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INDOLEDIONE-INDOLE REARRANGEMENT (REVIEW)

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

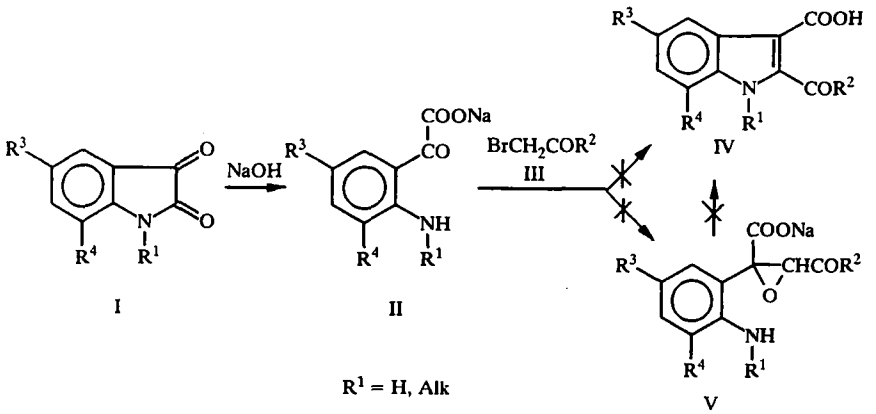
The indoledione-indole rearrangement is the first and almost the only method for the synthesis of 2-acylindole-3-carboxylic acids. Thanks to the easily obtained starting materials, and the possibility of varying the substituents at $C_{(4)}$-$C_{(6)}$ and in the acyl part of the molecule, they are valuable 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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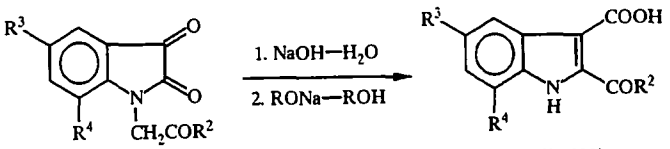
The interaction of *ortho*-aminophenylglyoxylic acids with halomethylketones III might be developed into a general synthesis for 2-acylindole-3-carboxylic acids IV and their N-alkyl derivatives V (Scheme 1). However, because of the low reactivity of the salts II with respect to N-alkylation, this reaction 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



VI IV 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.

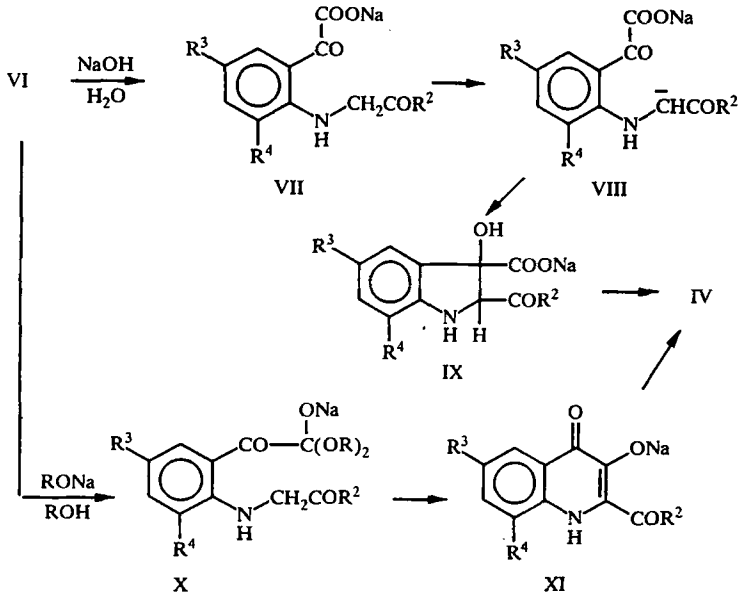
The acids IV were isolated as precipitates after dilution of the reaction mixture with water (~ 10-fold) and acidification of the solution to pH 1. They may be contaminated with impurities of an unexpected nature which are unaffected by dilution of the alkali. They are purified via their sodium salts: 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 pyrrole ring of acid IV under the influence of a sodium alkoxide occurs via a number of steps of addition and elimination of the alkoxide 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 ^1H 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].

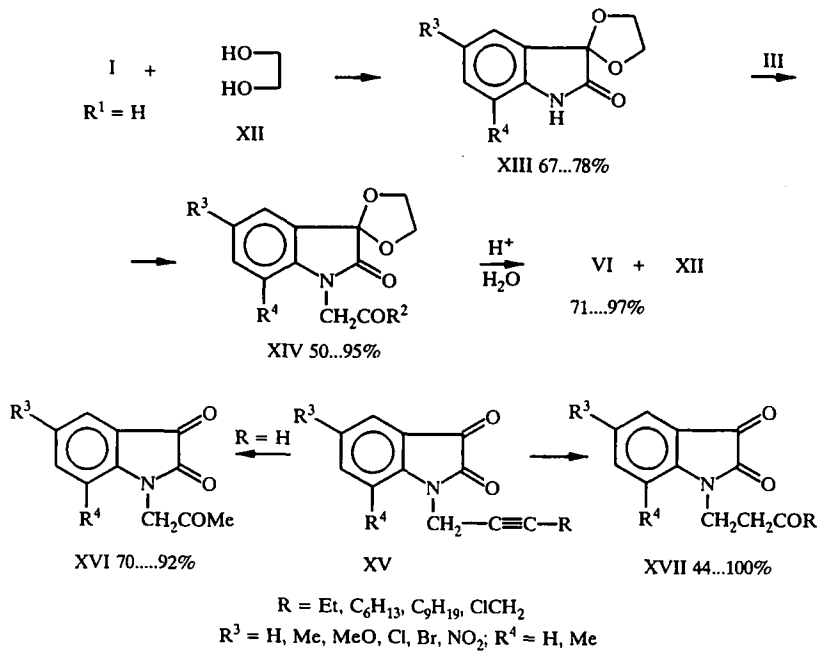
3. STARTING MATERIALS

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).

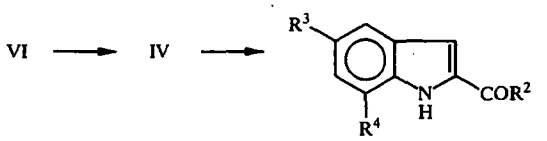
4. SYNTHESES BASED ON 2-ACYLINDOLE-3-CARBOXYLIC ACIDS, IV

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

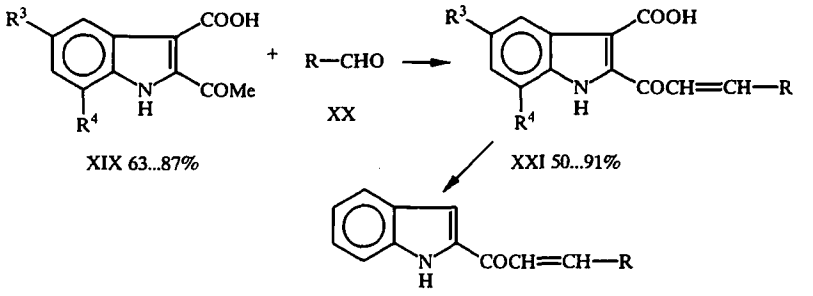
This reaction is the simplest method for the synthesis of 2-acylindoles XVIII. The usual starting materials are the diketones VI which are rearranged in a homogeneous 1:1 DMF–water medium containing up to 5% NaOH. The acids IV formed *in situ* are decarboxylated in the same solution. After cooling to 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].

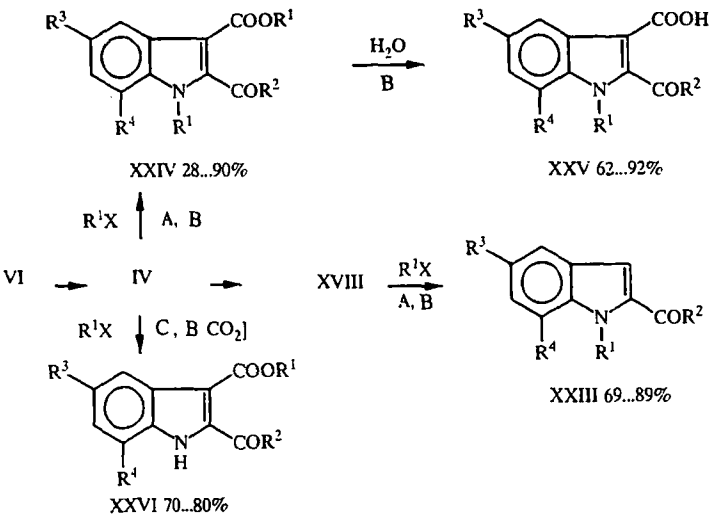
Acids XXI with an α,β-double bond in the acyl group were synthesized by crotonic condensation of 2-acetylindole-3-carboxylic acids XIX with aldehydes XX. They decarboxylate more easily than their saturated analogs to give the ketones XXII.

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≡C–CH_2, $C_{11}H_{23}$–C≡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].

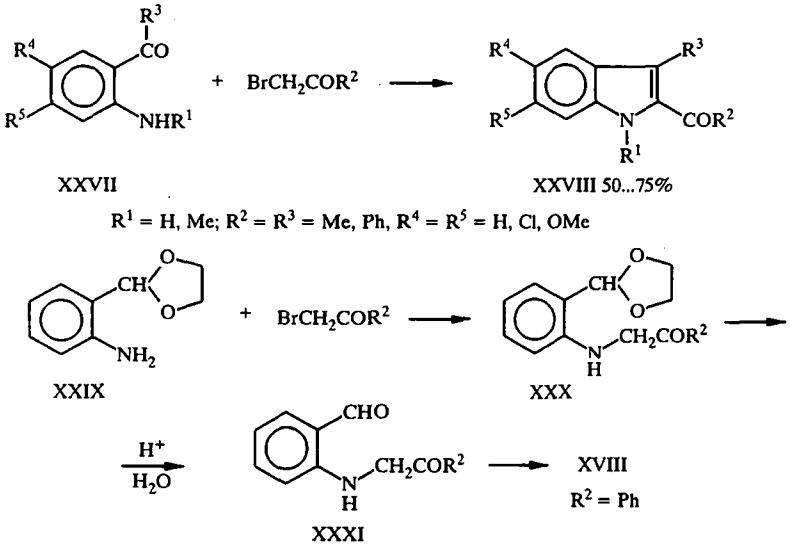
The behavior under electron impact of indolediones-2,3, their β-ethylene acetals and their physiologically active β-thiosemicarbazones has been studied to identify intermediate products of the indoledione-indole rearrangement [32-37]. Rearrangement of the semicarbazones to 3-mercaptooxyindoles under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

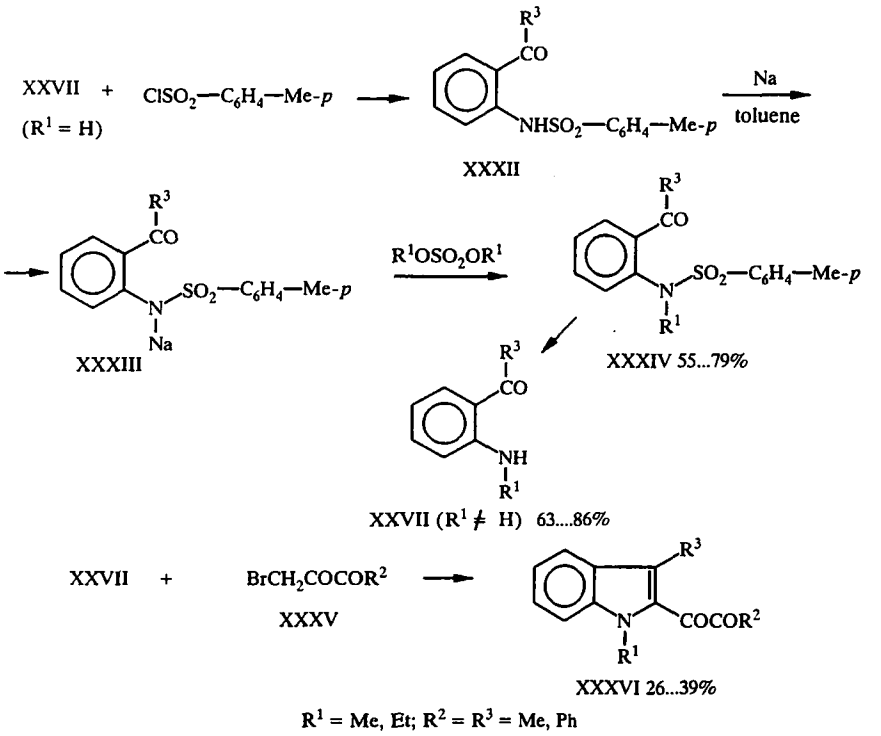


The basic fact which restricts the development of this reaction is the complexity of the synthesis of *ortho*-aminoketones XXVII, especially with R^1 = H. The latter were obtained via the tosylates XXXII which were converted into the Na-derivatives (XXXIII), alkylated with dialkyl sulfates and then hydrolyzed with acid to remove the tosyl group from compounds XXXIV. Condensation of compound XXVII with bromomethyldiketones XXXV to give the diketones XXXVI was accomplished at 75-80°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 its drawback is the impossibility of obtaining these substances with substituents at $C_{(3)}$.

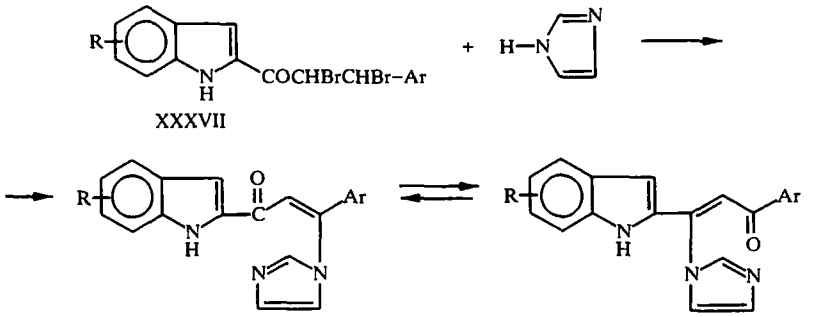
It follows from this discussion that the basic problems with the syntheses of 2-acylindoles from *ortho*-aminophenylcarbonyl compounds and halomethylketones remain the intermolecular condensation of compounds II and III and new routes to the *ortho*-aminoketones XXVII. With respect to solving the first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