditions that were described, only the bromomethylketone reacts, while its isomer is apparently dehydrobrominated. An attempt to replace potassium carbonate by the weaker base $KHCO_3$ resulted only in a twofold reduction of the reaction yield. In the 3-ethyleneacetal of the ketone I, the dioxolane ring is readily cleaved in an alcoholic solution of of hydrochloric acid. The resulting ketone I is readily cyclized under mild conditions to the acid IX.

In conclusion, let us note that the rearrangement of the ketone I to the acid IX is an intramolecular variant of the intermolecular condensation of ortho-aminophenylglyoxylic acid with a halomethylketone. The accomplishment of this condensation under mild conditions could be a simple, general method for obtaining the acid IX. However, such a synthesis has not yet been accomplished, owing to the inertness of the nitrogen atom with respect to alkylation of the halomethylketone, even in an aprotic solvent at elevated temperatures [8] under conditions of interfacial catalysis [9], and also owing to the difficulty of performing the Darzens reaction with subsequent recyclization of the resulting epoxy compound to form an indole system [10]. The preliminary introduction of the 2-oxoalkyl group at the nitrogen atom of the ortho-aminophenylglyoxalic acid by N-alkylation of the indole-2,3-dione, with subsequent opening of the five-membered ring, has made it possible to work out the rearrangement of the ketone I that has been described previously [2, 3] and in the foregoing material; this is still the sole method for obtaining the acid IX.

EXPERIMENTAL

The 1-phenylacylindole-2,3-dione, its 4-chloro(bromo) derivatives, and the 3-ethyleneacetal of indole-2,3-dione were obtained by methods described in [3]. The bromoketones were analyzed by means of GLC in a Chrom-5 instrument (katharometer) in a 1.2-m glass column packed with 5% SE-30 on Inerton AW, with oven temperatures of 70° and 95°, vaporizer and detector temperature 270°, carrier gas helium at 60 ml/min; ratio of bromomethylketone to methylbromoalkylketone in the products 3:1. The PMR spectra were taken in a Bruker AC-80 instrument, TMS internal standard. The melting points were determing in a Boetius instrument and were not corrected. The individuality of the compounds that were obtained was monitored by TLC on Silufol plates in 5:1 toluene–acetone and 4:1 benzene–acetone systems, development by iodine vapor.

The results of elemental analyses for C, H, and N matched the calculated values.

3-Ethyleneketal of 1-(4-methyl-2-oxopentyl)indole-2,3-dione ($C_{16}H_{19}NO_4$) (3-Ethyleneketal of Compound Id). In 75 ml of methanol, with heating, 15 g of urea and 25 g (0.25 mole) of 4-methyl-2-pentanone were dissolved with heating; the solution was cooled to 20°C, and 4.5 ml (0.087 mole) of bromine was added dropwise over a period of 2.5 h; after decolorization of the solution, 75 ml of methanol and 16 ml of water were added, after which the solution was allowed to stand overnight and then diluted with 800 ml of water and extracted with chloroform (4 × 100 ml). The combined chloroform extracts were washed with a 5% $NaHCO_3$ solution and then with water (3 × 50 ml) and dried with Na_2SO_4, after which the chloroform was driven off. Obtained 29.2 g of a mixture of bromides. Into 85 ml of DMF, the following were introduced successively: 18.5 g (0.097 mole) of the 3-ethyleneketal of indole-2,3-dione, 16.5 g (0.12 mole) of K_2CO_3, and 29.2 g of the mixture of bromides. This mixture was then heated for 4 h at 50-60°C. After diluting the reaction mixture with 800 ml of water, obtained 15.1 g of a substance that was purified by column chromatography on silica gel 100/400 μm (225 g), eluent

9.5:5 benzene–acetone. Yield of pure substance 14.4 g (51%), mp 111-112°C. PMR spectrum ($CDCl_3$): 0.92 (6H, d, J = 6.4 Hz, $2CH_3$); 2.16 (1H, m, J = 6.7 Hz, CH); 2.34 (2H, d, J = 7.2 Hz, $CHCH_2CO$); 4.20-4.66 (4H, m, $2CH_2O$); 4.37 (2H, s, CH_2N); 6.51-7.44 m.d. (4H, m, H_{arom}).

3-Ethyleneketal of 1-(3-Methylpentyl)indole-2,3-dione (3-Ethyleneketal of Compound Ic, $C_{16}H_{19}NO_4$). This compound was obtained analogously from the 3-ethyleneketal of indole-2,3-dione and a mixture of the bromides of 3-methyl-2-pentanol, but with replacement of the potassium carbonate by $KHCO_3$; obtained 6.65 g (24%) of this compound, mp 99-101°C. PMR spectrum ($CDCl_3$): 0.89 (3H, t, J = 7.3 Hz, CH_3); 1.11 (3H, d, J = 6.9 Hz, CH_3); CH_2 see table for compound Ic; 2.58 (1H, m, J = 6.8 Hz, CH); 4.38 (2H, s, CH_2N); 6.52-7.44 m.d. (4H, m, H_{arom}).

3-Ethyleneketal of 1-(2-Oxopentyl)indole-2,3-dione (3-Ethyleneketal of Compound Ib, $C_{15}H_{17}NO_4$). To a mixture of 100 ml of absolute DMF, 40 ml of absolute methanol, and 43 g (0.5 mole) of 2-pentanone, 10 ml (~0.2 mole) of bromine was added dropwise over a period of 45 min. The solution began to be decolorized in 25 min. To the colorless solution, 55.2 g (0.4 mole) of finely ground K_2CO_3 was added in portions, then 19.1 g (0.1 mole) of the 3-ethyleneketal of indole-2,3-dione was added; the mixture was heated for 3.5 h at 45-50°C and then treated as described above. Obtained 13.1 g (50%) of the pure substance with mp 105-106°C. PMR spectrum ($CDCl_3$): 0.9 (3H, t, J = 7.2 Hz, CH_3); 1.57 (2H, m, J = 6.9 Hz, CH_2); 2.43 (2H, t, J = 7.0 Hz, CH_2CO); 4.20-4.65 (4H, m, $2CH_2O$); 4.32 (2H, s, CH_2N); 6.52-7.44 m.d. (4H, m, H_{arom}).

3-Ethyleneketal of 1-(2-oxobutyl)indole-2,3-dione (3-ethyleneketal of Compound Ia, $C_{14}H_{15}NO_4$). From the 3-ketiyleneketal of indole-2,3-dione and a mixture of the bromides of 2-butanone, this compound was obtained with a yield of 50%, mp 66-67°C. PMR spectrum ($CDCl_3$): 1.06 (3H, t, J = 7.2 Hz, CH_3); 2.48 (2H, q, J = 7.3 Hz, CH_2); 4.20-4.65 (4H, m, $2CH_2O$); 4.54 (2H, s, CH_2N); 6.54-7.43 m.d. (4H, m, H_{arom}).

1-[2-Oxoalkyl(aryl)]indole-2,3-diones (I) (General Method). In a mixture of 40 ml of alcohol and 8.5 ml of concentrated HCl, 0.15 mole of the 3-ethyleneketal of compound Ia-d was dissolved, and the mixture was refluxed for 20-30 min and then cooled to 5°C. The precipitate was filtered out, washed with water to neutral reaction, and dried in air and then over P_2O_5. After driving off the alcohol, the precipitate was separated from the mother solution and treated as described above. For further purification, the combined precipitate was dissolved in a minimum quantity of boiling ethanol and then frozen for 24-48 h at −18°C. A different procedure was also used: After the end of the hydrolysis, the reaction mixture was diluted with 120 ml of water, and the precipitate was removed and recrystallized. The substance was vacuum-dried over P_2O_5. The constants of the substances that were obtained (compounds Ia-d) are listed in Table 1.

Recylization of Ketones I to Acids IX in Aqueous Caustic Solution. A 0.7-0.8 g quantity of the compound I was dissolved in 30 ml of 1% NaOH solution and stirred for 2.5 h at ~20°C, after which it was poured into a mixture of 22 ml of water and 3 ml of concentrated HCl. The precipitate was separated by centrifuging (3000-6000 rpm) and washed with water (3 × 5 ml), each time repeating the centrifuging operation; the product was then dried over P_2O_5 at 20°C. Yield about 90%. Compounds IXa,b were crystallized from a large volume of alcohol, IXc,d from 60-70% aqueous alcohol. In both cases it was necessary to use a funnel for hot filtration.

Rearrangement of Ketones I to Acids IX in Alcohol Solution of Sodium Alcoholate.

4-Bromobenzoylindolyl-3-carboxylic Acid (IXf). To a chilled solution of sodium butylate, prepared from 0.69 g (0.03 mole) of metallic sodium and 50 ml of butanol, 3.44 g (0.01 mole) of 4-bromophenacylindole-2,3-dione was added. The intensity of the red color of the solution decreased after 10-15 min; at 1 h, a curdlike precipitate began to form. The mixture was held for 3 h at 20°C and then poured into a mixture of 500 ml of water and 5 ml of concentrated HCl. The yellow precipitate was filtered off, washed with water to neutral reaction, dissolved in 150 ml of boiling alcohol, cooled, and left overnight at −18°C. Obtained 2.8 g (81%) of 4-bromobenzoylindolyl-3-carboxylic acid, mp 222-223°C (decomp.). According to [3], mp 221-224°C. When the quantity of sodium butylate was doubled, the yield was quantitative. Mass spectrum* m/z (and I_{rel}, %): 345 (14), 343 (14), 327 (10), 325 (10), 302 (14), 301 (89), 300 (22), 299 (100), 298 (10), 256 (8), 247 (8), 246 (20), 221 (24), 220 (78), 219 (16), 191 (20), 190 (24), 185 (24), 183 (24), 165 (16), 164 (10), 168 (8), 157 (32), 155 (32), 148 (8), 145 (8), 144 (86), 129 (14), 116 (30), 115 (27), 114 (20), 111 (10), 110 (14), 97 (20), 96 (14), 95 (14), 89 (86), 85 (20), 83 (27), 81 (24).

4-Chlorobenzoylindolyl-3-carboxylic Acid (IXe). This compound was obtained in 72% yield by the same procedure; mp 199-200°C. According to [3], mp 195°C. Mass spectrum: 301 (22), 300 (12), 299 (75), 283 (22), 282 (16), 281 (75), 257 (17), 255 (70), 254 (14), 253 (39), 220 (33), 191 (13), 191 (13), 190 (25), 175 (8), 143 (19), 141 (22), 116 (14), 115 (19), 114 (33), 113 (31), 111 (100), 89 (53), 88 (12), 83 (13), 81 (13).

*Here and subsequently, values are given for m/z (and relative intensity in %).

The same procedure was used in obtaining the acids XIa-d (Table 1).

Methyl Ester of 2-benzoylindolyl-3-carboxylic Acid. A. To a solution of sodium alcoholate (prepared from 0.4 g of metallic sodium and 30 ml of absolute methanol), 1.33 g (0.005 mole) of 1-phenacylindole-2,3-dione was added, and the mixture was held for 3 h at 20°C. Then 0.3 ml of water was added, the mixture was stirred for 10 min, the methanol was removed under vacuum, and 15 ml of a 9:1 mixture of DMF and water was added to the residue, after which carbon dioxide was passed through the liquid until a neutral reaction was obtained. To the resulting slurry, 3.5 g (0.025 mole) of methyl iodide was added; the mixture was stirred overnight and then diluted with 120 ml of water and acidified to pH 1; the precipitate was removed rapidly, washed with water to neutral reaction, and dried over P_2O_5. Obtained 1.2 g of a mixture of substances, which, according to the results of TLC in a 5:1 toluene–acetone system, consisted mainly of the methyl ester of 2-benzoylindolyl-3-carboxylic acid (R_f 0.74), the corresponding free acid (R_f 0.43), and traces of an unidentified substance with R_f 0.92. The precipitate was chromatographed in a column (220 × 30 mm) with silica gel L 160/100 μm in a 5:1 toluene–acetone system, recovering 1.1 g of the pure methyl ester of 2-benzoylindolyl-3-carboxylic acid with mp 177-178°C. PMR spectrum ($CDCl_3$): 3.39 (3H, s, CH_3); 7.20-8.23 (9H, m, H_{arom}); 9.64 ppm (1H, s, NH). The aqueous solution that remained after removing the precipitate was immediately neutralized with NaOH and extracted with benzene (5 × 60 ml); the benzene extract was washed with water (5 × 40 ml) and evaporated down. Recovered 0.15 g of a mixture of substances, which, according to TLC, consisted of the methyl ester of 2-benzoylindolyl-3-carboxylic acid with small amounts of its 1-methyl derivative (R_f 0.86). This fraction was not subjected to preparative separation, in view of the closeness of values of R_f of these substances.

B. To a methanol solution of sodium methylate (from 0.2 g of sodium and 20 ml of methanol), 0.5 g of the methyl ester of 2-benzoylindolyl-3-carboxylic acid was added; the mixture was held for 3 h at 20°C, diluted with 100 ml of water, and acidified to pH 1; the precipitate was removed, and the aqueous solution was treated as described above. According to TLC data, neither fraction contained even a trace of the acid IX.

1-(p-Toluenesulfonylmethyl)indole-2,3-dione ($C_{16}H_{13}NO_4S$). A mixture of 100 ml of anhydrous DMSO, 29 g (0.15 mole) of 1-chloromethylindole-2,3-dione, and 40 g (0.22 mole) of sodium sulfamate was stirred for 5 h at 20°C and then 3 h at 60-70°C, after which it was cooled and poured into a solution of 100 g of KCl in 600 ml of water. The precipitate, which had an intense yellow color, was removed and washed with water (5 × 200 ml) and then with methanol (3 × 50 ml). The product, which was difficultly soluble in organic solvents, was crystallized from a large volume of acetone. Yield 10 g (21%), mp 262-263°C. Mass spectrum m/z (I_{rel}, %): 315 (4), 162 (2), 161 (4), 160 (25), 155 (2), 147 (6), 146 (7), 132 (100).

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INDOLEDIONE-INDOLE REARRANGEMENT (REVIEW)

M. A. Rekhter

The indoledione-indole rearrangement, which occurs during the basic condensation of ortho-*aminophenylcarbonyl compounds* (ortho-*aminophenylglyoxylic acid,* ortho-*aminoketones) with halomethylketones, is reviewed.*

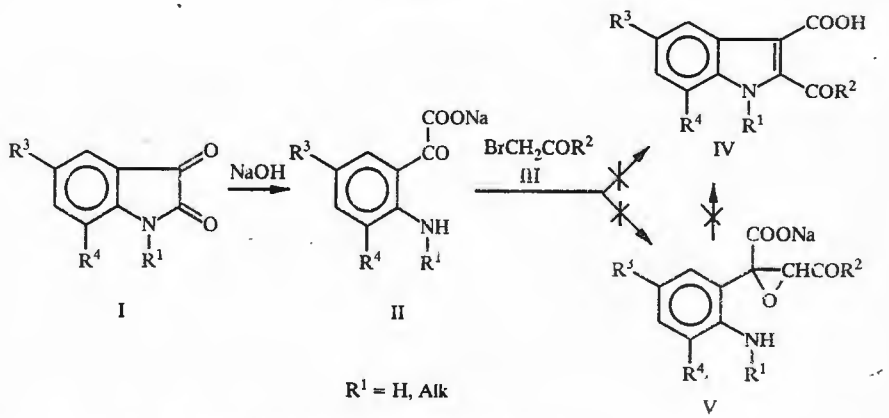
The indoledione-indole rearrangement is the first and almost the only method for the synthesis of 2-acylindole-3-carboxylic acids. Thanks to the easily obtained starting materials, and the possibility of varying the substituents at $C_{(4)}$-$C_{(6)}$ and in the acyl part of the molecule, they are valuable starting materials. Many 2-acylindoles have been prepared in this manner and, along with information on the condensation of *ortho*-aminoketones with halomethylketones, this allows discussion of the synthesis of a number of indoles and quinolines from a single point of view.

Condensation of *ortho*-aminophenylcarbonyl compounds with halomethylketones is a general method for the synthesis of indoles with an acyl group at $C_{(2)}$. Condensation of *ortho*-aminophenylcarbonyl compounds with ketones and their derivatives is a general method for the synthesis of indoles and quinolines. If the methylene carbon of the $-CH_2-CO-$ group becomes part of the heterocycle, the product is an indole, whereas if both carbons are included the product is a quinoline.

The indoledione-indole rearrangement has the same importance in the chemistry of indoles as the Pfizinger reaction in the chemistry of quinolines. The condensation of *ortho*-aminoketones with halomethylketones may be described as the indole analog of the Friedländer reaction.

The indoledione-indole reaction was discovered in 1977 [1] when the starting materials needed for the reaction were first described [2, 3]. It was indispensable in the search for sedative materials of a new type [4].

Scheme 1



1. CONDITIONS FOR CARRYING OUT THE REARRANGEMENT

ortho-Aminophenylglyoxylic acids are readily formed *in situ* by the influence of an alkali (usually NaOH) on indolediones-2,3 (isatins) I [5]. They are isolated as precipitates of the sodium salts II using a published method in saturated aqueous NaCl solution.

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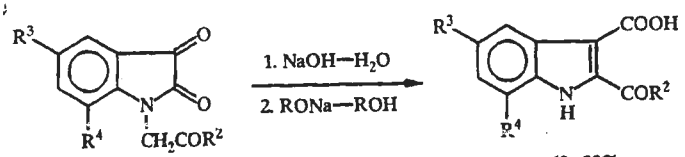
The interaction of *ortho*-aminophenylglyoxylic acids with halomethylketones III might be developed into a general synthesis for 2-acylindole-3-carboxylic acids IV and their N-alkyl derivatives V (Scheme 1). However, because of the low reactivity of the salts II with respect to N-alkylation, this reaction does not occur either in an aprotic solvent (DMF) at increased temperature [6], or in strongly basic media (DMSO-NaOH) [7], or with phase transfer catalysis [8] because of the difficulty of obtaining the epoxycompounds V and their conversion into the acids IV [9]. The intramolecular variant of this condensation has been thoroughly studied and is known as the "indoledione-indole rearrangement" [10]. It differs from the intermolecular condensation of compounds II and III by the initial introduction of the R_2COCH_2 fragment of the halomethylketone at the nitrogen atom of the indolediones-2,3 before opening of the 5-membered ring.

The indoledione-indole rearrangement is the isomerization of 1-[2-oxoalkyl(aryl, hetaryl)]indolediones-2,3 VI into 2-acylindole-3-carboxylic acids IV in aqueous alkali solutions, superbasic media, and alcoholic solutions of sodium alkoxides (Scheme 2).

Scheme 2



63...90%

R^2 = Me, Et, *n*-Pr, CHMe–CH_2Me, CH_2–$CHMe_2$, $CHEt_2$; Ph, 4-Br–Ph, 4-Cl–Ph; R^3 = H, Me, MeO, Cl, Br; R^4 = H, Me

R^3 and R^4 are used for substituents at $C_{(5)}$ and $C_{(7)}$ in formulas IV and VI since these were used in the experiments, but compounds with these substituents at $C_{(4)}$ and $C_{(6)}$ may be used as well.

0.4-1.0% of alkali in water is sufficient for isomerization of compounds VI with primary and secondary R^2 radicals [1, 7, 11-13], whereas for tertiary radicals [14] a superbasic medium of DMSO–water (9:1) containing 5-10% NaOH was necessary [10, 15]. Comparison of these conditions indicates that the effect of the solvent (DMSO) plays a greater role than the strength of the base. It is less sensitive than water to the steric hindrance created by these radicals during the generation of the intermediate VIII and especially its cyclization into the indoline IX, and it accelerates their formation.

The diketones VI with R^2 = Ar and the acids IV formed from them are poorly soluble in water. The water is mixed with an organic solvent (acetone, dioxane, DMF, methanol, ethanol) to carry out the rearrangement in a homogenous medium. The products from protonic solvents, e.g., 80% aqueous alcohols, are purer. The concentration of alkali reached 5% [1, 13, 16]. Sodium alkoxides used (1-3%) were the methoxide, ethoxide and *n*-butoxide in the corresponding alcohols [12].

Rearrangement occurred in all media in 1-3 h at 5-20°C. In general, minimal amounts of by-products were formed; sometimes they were completely absent.

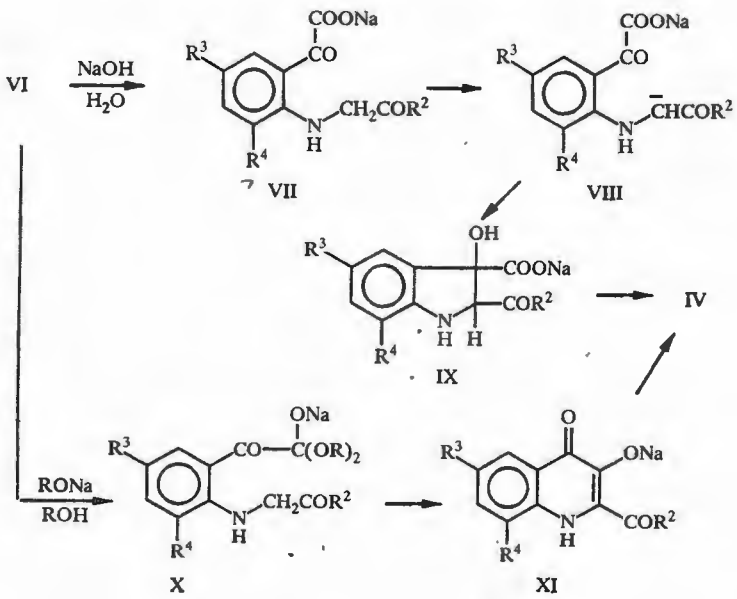
The acids IV were isolated as precipitates after dilution of the reaction mixture with water (~10-fold) and acidification of the solution to pH 1. They may be contaminated with impurities of an unexpected nature which are unaffected by dilution of the alkali. They are purified via their sodium salts: the acids are suspended in 1-2% aqueous NaOH solution, and extraction with ether (or another organic solvent) removes the impurities. Acidification of the aqueous layer to pH 1 precipitates the pure acid IV. The same method is also suitable for N-substituted acids (see below) [10].

2. DUAL MECHANISMS FOR THE REARRANGEMENT

A distinguishing characteristic of the indoledione-indole rearrangement is its dual mechanisms. The process begins by opening of the five-membered ring of the diketone VI. In alkaline and superbasic media the sodium salt of an N-2-oxoalkyl-(aryl, heteraryl)*ortho*-aminophenylglyoxylic acid VII is formed which is further converted to the products V, probably via the intermediates VIII and IX. In alcoholic solutions of sodium alkoxides the sodium salts of the nonpolar orthoesters X are formed. The two forms of the carboxyl groups in compounds VII and X determine the dual mechanism of the rearrangement to a considerable degree. Blocking of the carboxylic acid group by the sodium ion in the first compound favors the formation of the pyrrole ring in acid IV by an intramolecular aldol-crotonic condensation mechanism. Activation of the same carboxyl group in the form of a nonpolar orthoester in the second compound leads to the inclusion of its carbon atom in the pyridine ring of

the quinolines XI by an intramolecular ester condensation mechanism. Ring contraction of the pyridine ring to the ring of acid IV under the influence of a sodium alkoxide occurs via a number of steps of addition and elimination of the ion as described in [12] (Scheme 3).

Scheme 3



It is seen from a comparison of the two mechanisms for the rearrangement that the carbon atoms of the methylene group at the N-atom of the diketones VI become atom $C_{(2)}$ of the pyrrole ring of the acids IV. The $C_{(3)}$ atom bonded to the carboxyl group is formed from both CO groups. In alkaline media the β-CO is transformed into $C_{(3)}$, whereas the α-CO is transformed into the carboxyl group. In alcoholic media the reverse is true. Although the intermediates were not isolated, the described dual mechanism was unambiguously demonstrated by carrying out the reaction with a diketone VI containing either α-^{13}CO or β-^{13}CO [10]. The structure of acid IV was confirmed by ^{1}H and ^{13}C NMR and mass spectroscopy [17].

The indoledione-indole rearrangement is an intramolecular reduction reaction in which the oxidized form of indole (the isatin ring) is converted into its reduced form (the indole ring) under the influence of alkali or sodium alkoxide. It is a unique method for the synthesis of acids IV so that the formation of these acids in alkaline and alcoholic media can be described as a retrosynthesis [12].

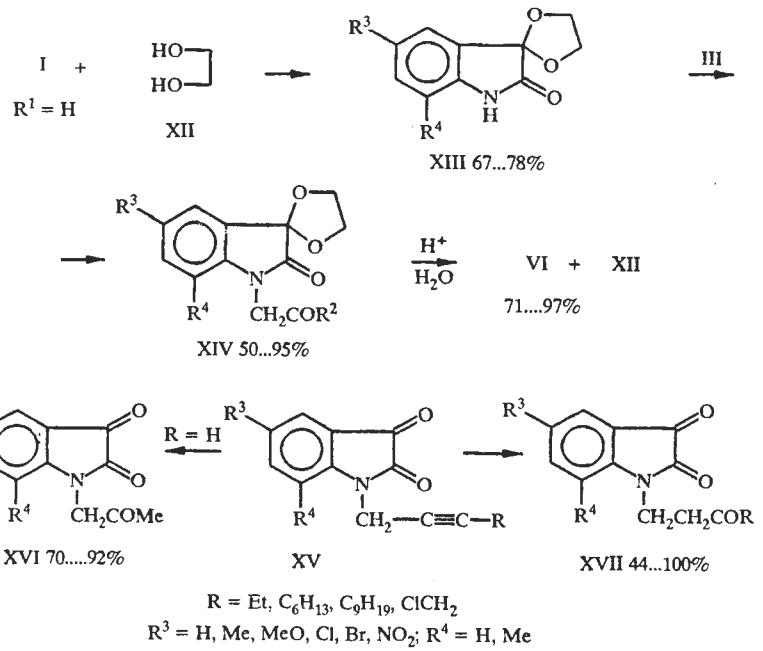
3. STARTING MATERIALS

The general method for preparing substituted isatins VI is based on the condensation of β-ethylene acetals of indolediones-2,3, prepared from isatins and ethylene glycol XII, with halomethylketones III with subsequent removal of the dioxolane ring of compounds XIV by boiling for a short time with a 1:4(5) mixture of hydrochloric and acetic acids, an ethanolic solution of hydrochloric acid (4-5%), or by keeping an equimolar mixture of XIV and $SnCl_4$ at −10 to −15°C for 3 h [2, 7, 12, 14, 16] (Scheme 4).

Alkali metal hydrides and K_2CO_3 in DMF were used as condensing agents [2, 3, 7, 11, 12, 14, 16, 18-21].

Special attention is paid to halomethylketones of type III from which the acyl part of acid IV is formed. When the following compounds were used in the reaction with ethylene acetals XIII: chloro- and bromoacetone, phenacyl bromide, its 4-bromo- and 4-chloro-derivatives and, of particular importance, a mixture of bromomethyl- and methylbromoalkylketones [12], only the former reacted and the second was apparently dehydrobrominated. Variation of the acyl part of acid IV was achieved with chloromethylketones obtained in particular by the condensation of acid chlorides with diazomethane. Dialkylacetic acids made by the malonic ester synthesis are the best starting materials for acids IV containing secondary radicals R [7].

Scheme 4



Attempts at carrying out consecutively all steps of the rearrangement in a single vessel were unsuccessful because of the weakly basic properties of DMF, bonded to mineral acids as unstable salts which prevented scission of the dioxolane ring of compounds XIV. Therefore, separate steps were required. However, DMF was used as an acid amide, facilitating the formation of bromomethyl ketones by bromination of methyl ketones, and simultaneously as a solvent for their N-alkylation with the β-ethylene acetals XIII. Examples of consecutive occurrence of these two stages in the same flask have been published [12, 14]. The preparation of diketones VI from the ethylene acetals XIV and their isomerization to the acids IV can be carried out analogously.

Direct N-alkylation of indolediones-2,3 I with halomethylketones gave products of the Darzens reaction [7, 22].

A particular method for the synthesis of the isatins VI is hydration of the triple bond in 1-(propyn-2-yl)indolediones-2,3 XV (R = H) under conditions of the Kucherov reaction to give N-acetonyl substituted isatins XVI [11]. The reaction is governed in large measure by Markovnikov's rule and to a lesser extent by the orienting influence of the nitrogen atom. Disubstituted acetylenes XV cannot be used to obtain the diketones VI because their hydration is determined exclusively by the influence of the nitrogen atom and gives 1-(3-oxoalkyl)indolediones-2,3 XVII [7, 23]. They are subsequently recyclized to 1,4-dihydro-3-acylquinolin-4-carboxylic acids in 8-10% boiling aqueous alkali solution for 1-3 h [24] (isatin-1,4-dihydroquinoline rearrangement).

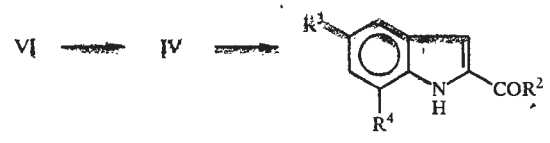
4. SYNTHESES BASED ON 2-ACYLINDOLE-3-CARBOXYLIC ACIDS, IV

2-Acylindoles without substituents at $C_{(3)}$, including α,β-double bonds in the acyl radical, 1-alkyl-2-acylindole-3-carboxylic acids and their esters, esters and amides of acids IV, are not formed under standard conditions for carrying out the rearrangement. Thanks to the facile conversions of the acids IV they remain accessible substances.

4.1. Decarboxylation of Acids IV

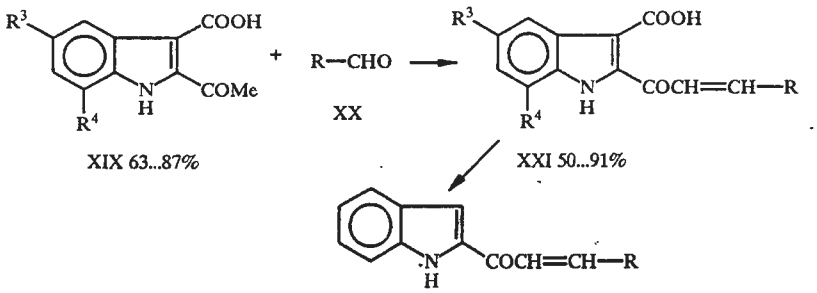
This reaction is the simplest method for the synthesis of 2-acylindoles XVIII. The usual starting materials are the diketones VI which are rearranged in a homogeneous 1:1 DMF–water medium containing up to 5% NaOH. The acids IV formed *in situ* are decarboxylated in the same solution. After cooling to 2-4°C the reaction products crystallized in analytically pure form [13, 25] (Scheme 5).

Scheme 5



XVIII 72...97%

R^2 = Me, $CHEt_2$, Ph, 4-Br–C_6H_4, 4-Cl–C_6H_4; R^3 = H, Me, MeO, Br, Cl; R^4 = H, Me



XIX 63...87%

XXI 50...91%

XXII 70...90%

R = Ph, 3-NO_2–C_6H_4,  , R^3 = R^4 = H

The 2-aroylindoles are completely stable and have been kept for more than 20 years without visible change. However, decarboxylation of acids IV with aliphatic radicals R^2 may be complicated by aldol-crotonic autocondensation of the reaction products XVIII (especially with R^2 = Me). In this case the alkali is neutralized with CO_2 after the rearrangement and the salt of the acid IV obtained is decarboxylated by boiling for 1.5-3 h [7, 13]. Another method consists of isolating the acid IV from the reaction mixture and heating it in boiling pyridine in the presence of a small amount of aqueous NaOH [13, 26].

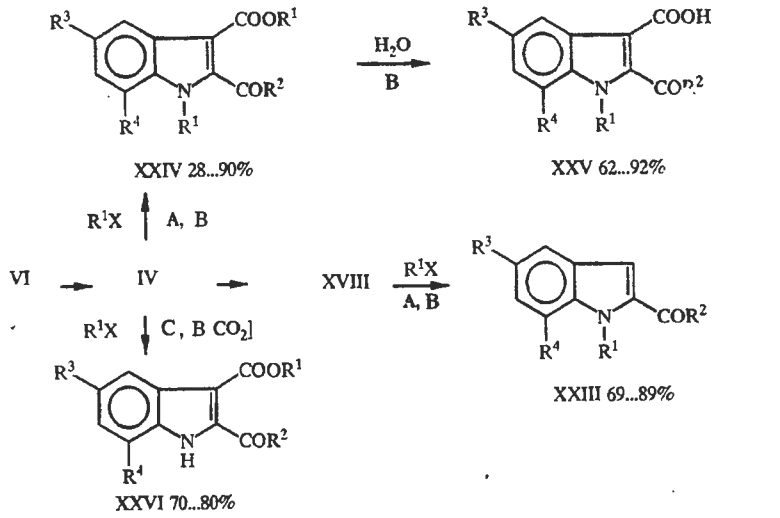
Acids XXI with an α,β-double bond in the acyl group were synthesized by crotonic condensation of 2-acetylindole-3-carboxylic acids XIX with aldehydes XX. They decarboxylate more easily than their saturated analogs to give the ketones XXII.

4.2. N-Alkylation of 2-Acylindoles in Superbasic Media

2-Acylindoles XVIII were alkylated at the nitrogen atom with alkyl halides R^1X in superbasic medium A (anhydrous DMSO (HMPT)-NaOH) to give the ketones XXIII in practically quantitative yield. Esters of 1-alkyl-2-acylindole-3-carboxylic acids XXIV were obtained under analogous conditions from the acids IV. They are stable to hydrolysis in alkali solutions, but are saponified completely to the acids XXV at 5-20°C in 1-4 h in superbasic medium B ((9:1) DMSO–water with 5-10% NaOH) [10, 15]. The diketones VI can be used as starting materials in this medium. They are recyclized to acids IV which are then alkylated with alkyl halides without isolation. With an equimolar ratio of R^1X–NaOH the reaction products are the esters XXIV, whereas with an excess of alkali the products are the acids XXV. In the weaker superbasic medium B with composition (9:1) DMSO–water with 5-10% NaOH, esterification of the carboxyl group to give the esters XXVI is the basic reaction, but the esters XXIV are present as impurities which are difficult to separate, even by chromatographic methods. The best method for preparation of the pure ethers XXVI from the diketones VI involves neutralization of the alkali with CO_2 before addition of the alkyl halide to the reaction mixture [10] (Scheme 6).

In normal alkaline media, 2-acylindoles are alkylated at the nitrogen atom with difficulty, under vigorous conditions, and in poor yields [27]. This also applies to alkylation of acids IV under conditions of phase transfer catalysis. The starting materials used were the diketones VI. Only with "ion pair extraction" for 24 h at 20°C with a molar ratio of VI(IV):R^1X:TEBAX of 1:5(6):1 were the esters XXIV obtained successfully (60-70% yield) [10].

Scheme 6



R^1 = Me, Et, *n*-Pr, *n*-Bu, $PhCH_2$, $CH_2{=}CH{-}CH_2$, $Me{-}C(Cl){=}CH{-}CH_2$, $HC{\equiv}C{-}CH_2$, $C_{11}H_{23}{-}C{\equiv}C{-}CH_2$;
R^2 = Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4; $R^3 = R^4$ = H

4.3. Modification of the Functional Groups in Acids IV

The known reaction of acid chlorides with ammonia has been extended to prepare amides of the acids IV (R^2 = Me). The esters XXVI do not react with ammonia. The acetyl group of these acids has been reduced to hydroxyethyl with $NaBH_4$ [11].

5. SOME QUESTIONS RELATED TO THE INDOLEDIONE-INDOLE REARRANGEMENT

Heating aqueous solutions of each of the starting materials to boiling before mixing prevents partial saponification of the reaction mixture with formation of 5-methoxyisatin by the Sandmeyer reaction [28].

A general method for the N-alkylation of indolediones-2,3 and their β-ethylene acetals with the corresponding alkyl halides and halomethylketones in K_2CO_3-DMF has been developed [12, 20, 21]. The high yield (84-97%) of N-methylisatin permits the simplification of the technological production of the medicinal metisazon, used for the treatment of viral diseases of agricultural animals and poultry [29, 30].

The previously unknown 5-pyridazo[4,5-*b*]indoles are now available thanks to the condensation of acids IV with hydrazine [3].

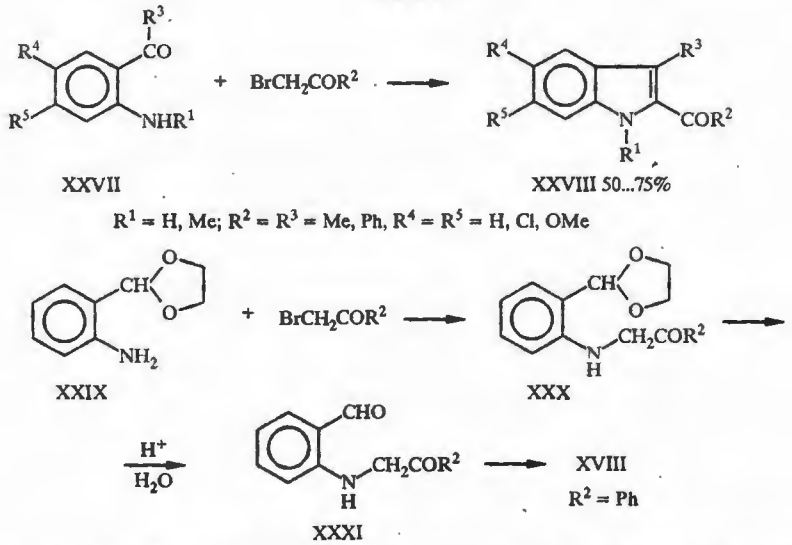
The behavior under electron impact of indolediones-2,3, their β-ethylene acetals and their physiologically active β-thiosemicarbazones has been studied to identify intermediate products of the indoledione-indole rearrangement [32-37]. Rearrangement of the semicarbazones to 3-mercaptooxyindoles under electron impact was discovered [35].

The biological activity of the substances obtained has been studied [38-43].

6. SYNTHESES OF 2-ACYLINDOLES FROM *ortho*-AMINOKETONES AND HALOMETHYLKETONES

2-Acylindoles XXVIII were obtained by heating the aminoketones XXVII and bromomethyl ketones III at 80-90°C in anhydrous DMF for 16 h. 2-Benzoylindole XVIII (R^2 = Ph) was obtained from the acetal of *ortho*-aminobenzaldehyde XXIX and phenacyl bromide via the acetal XXX and the aldehyde XXXI [44] (Scheme 7).

Scheme 7

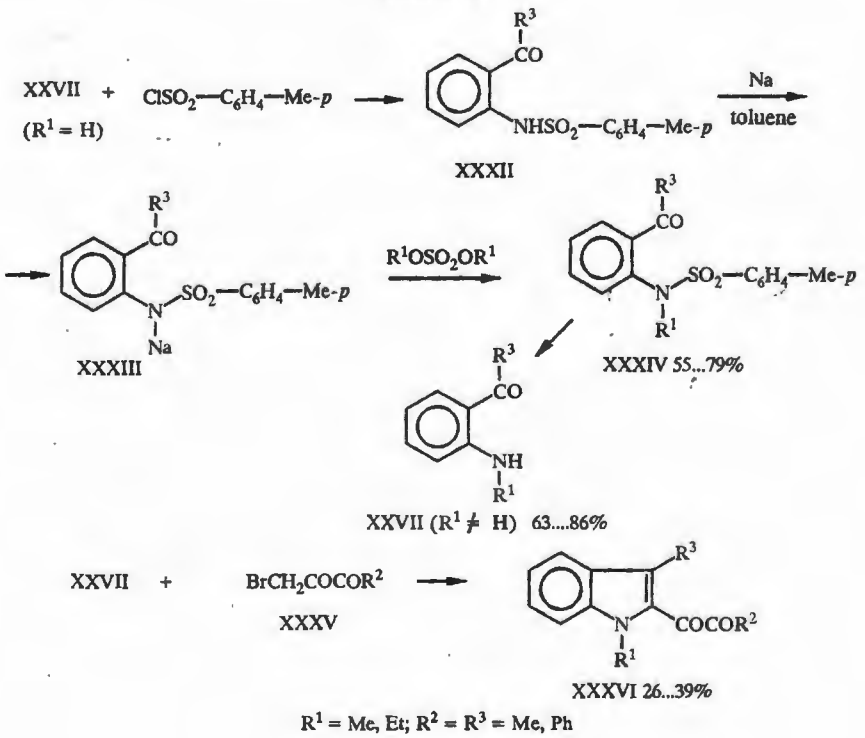


The basic fact which restricts the development of this reaction is the complexity of the synthesis of *ortho*-aminoketon XXVII, especially with $R^1 = H$. The latter were obtained via the tosylates XXXII which were converted into the Na-derivativ (XXXIII), alkylated with dialkyl sulfates and then hydrolyzed with acid to remove the tosyl group from compounds XXXI Condensation of compound XXVII with bromomethyldiketones XXXV to give the diketones XXXVI was accomplished at 7 80°C in ethanol with $NaHCO_3$ as the condensing reagent [45] (Scheme 8).

The advantage of the synthesis of 1-alkyl-2-acylindoles via the indoledione-indole rearrangement is evident, but drawback is the impossibility of obtaining these substances with substituents at $C_{(3)}$.

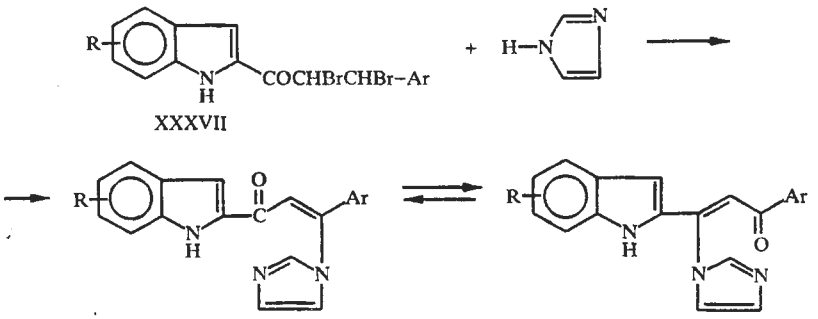
It follows from this discussion that the basic problems with the syntheses of 2-acylindoles from *orth* aminophenylcarbonyl compounds and halomethylketones remain the intermolecular condensation of compounds II and III a new routes to the *ortho*-aminoketones XXVII. With respect to solving the first of these it is expedient to pay particular attenti to direct N-alkylation of 2,3-indolediones with halomethylketones. A route of this type not only simplifies the syntheses of t diketones VI and acids IV, but also leads to the indoledione-indole rearrangement by intermolecular condensation, which, noted, occurs under mild conditions with negligible formation of by-products. It is possible that opening of unstable rings heterocycles may lead to a new method for preparing *ortho*-aminoketones.

Scheme 8



In a plan for searching for biologically active substances the extension of the enamine-enamine rearrangement [46-48] to the dibromides of unsaturated ketones XXXVII (Scheme 9) has promise.

Scheme 9



The corresponding unsaturated ketones XXII are readily obtained from the products of the indoledione-indole rearrangement (Scheme 5).

This review is the first general paper in the field of the indoledione-indole rearrangement. This rearrangement was not mentioned in previous reviews [49, 50].

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DISCUSSION

THE COMPLEMENTARITY PRINCIPLE IN CHEMICAL REACTIONS

VARIETY OF EXAMPLES

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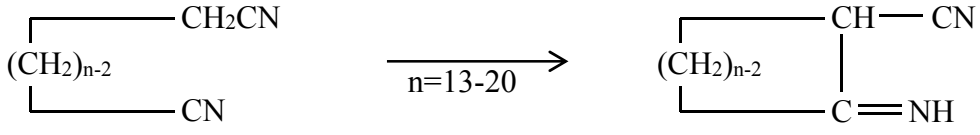
The different examples of pair's opposites are described and analyzed.

Keywords: macrocycles, tetrathiafulvalene, α, β – Particles, crown ether, cryptand.

Based on the concepts presented in the preliminary communications[1,2] we suggest new pairs of the opposites.

A Principle of Maximum Convergence of Molecules in the Synthesis of Macrocycles.

Synthesis of macrocycles on the Ruggli principle:[3]

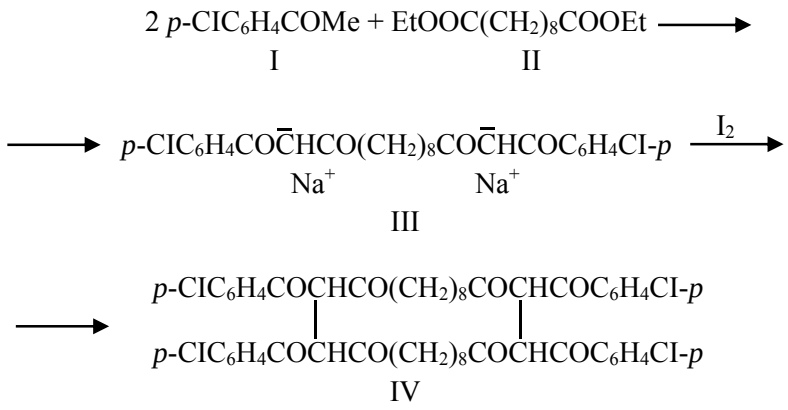


Opposites. 1. In addition to the Ruggli principle, a principle exists of the maximum approximation of bifunctional molecules in the formation of macrocycles by

intermolecular doubling of methylene-separated 1,3-diketones, β-keto esters and β-keto sulfones under the action of iodine or formaldehyde.

Orienting point: the well-known doubling of acetilacetonate Na and ethyl-acetonacetate under the action of iodine or formaldehyde.

Low-temperature solid-phase synthesis, *viz.*, freezing of reactants for 3-5 days in a minimum volume of a solvent at different temperatures (from -20°C to -196°C) decreases sharply the entropy barrier to the formation of macrocycles and favours retention of the geometry of their starting state (III)

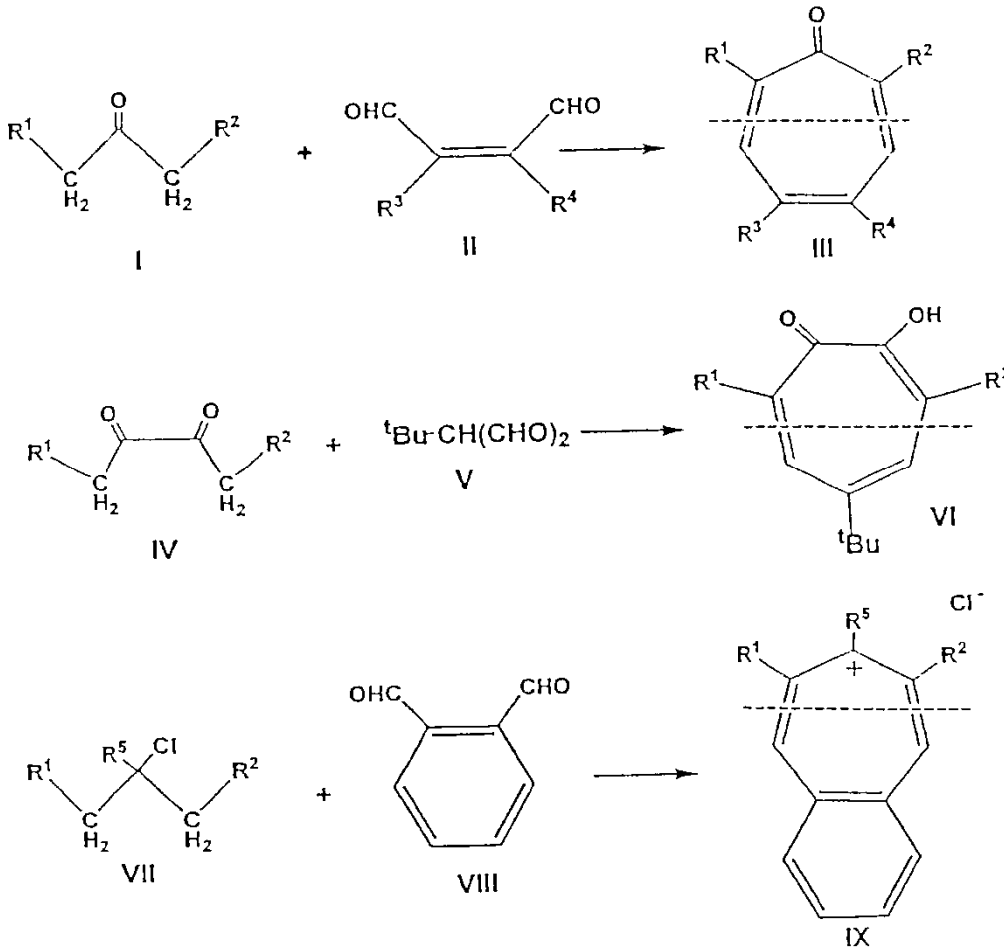


A Unified Approach to the Synthesis of Tropones, Tropolones, Tropylium Salts and Benzannulated Derivatives Thereof.

2. Block-synthesis of molecules and disintegration of a molecule into separate units are regarded as the opposites. Orienting point: synthesis of alkaloid in "physiological conditions".

Seven-membered rings are arbitrarily disassembled by dotted lines into fragments with three and four carbon atoms. Their synthesis by aldol condensation (1- 3) requires

compounds with the same number of carbon atoms. The reactions are catalysed by pyridinium perchlorate, p-toluenesolfonic acid in nitromethane, piperidinium acetate, acetic and propionic acids. [3]



(1)

(2)

(3)

I, III, IV, VI: $R^1 = R^2 = COOEt$;

I, III, IV, VI,VII, IX: $R^1 = R^2 = ClC_6H_4CO$; $R^3 = R^4 = H$, Ph; $R^5 = H$, Cl

Two Versions of the Propargyl Rearrangement of β-Dicarbonyl Compounds.

3. The propargyl rearrangement occurs both without alteration of the carbon skeleton and involving its transformation (a non-classical version of the rearrangement). Orienting point: the mechanism of propargyl rearrangement.

A non-classic version (Equations 1 and 2). Coupling of copper acetylides (I) with dihalogen derivatives of dibenzoylmethane (II) and ethyl acetoacetate (III) under conditions of low-temperature solid-phase synthesis affords bisacetylenes (IV, V). Upon boiling in nitromethane in the presence of Py $HClO_4$: TsOH as a catalyst, they were converted into acetylene-allenes (VI, VII). In compound (V), it was the acetyl group that underwent migration.

$$2\ R{-}C{\equiv}C{-}Cu + (PhCO)_2CBr_2 \rightarrow (PhCO)_2C(C{\equiv}C{-}R)_2 \rightarrow$$

I II IV

$$\rightarrow R{-}C{\equiv}C{-}C(COPh){=}C{=}C(COPh)R \qquad (1)$$

VI

$$2\ R{-}C{\equiv}C{-}Cu + MeCOCBr_2CO_2Et \rightarrow (MeCO)(CO_2Et)C(C{\equiv}C{-}R)_2 \rightarrow$$

I III V

$$\rightarrow R{-}C{\equiv}C{-}C(CO_2Et){=}C{=}C(COMe)R \qquad (2)$$

VII

R = hetaryl, aryl, alkyl

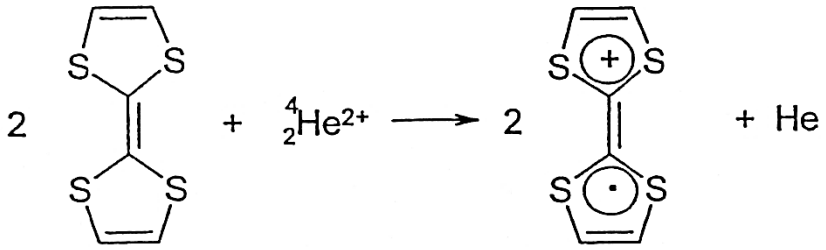
For conditions of the classic version see Ref. 4

On the Natural Electrophiles and Nucleophile.

Tetrathiafulvalene (TTF) I (or its analogues) is considered as an olefin with an exceptionally high electron density of the double bond. Upon easy loss of an electron, this π-donor is stabilized as an aromatic radical cation III. On the other hand, tetracyanoquinodimethane (TCNQ) V (or its analogues) belongs to potent electron

acceptors, and is converted in a stable radical anion VII upon electron capture. Equimolar amounts of TTF and TCNQ react in cold acetonitrile to form a charge transfer complex. Electric conductivity of the complex is similar to that of copper.

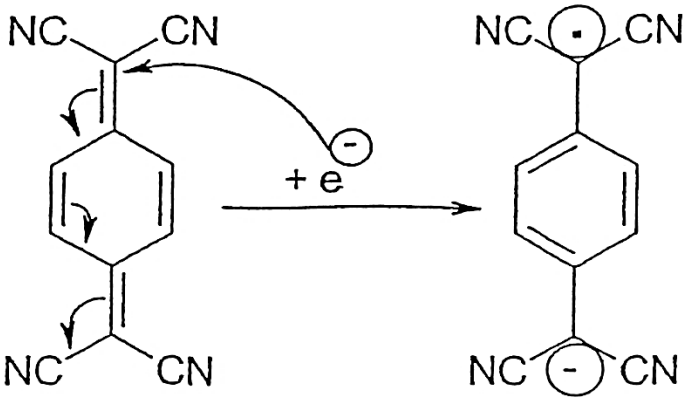
TCNQ can be replaced by an α particle II in the reaction with TTF:



I II III IV

This process is carried out in a highly dilute solution cooled to different temperatures or in a frozen state (liquid nitrogen) in an atmosphere of argon.

Under analogous conditions, TCNQ reacts with electron generated upon β - decay.



V VI VII

The number of such organic metals is increasing swiftly. [5] However, the choice of the necessary π-Donor and π-Acceptor for the reaction with α- and β- particles is rather

easy: the higher the electric conductivity of the charge transfer complex the more efficient the individual constituent π-Donor and π-Acceptor.

In the case of β^+ - decay, one expect annihilation of an electron - positron pair with evolution of two quanta of energy.

Thus, the pair of opposites: α - particle escapes from atomic nucleus of natural isotopes with energy 2-8 MeV and velocity 10^7 m/s in vacuum as radioactive emanation (physical encyclopedic dictionary) and as a substance (He^{2+} - cation), which reacts with TTV in solution. Orienting point: the reaction between α - particle and oxygen in air (the track length form only several cm).

THE NEW RULE

Pb212 – Bi212 – Tl208 – Pb208 (β^-, α, β^-; T½=10,64h; 60,5m; 3,4m; stable). For experimentation investigation. (***a***)

Ni66 – Cu66 – Zn66 (β^-; β^-; 54,6h; 5,1m; stable). (***b***)

Nd140 – Pr140 – Ce140 (EC; β^+; 3,37d; 3,4m; stable). (***c***)

Sm142 – Pm142 – Nd142 (β^+, EC ; β^+, EC ; β^+; 72m; 40,2S; stable). (***d***)

Lu167 – Yb167 – Tm167 – Ez167 (β^+, EC ; β^+, EC ; EC; 51m; 17,7m; 9,25d, stable). (***e***)

Th234 – Pa234 – U234 (β^-; β^-; 24,7d; 6,6h; $2{,}455\cdot10^5$y.) (***f***)

Orienting point: a mechanism of reaction occupy an intermediate position between reactante and reaction product.

Individual synthesis of complexes of short-lived nuclides is not possible, however, a collective method allows one to establish the fact of the formation *in situ* within complexes of long-lived nuclides, to elucidate their structures and to describe their physical and chemical properties. Chains of conversions of nuclides where short-lived nuclides occupy an intermediate position between relatively long-lived and stable (long-lived) ones.

Following dissolution of the first nuclide of each chain (***a***)-(***f***) in an acid and addition of a complex-forming reagent to the salt formed, one obtains a primary complex. A series of β^+- and β^--decays and/or electron capture results in spontaneous formation of other complexes of the series. In fact, experiments are carried out with the terminal long-lived members of the series, and the conclusions drawn are used for inferring the structures of the intermediate short-lived members.

We formulate a rule: ‘If the terminal members in the chain of conversions of several complexes possess identical geometrical structure, then this structure is also inherent in every intermediate member’.

Well-known complexes of ethylenediaminetetraacetic acid (H_4edta) with elements in the oxidation states 2+, 3+ and 4+ are taken as examples. The anion (edta) is the most suitable chelating reagent. Due to its geometry, the anion coordinates to all six octahedral positions of the metal ions. X-ray diffraction data of complexes of chemical elements with H_4edta show that all of them possess octahedral structure. Such a complex and a complex with a nuclide represent isomers with identical compositions, geometrical structures, physical, chemical and spectroscopic properties. Therefore, a hitherto non-documented complex of H_4edta with a nuclide should possess the same physical and chemical properties as those of the examined analogous complex of an element with the octahedral structure, irrespective of the half-life period and the kind of decay of the central ion. Such should be the expected structure of each of the complexes with H_4edta in the chains of conversions (***a***)-(***f***) where the first complex is obtained under the conditions identical with those for the like chemical element; in this case the octahedral structure can be considered to be proven experimentally.

The terminal member in the chain of conversions of the edta complexes is the major carrier of information on the conversions. The main attention is paid to its identification by X-ray diffraction or mass spectrometry. Coincidence of the X-ray diffraction data or mass spectrum of this member with those of the like chemical element with the octahedral structure allows one to conclude on the similar structure of each of the intermediate member with a short-lived nuclide (Fig. 1).

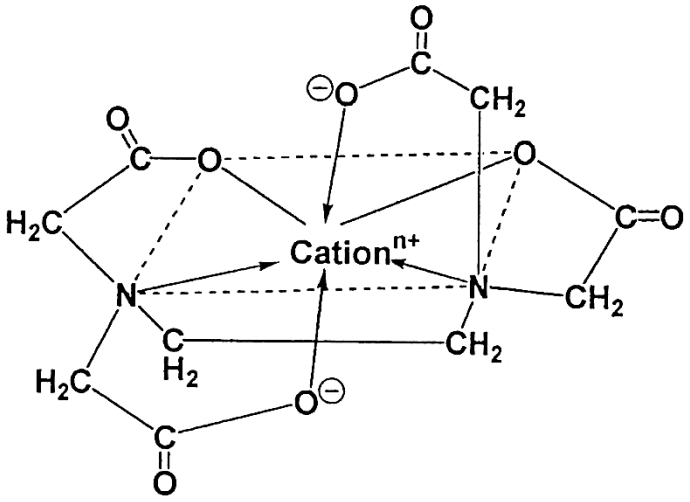


Fig. 1. The octahedral structure of each of the edta complexes in the chains of conversions (***a***)-(***f***). The central ion charges (***n***) are 2+(***a***)-(***b***), 3+(***c***)-(***e***) and 4+ (***f***); the charges of the respective complexes are 2-, 1- and 0.

Thus, the geometrical structure of the first member of the chain of conversion, the oxidation state and the coordination number of the central ion known prior to analysis predetermine the geometrical structure, the oxidation state and the coordination number of each subsequent member. Thus, the conversions of the edta complexes are reduced to the conversions of the central ions. No alternative to this method exists.

Radioactive decay of complexes of certain radioactive metals with polydentate ligands can be employed for the preparation of complexes of non-metals. Crown ethers and cryptands are of special importance as complex-forming reagents. The presence of several heteroatoms involved in chemical bonding decreases the positive charge of the central ion to shift it to the state resembling a fee atom.

The preparation, structure elucidation and storage of complexes of non-metals is only possible at low temperature in an atmosphere of argon.

Stable complexes of caesium cation with 'pyrocatechol hexaether' and of rubidium cation with [2.2.2]-cryptand are well known. The procedures used for their preparation can be adopted to synthesise complexes with central ions of $^{129}_{55}$ Cs (β^+, EC; T½ 32.06 h) and $^{82}_{37}$ Rb (β^+, EC; T½ 6.3 h), which undergo spontaneous decay with formation of complexes of non-radioactive cations of $^{129}_{54}$Xe and $^{82}_{36}$Kr (Fig.2 and Fig.3).

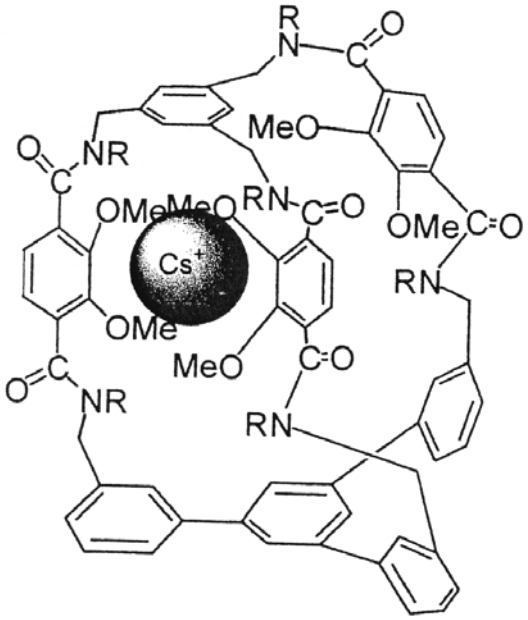


Fig. 2. Structure of the complex of Cs^+($^{129}_{55}Cs^+$, $^{129}_{54}Xe^+$) with "pyrocatechol hexaether" (R=Bn)

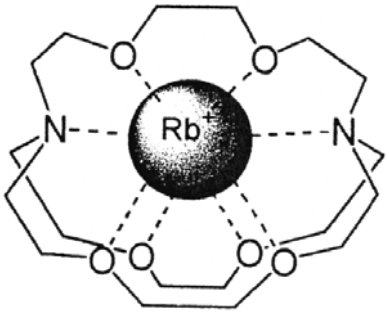


Fig. 3. Structure of the complex of Rb^+($^{82}_{37}Rb^+$, $^{82}_{36}Kr^+$) with [2.2.2]-cryptand

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Summary.

The diversity of the listed examples witnesses the general nature of the method as a whole: a new principle of macrocycle synthesis under conditions of maximum approaching of bifunctional molecules to each other during the process of their intermolecular doubling has been revealed; a uniform approach of synthesising tropones, tropolones and tropylium salts via a uniform aldol condensation mechanism has been found, for the first time the cases of a molecule's carbon skeleton changing during the process of acetylene bond transformation into allene bond have been described, for the first time the reaction equations have been recorded for tetrathiafulvalene and tetracyanoquinodimethane reacting with α- and β-particles, which have lost their energy and are reacting like regular substances, an analysis method has been described, in which a substance structure is being determined without experimenting on the substance directly. Radioactive decay of complexes of certain radioactive metals with polydentate ligands can be employed for the preparation of complexes of non-metals.

The Summary is intended for the Journal of Reports in Organic Chemistry.

Four mechanisms of substitution reaction

Eiectrophilic, nucleophilic and radical substitution reaction mechanisms differ to complete incompatibility and are common for the intermolecular transformations. The only thing that unites them is breaking of the previous chemical bonds and forming of new bonds. Therefore, they are considered together in a pair of opposites nominally, as a "single mechanism". The exact opposite is the intramolecular mechanism, with no breaking of the chemical bonds between the ligands and the central ion in the intramolecular (intranuclear) mechanism in the process of the transformation of a radioactive atom in a molecule into another radioactive atom or a stable atom. Resulting is the new reaction products. That particular mechanism was missing to state the pairs of opposites before. Henceforth the substitution reaction has four mechanisms.

The intramolecular mechanism of substitution reaction plays a key role in the radioactive-transformation series of substances, in particular, complexes.

The preparation, structure elucidation and storage of complexes of non-metals is only possible at low temperature in an atmosphere of argon.

Stable complexes of caesium cation with ‘pyrocatechol hexaether’ and of rubidium cation with [2.2.2]-cryptand are well known. The procedures used for their preparation can be adopted to synthesise complexes with central ions of $^{129}_{55}$Cs ($ß^+$, EC; $T_{1/2}$ 32.06 h) and $^{82}_{37}$ Rb ($ß^+$, EC; $T_{1/2}$ 6.3 h), which undergo spontaneous decay with formation of complexes of non-radioactive cations of $^{129}_{54}$ Xe and $^{82}_{36}$Kr.