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SYNTHESES OF 1-ALKYL-2-ACYLINDOLES, 1-ALKYL-2-ACYLINDOLE-3-CARBOXYLIC ACIDS, AND THEIR ESTERS, IN SUPERBASIC MEDIA

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2-Acylindoles and 2-acylindole-3-carboxylic acids are readily alkylated at the nitrogen atom by haloalkanes in a superbasic medium (DMSO + NaOH). For the carboxylic acids, this reaction may proceed either entirely at the nitrogen atom, or at both the the nitrogen atom and the carboxyl group, depending on the content of water in the medium and the alkali–haloalkane ratio.

In ordinary alkaline media, 2-acylindoles are N-alkylated with difficulty, and only under severe conditions and with low yields [1]. In superbasic media, however, this process goes forward at 5-20°C and is general in character. Here, the superbasic medium may be anhydrous DMSO (or HMPA) + powdered NaOH (medium A), or DMSO–water (9:1) + NaOH (5-10%) (medium B). The effect obtained by the use of these media is apparently due to the facile deprotonation (in these media) of the N–H group of the 2-acylindoles that are used as the initial compounds. The resulting anions are N-alkylated by haloalkanes R^1X.

In the interest of simplifying the preparation of the 2-acylindoles and performing two or three stages of the synthesis without isolating the intermediate products, it is preferable to use as the initial compounds 1-[2-oxoalkyl(aryl, hetaryl)]indole-2,3-diones (Ia-c). In ordinary alkaline media, these compounds are known to be recyclized to form 2-acylindole-3-carboxylic acids (II) at 20°C [2-4] and to form 2-acylindoles (III) at 60-70°C [5]. The same sort of conversions are characteristic for these compounds in medium B. This is illustrated by the synthesis of acids (IVf,j), carried out in a single flask by recyclization of the diketone Ia to the acid IIa, and its treatment with benzyl chloride and 1,3-dichloro-2-butene.

The preparation of compounds II and III in medium B is sometimes accompanied by the appearance of colored impurities that have not been identified, impurities that are also precipitated in the reaction products. In this case, a change is made to successive use of two media: first an ordinary basic medium, DMSO–water (2:1 to 3:1) + NaOH (1-5%) (medium C), in which recyclization of the diketones I takes place; and then medium B for alkylation of the acids II. After the initial recyclization has been completed, medium C is transformed to medium B (C → B) by adding extra quantities of DMSO and powdered NaOH. When compounds II and III are initially prepared in an ordinary alkaline medium, there is little or no formation of colored impurities.

1-Alkyl-2-acylindoles (Va,c,d) are synthesized from the ketone IIIa and methyl iodide (or n-propyl iodide) and allyl bromide in medium B through the pathway I-II-III-V; compound Vb is synthesized from the ketone IIIb and methyl iodide in medium A (Scheme 1). In these syntheses, NaOH may be replaced by KOH in either medium. In the case of the acids II, the use of KOH is undesirable, as it results in the formation of large quantities of byproducts.

Syntheses of the 1-alkyl-2-acylindole-3-carboxylic acids IVa-k are based on saponification of their esters (VI) in medium B at 5-20°C, performed by two different methods along the pathway I-II-VI-IV. The acids IIa-c are used as initial compounds; they are prepared from the diketones Ia-c and used *in situ*, or they may be first separated from the alkaline medium [2].

In the first method, the reactants are taken in a mole ratio II(I):R^1X:NaOH = 1:(1-3):(2-10). With excess caustic relative to the haloalkane, the nitrogen atom and the carboxyl groups are alkylated, with simultaneous saponification of the

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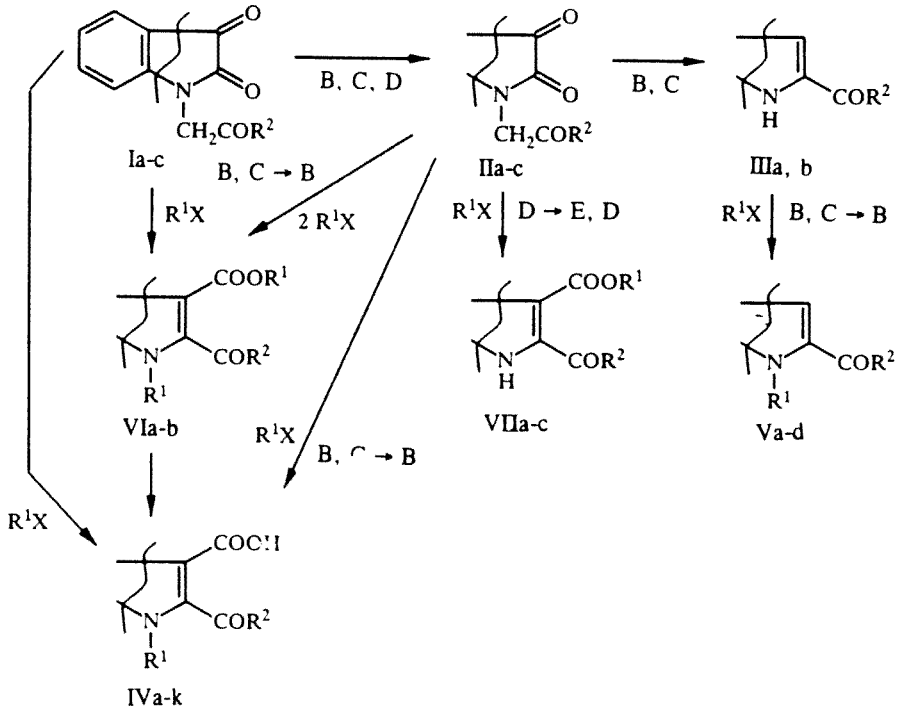
TABLE 1. 1-Alkyl-2-acylindole-3-carboxylic Acids IVb,d,g-i Obtained by Selective N-Alkylation of 2-Acylindole-3-carboxylic Acids IIa,b,c

Initial compound	Mole ratio I(II) : R^1X : NaOH	Acid obtained	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
				C	H	N	Hal		
Ia	1 : 2,4 : 5,6	IV b	$C_{17}H_{13}NO_3$	64,6 65,1	4,1 3,9	4,2 4,5	—	238...240	72
Ia	1 : 3 : 6	IV d	$C_{19}H_{17}NO_3$	74,2 74,3	5,6 5,6	4,4 4,6	—	206...207	79
Ia	1 : 2 : 10	IV f	$C_{23}H_{17}NO_3$	77,4 77,7	4,8 4,8	3,9 3,9	—	251...253	92
IIa	1 : 3 : 6	IV g	$C_{19}H_{15}NO_3$	74,9 74,7	5,3 5,0	4,4 4,6	—	226...227	73
Ib	1 : 2 : 5	IV h	$C_{19}H_{14}ClNO_3$	66,5 67,2	4,0 4,2	4,0 4,1	10,3 10,4	232...234	68
Ic	1 : 2 : 5	IV i	$C_{19}H_{14}BrNO_3$	59,8 59,4	3,8 3,7	3,8 3,7	20,5 20,8	235...236	90

resulting ester groups in compounds VI. At the end of the reaction, the carboxyl groups of the acids IV remain unchanged. This process is called selective N-alkylation of the acids II. The most graphic illustration of this process is the N-benzylation of the acid IIa, forming the acid IVf (yield 92%). The other acids IVb,d,g-i are shown in Table 1.

Scheme 1



Ia, IIa, IIIa, IVa,c-g,l,m, Va, VIa,c,d,f-h, VIIa-c: R^2 is C_6H_5. Ib, IIb, IVb,h: R^2 is 4-ClC_6H_4. Ic, IIc, IIIb, IVi, Vb, VIb,e: R^2 is 4-BrC_6H_4. IVa,b, Va,b, VIa,b, VIIa: R^1 is CH_3. IVc, VIc, VIIb: R^1 is C_2H_5. IVd, Vc, VId,e, VIIc: R^1 is C_3H_7. IVe, Ve: R^1 is C_4H_9. IVf: R^1 is $CH_2C_6H_5$. IVg-i, Vd, VIg: R^1 is $-CH_2-CH=CH_2$. IVj: R^1 is $CH_3-C(Cl)=CH-CH_2-$. IVk: R^1 is $C_{11}H_{23}-C\equiv C-CH_2-$. VIh: R^1 is $CH\equiv C-CH_2-$. X is Br or I.

TABLE 2. Esters of 1-Alkyl-2-acylindole-3-carboxylic Acids VIa-h and XII Recovered from Media A and B, and Esters Obtained under Conditions of Interfacial Catalysis

Ester	Empirical formula	Found, % / Calculated, %			mp, °C	PMR spectrum, δ, ppm (and J, Hz)	Yield, %
		C	H	N			
VIa	$C_{18}H_{15}NO_3$	73.4 / 73.7	5.5 / 5.2	4.9 / 4.8	146...147	3,12 (3H, s, MeN), 3,16 (3H, s, MeO), 7,25...8,23 (9H, m, H_{arom})	90
VIb*	$C_{18}H_{14}BrNO_3$	58.7 / 58.1	4.1 / 3.8	3.8 / 3.8	186...186,5	3,61 (3H, s, MeN), 3,71 (3H, s, MeO), 7,25...8,28 (8H, m, H_{arom})	68
VIc	$C_{20}H_{19}NO_3$	75.2 / 74.7	6.0 / 6.0	4.4 / 4.4	83...84	0,94 (3H, t, J = 7,1, CH_3CH_2N), 1,35 (3H, t, J = 7,1, CH_3CH_2O), 3,79 (2H, q, J = 7,2, CH_2N), 4,17 (2H, q, J = 7,1, CH_2O), 7,25...7,97 (9H, m, H_{arom})	69
VId	$C_{22}H_{23}NO_3$	75.2 / 75.6	6.5 / 6.6	3.8 / 4.0	80...81	0,82 (3H, t, J = 7,1, CH_3CH_2N), 0,84 (3H, t, J = 5,8, CH_3CH_2O), 1,16...1,90 (4H, m, $2CH_2$), 3,93 (2H, t, J = 6,5, CH_2N), 4,16 (2H, t, J = 7,5, CH_2O), 7,24...8,31 (8H, m, H_{arom})	76
VIe†	$C_{22}H_{22}BrNO_3$	61.8 / 61.7	5.3 / 5.2	3.2 / 3.3	50...52	0,82 (3H, t, J = 7,1, CH_3CH_2N), 0,84 (3H, t, J = 6,7, CH_3CH_2O), 1,24...1,79 (4H, m, CH_2), 3,96 (2H, t, CH_2N), 4,08 (2H, t, CH_2O), 7,21...7,87 (8H, m, H_{arom})	60
VIf	$C_{24}H_{27}NO_3$	76.5 / 76.4	7.4 / 7.2	3.3 / 3.7	45...46	–	68
VIg	$C_{22}H_{19}NO_3$	76.8 / 76,5	5.5 / 5,5	4.0 / 4,1	45	–	67
VIh	$C_{22}H_{15}NO_3$	78.0 / 77.4	4.5 / 4.4	3.8 / 4,1	120...121	2,77 (1H, t, J = 2,5, HC ≡ CCH_2N), 2,86 (1H, J = 2,5, HC ≡ CCH_2O), 4,61 (2H, d, J = 2,5, CH_2N), 5,10 (2H, d, J = 2,5, CH_2O), 7,29...8,31 (8H, m, H_{arom})	28
XII	$C_{20}H_{17}NO_3$	75.0 / 75,2	5.4 / 5,4	4.3 / 4,4	152	–	79

*Found, %: Br 21.2. Calculated, %: Br 21.5.

†Found, %: Br 19.0. Calculated, %: Br 18.7.

Mass spectrum, *m/z* (and I_{rel}, %) 430 (21), 429 (96), 428 (29), 427 (100), 370 (19), 369 (32), 368 (21), 367 (25), 289 (25), 266 (22), 261 (11), 229 (18), 227 (19), 204 (18), 203 (18), 202 (96), 201 (32), 200 (86), 199 (32), 198 (18), 188 (18), 187 (11), 186 (93), 184 (79), 180 (50), 171 (18), 170 (11), 169 (21), 168 (18), 164 (18), 163 (29), 161 (18), 157 (39), 155 (36), 152 (11), 151 (19), 149 (25), 146 (21), 137 (39), 136 (14), 129 (25), 127 (29), 125 (43), 123 (25), 122 (22), 121 (18), 120 (32), 119 (96), 107 (14), 106 (11), 105 (82), 104 (18).

TABLE 3. 1-Alkyl-2-acylindole-3-carboxylic Acids IVa,c,d,e,g Prepared by Saponification of Their Esters VIa,c,d,e,g That Were First Separated from Medium A and B, and Also by Saponification of Esters Obtained under Conditions of Interfacial Catalysis

Initial ester VI	Acid product IV	Empirical formula	Found, % / Calculated, %			PMR spectrum, δ, ppm (and J, Hz)	Mass spectrum, *m/z* (and I_{rel}, %)	mp, °C	Yield, %
			C	H	N				
VIa	IVa	$C_{17}H_{13}NO_3$	73.6 73,1	4.7 4,7	4.8 5,0	3,76 (3H, s, CH_3), 7,32...8,30 ppm (9H, m, H_{arom})	280(13), 279(67), 261(25), 260(88), 232(22), 218(13), 217(88), 175(33), 174(50), 173(44), 171(19), 147(21), 145(29), 128(21), 115(13), 114(11), 109(13), 105(42), 103(11), 102(11), 101(11), 91(25), 89(17), 88(13), 85(11), 84(12), 83(13), 78(12), 77(100), 76(21), 75(17), 73(13), 69 (13), 60(13), 57 (27), 55(25)	257...258	77
VIc	IVc	$C_{18}H_{15}NO_3$	73.3 73,7	5.4 5,2	5.2 4,8	1,29 (3H, t, J = 7,1, CH_3), 4,24 (2H, q, J = 7,1, CH_2), 7,33...8,29 ppm (9H, m, H_{arom})	294(25), 293(100), 275(60), 274(96), 260(30), 248(17), 246(17), 232(17), 218(15), 204(12), 105(41), 91(30), 77(83)	250...251	78
VId	IVd	$C_{19}H_{17}NO_3$	74.2 74,3	5.6 5,6	4.4 4,6	0,93 (3H, t, J = 7,3, CH_3), 1,62 (2H, m, J = 7,3, CH_2), 3,13 (2H, t, J = 7,3, CH_2– N), 7,11...8,12 ppm (9H, m, H_{arom})	308(25), 307(100), 290(12), 289(50), 288(75), 260(44), 248(12), 247(12), 232(12), 130(44), 127(36), 91(88), 87(75)	206...207	79
VIe	IVe	$C_{20}H_{19}NO_3 \cdot H_2O$	70.8 70.8	5.7 6,2	3.8 4,1	0,64 (3H, t, J = 5,6, CH_3), 0,81...1,25 (4H, m, $2CH_2$), 7,28...8,32 ppm (9H, m, H_{arom})	322(27), 321(100), 304(14), 303(59), 302(76), 260(47), 232(24), 204(41), 198(63)	218...219	75
VIg	IVg	$C_{19}H_{15}NO_3$	74.9 74,7	5.3 5,0	4.4 4,6		306(16), 305(68), 288(31), 287(47), 260(15), 259(16), 258(22), 230(22), 228(12), 210(62), 190(12), 183(12), 182(80), 170(12), 154(31), 115(16), 105(69), 63(12), 62(16), 60(19), 55(19), 44(19), 43(50), 42(13), 41(53)	226...227	65

The second method, which is a modification of the first method, differs in separating the stages of obtaining the esters VI and their subsequent saponification to the acids IV. The reactions begin with an equimolar ratio of R^1X to NaOH, or with excess R^1X. In this stage, the main product is the ester VI, which is separated and then, if necessary, saponified to the corresponding acid (IVa,c,d,e,g, Table 3). The syntheses of the acids IV are also accomplished without separating the esters VI. To do this, the reaction mixture containing the ester VI is fortified with an additional quantity of powdered NaOH, sufficient to give a calculated amount of 1.5-4 moles per mole of ester; then the mixture is stirred for a period that depends on the particular radical R^1 in the ester group: 1-2 h for the allyl ester, 3 h for the methyl or ethyl ester, and 4 h for the n-propyl or n-butyl ester. This method is used in cases in which, along with the acids II, their esters are required, with successive use of media A and B; it is also used in working with halides that are sensitive to the excess caustic of medium B (1,3-dichloro-2-butene).

In both methods, the acids IVa-k are recovered in the form of precipitates, with certain byproducts also showing up in the precipitates. The purification method is based on differences in their reaction to dilute aqueous caustic solutions. The raw precipitates are shaken vigorously with a 1-2% NaOH solution; the byproducts, which are indifferent to caustic, are removed by extraction with ether or some other organic solvent; then, by acidification of the aqueous layer to pH 1, the purified acids IVa-k are precipitated from the solution of their Na salts.

In medium A, water is formed only by deprotonation of the N-H group of the acids II and ketones III, and, for the acids, also as a result of their neutralization by caustic. However, the concentration of water is not sufficient to bring about recyclization of the diketones I to compounds II and III. Therefore, compounds II and III must first be obtained in ordinary alkaline media and then brought into reaction as the initial compounds in this same medium A. Although media A and B are often undistinguishable from each other in terms of NaOH conter' the concentration of water in medium A is likewise inadequate for saponification of the esters. For this reason, medium A is unsuitable for use in obtaining the acids IV by the first method. Method A finds its application in syntheses of the ketones V and esters VI (Table 2), and also the acids IV when media A and B are used consecutively; in this case, the ester VI is prepared in the first medium, which is transformed into the second medium by the addition of the calculated quantities of water and powdered NaOH to the reaction mixture, after which the saponification is performed as described above.

In a weaker superbasic medium consisting of DMF (or HMPA)–water (9:1) + NaOH (5-10%) (medium D), the acids II are alkylated at the nitrogen atom only with difficulty, but are alkylated readily at the carboxyl group. The resulting esters VII contain as impurities the esters VI, which are not easy to remove, even by chromatographic methods [4]. In a modified method for the synthesis of the esters VIIa-c, the initial diketone Ia is recyclized to the acid IIa in medium D, the caustic is neutralized with carbon dioxide, and the Na salt that is obtained is alkylated by methyl iodide (or ethyl or n-propyl iodide) in a neutral medium consisting of DMF (or HMPA)–water (9:1) (medium E).

Thus, depending on the content of water in medium A or B and on the ratio R^1X–NaOH in the medium, the acids II are alkylated either to the acids IV or their esters. In order to simplify the syntheses of the 2-acylindoles IV-VI, it is necessary to take the diketones I in medium B.

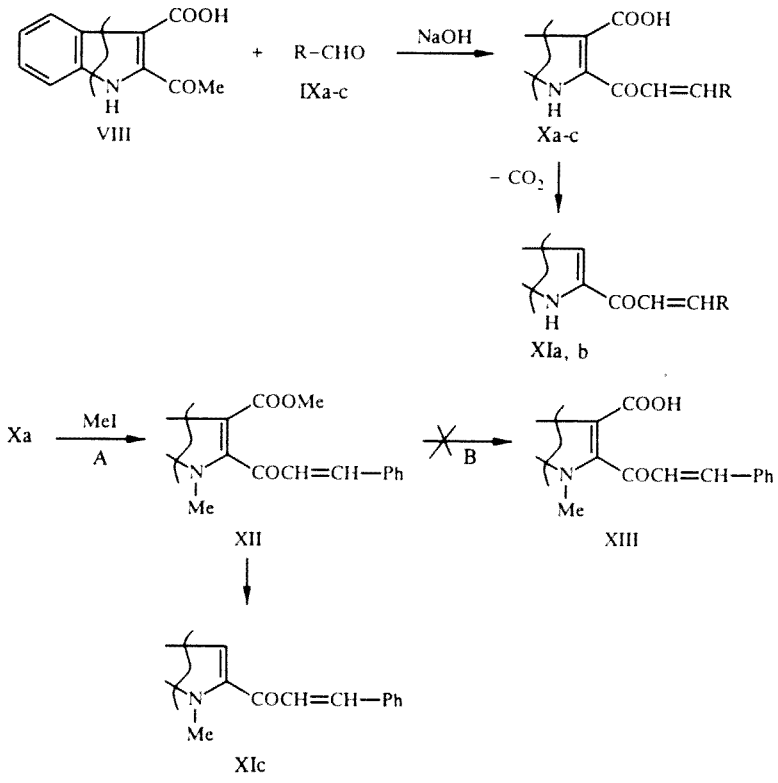
The syntheses of the 2-acylindoles IV and VI in superbasic media was compared with the preparation of these compounds by interfacial catalysis (IFC). As catalysts we used triethylbenzylammonium chloride (TEBA). We found that IFC leads only to the esters VI, with a yield of 60-70%. The alkylation of the acids IIa to the esters VIa,c,d,f is accomplished in 24 h at 20°C under "conditions of extraction of ion pairs," and with a mole ratio of I (or II):R^1X:TEBA = 1:(5-6):1. The esters VI are resistant to hydrolysis in ordinary alkaline media; this apparently explains the unsuccessful attempts to use IFC to obtain the acids IV as well. This is an obvious indication of the advantages of using media A and B over the use of IFC.

Of the R^1X halides that were listed above, 1-chloro-2-propyne and 1,3-dichloro-2-butene are unstable in superbasic media. The reaction of the first of these compounds with the acid IIa in media A and B leads to the ester VIh with a yield of 28%. This is due to the presence of the terminal triple bond in the 1-chloro-2-propyne, as confirmed by the synthesis of the acid IVk (47%) with the use of half the quantity of 1-bromo-2-tetradecyne. The 1,3-dichloro-2-butene begins to decompose even at the moment it is introduced into medium B at 20-25°C. We were able to synthesize the acid IVj successfully after lowering the reaction mixture temperature to 0-5°C in the stage of forming its ester, using a considerable excess of the 1,3-dichloro-2-butene.

Alkylation of the 2-acylindoles II and III was accomplished with an equimolar ratio of II (or I) to R^1X, or with an excess of the halide. Synthesis of the acid IVk is presented as an illustration. To separate this acid from the initial acid IIa, we used column chromatography on silica gel. The use of excess alkylating reagent (usually a 1.5-fold to 3-fold excess) makes it possible not only to obtain high yields of the final products, but also to purify them by recrystallization.

Crotonic condensation of 2-acetylindole-3-carboxylic acid (VIII) with the aldehydes IXa-c affords the acids Xa-c with a double bond in the acyl radical, and then the 2-acylindoles (XIa,b), under the conditions of [5]. After methylation of the acid Xa in medium A, the ester XII is recovered; however, we were unable to saponify this to the expected acid XIII, owing to facile decarboxylation of the acid. The final product is the unsaturated ketone XIc; the synthesis of this substance and other similar compounds will be described later. These results indicate that after the introduction of a double bond into the acyl part of the acids IV, they become unstable in medium B; and hence these compounds are still unobtainable.

Scheme 2

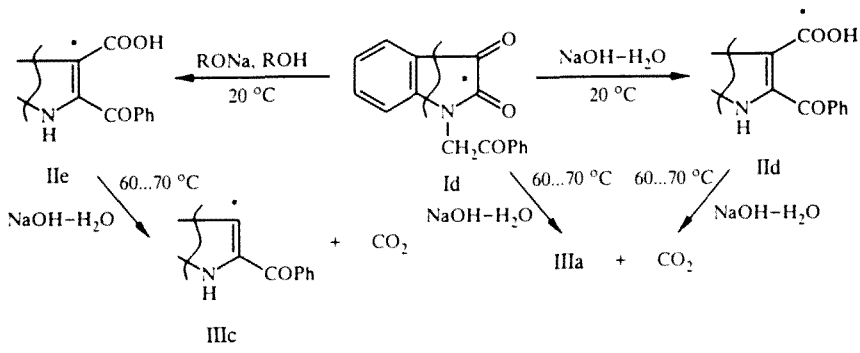


IX–XI a) R = Ph, b)R = 3-NO_2-C_6H_4; c)R = 2-furyl

The large amount of experimental material on 2-acylindoles that has been described above, along with that reported previously [2-5] has created a need for a new term, "indoledione-indole rearrangement," which conveys the essence of the conversions we have described. This term is applied to the isomerization of 1-[2-oxoalkyl(aryl,hetaryl)]indole-2,3-diones I to 2-acylindole-3-carboxylic acids II under conditions of basic catalysis. In this rearrangement, the diketones I are the synthons through which the 2-acylindoles II-VII have become accessible.

The indoledione-indole rearrangement proceeds through two different mechanisms of forming the pyrrole ring of the acids II, depending on the catalyst employed (NaOH or sodium alcoholate) and on the medium [4]. For the approach that is proposed below as proof of its dual mechanism, all that is important is the transformation of the α-CO or β-CO group of the diketones I into the carboxylic group of the acids II. In aqueous caustic or in the superbasic medium B, the α-CO group enters into reaction; in an alcoholic solution of sodium alcoholate, it is the β-CO group. In order to distinguish each of these in the carboxyl group, diketones I with ^{13}C atoms in the pyrrole ring must be used. For example, upon rearrangement of the compound Id in the two media at 20°C, the acids IId,e are formed; these can be distinguished by their mass spectra. However, it is preferable to decarboxylate these acids and subsequently analyze the ketones IIIa,c for the presence of the ^{13}C atom. In Scheme 3 it is shown that in aqueous caustic or the superbasic medium B, the ordinary ketone IIIa is formed; in an alcoholic solution of sodium alcoholate, the same ketone IIIc is formed, but labeled at the $C_{(3)}$ atom. The recovery of this product not only confirms the transformation of the β-CO group of the diketone Id to the carboxyl group of the acid IIe, but also provides evidence in favor of the mechanism of indoledione-indole rearrangement in an alcoholic solution of sodium alcoholate [4].

Scheme 3



It should be noted that the conversions described in Scheme 3, i.e., conversions of the diketone Id to the acids IId,e and then to the ketones IIIa,c, have not yet been accomplished experimentally. However, in accordance with this scheme and under the same conditions, numerous compounds II and III have been synthesized with invariably good, reproducible results; and the ketones III after the reaction are usually recovered in analytically pure form. The only difference between the proposed approach to investigation of the mechanism of the indoledione-indole rearrangement and the syntheses of compounds II and III that have been performed [2-5] is that those syntheses were performed on diketones I that did not contain any labeled atoms.

The published synthesis of an indole-2,3-dione with an α-CO group [6] simplifies the problem of synthesizing the diketone Id. If the ^{13}C atom in this compound is shifted to the β-position, we will then obtain in an aqueous medium the acid IIe, and from it the ketone VIc; in an alcoholic solution of sodium alcoholate, we will obtain the acid IId, then decarboxylate it to the ketone VIa.

Since there are broad possibilities for varying the substituents in the benzene ring, in the acyl part and also on the nitrogen atom of the 2-acylindoles II-VII, we can regard the indoledione-indole rearrangement and the conversions based on this rearrangement as a general method for the synthesis of indoles.

EXPERIMENTAL

In these experiments we used freshly distilled haloalkanes and powdered carbonate-free NaOH. Anhydrous DMSO and hexametapol (HMPA) were prepared for use by conventional procedures. Melting points were determined on a Boetius stage and were not corrected. The individuality of compounds IVa-k was monitored by means of TLC on Silufol plates in systems consisting of ethyl acetate and hexane (1:2) and benzene (or toluene) and acetone (4:1, 5:1, and 6:1); compounds Va-d and VIa-h were monitored similarly in an ethyl acetate–hexane system (1:4) and in pure benzene. The spots were developed in iodine vapor. The individuality of compounds IVg-k, Vd, and VIg,h was also monitored by development of the spots in an aqueous $KMnO_4$ solution.

The results of elemental analyses for C, H, N, and halogens matched the calculated values. Compounds Ia-c and IIa-c have been described in [2], compounds IIIa,b in [5].

Compounds IVa-k were purified through their Na salts and further purified if necessary by recrystallization from diisopropyl ether, alcohols (methyl, ethyl, isopropyl), or 60-70% aqueous alcohol. The esters VIa-h were recrystallized from hexane. In all cases, the crystallization was performed over the course of 24-48 h at −18°C. PMR spectra were taken in a Bruker-80 instrument for the acids IVa,c,d,e,g in DMSO-d_6, and for the esters VIc-h in $CDCl_3$. Mass spectra were taken in MKh-1320 instruments, with the sample introduced into the ion source.

Medium A was prepared by adding powdered NaOH to anhydrous DMSO (or HMPA). After this mixture was stirred for 5-10 min, introduction of the reactants was commenced.

Medium B was obtained by vigorous stirring of an aqueous NaOH solution with DMSO. Heating of the water to 50-60°C was permitted in order to dissolve the NaOH before dilution with the DMSO. After cooling the solution to 5-20°C, medium B was ready for carrying out the reaction.

Medium C was prepared by mixing DMSO with an aqueous caustic solution; medium D was prepared by the same method, but with the DMSO replaced by DMF or HMPA.

Concentrations of NaOH in media A, B, C, and D are stated in percentage of total weight of the solution.

1-Methyl-2-(4-bromobenzoyl)indole (Vb). To 10 ml of anhydrous DMSO, 0.3 g (7.5 mmoles) of powdered NaOH was added, and then 1.5 g (5 mmoles) of 2-(4-bromobenzoyl)indole IIIb. The mixture was stirred for 30 min, after which 1.07 g (7.5 mmoles) of CH_3I was added. The reaction mixture was held for 2 h and then diluted with 100 ml of water; the resulting emulsion was broken by adding concentrated HCl. The precipitate was separated and dried in air, then over P_2O_5. By recrystallization from hexane at -10°C, obtained the ketone Vb with a yield of 1.4 g (89%), mp 127-127.5°C. Found, %: C 60.8, H 4.2, N 4.3, Br 24.8. $C_{16}H_{12}BrNO$. Calculated, %: C 61.2, H 3.8, N 4.5, Br 25.4.

1-n-Propyl-3-benzoylindole (Vc). A 0.3-g quantity (7.5 mmoles) of NaOH was dissolved in 2 ml of water, and 4 ml of DMSO was added, followed by 0.53 g (2 mmoles) of 1-phenacylindole-2,3-dione Ia; the mixture was heated for 3 h at 60°C and then cooled to room temperature. Next, 14 ml of DMSO was added, followed by 0.4 g (10 mmoles) of powdered NaOH and 0.68 g (4 mmoles) of n-C_3H_7I; the reaction mixture was stirred for 2 h at the same temperature (60°C), and then the reaction mixture was poured into 200 ml of dilute (1:20) hydrochloric acid. The precipitate of the ketone Vc was separated, washed with water to neutral reaction, and purified in a column with silica gel L 160/100 μ (30 g). Yield of compound Vc 69%, mp 78-79°C (from pentane). PMR spectrum (acetone-d_6): 0.95 (3H, t, J = 7.3, CH_3), 2.07 (2H, t, J = 7.3, CH_2), 4.05 (2H, t, J = 7.3, N−CH_2), 7.04 (1H, s, 3-H), 7.16-8.01 ppm (9H, m, H_{arom}). Found, %: C 82.4, H 6.1, N 5.0. $C_{18}H_{17}NO$. Calculated, %: C 82.1, H 6.1, N 5.0.

The compounds listed below were obtained analogously.

1-Methyl-2-benzoylindole (Va). Yield 76%, mp 44.5-46.5°C. PMR spectrum (acetone-d_6): 4.28 (3H, s, CH_3), 7.41-7.89 ppm (9H, m, H_{arom}). Found, %: C 81.5, H 5.8, N 6.4. $C_{16}H_{13}NO$. Calculated, %: C 81.7, H 5.6, N 6.0.

1-Allyl-2-benzoylindole (Vd). Yield 77%, mp 71-72°C. Mass spectrum: 216(M^+), 260(24), 245(14), 244(35), 243(8), 234(9), 233(6), 232(9), 217(8), 201(8), 181(24), 165(8), 156(25), 154(9), 129(6), 128(9), 115(11), 105(31), 77(40). Found, %: C 82.9, H 6.4, N 5.3. $C_{18}H_{15}NO$. Calculated, %: C 82.9, H 6.4, N 5.3.

Synthesis of 1-Alkyl-2-acylindole-3-carboxylic Acids by Selective N-Alkylation of 2-Acylindole-3-carboxylic Acids.

1-Benzyl-2-benzoylindole-3-carboxylic Acid (IVf). A. To a solution of 0.4 g (10 mmoles) of NaOH in 2 ml of water, 6 ml of DMSO was added, after which 1.06 g (4 mmoles) of 1-phenacylindole-2,3-dione Ia was added at 20°C while stirring. After 3 h, 12 ml of DMSO was added, then 1.2 g (30 mmoles) of powdered NaOH; the reaction mixture was held for 1 h at the same temperature (20°C), and then 1.01 g (8 mmoles) of benzyl chloride was added. After 3 h, the reaction was mixture was poured into 200 ml of dilute (1:20) HCl. The precipitate was separated, washed with water, dispersed in 200 ml of a 1% aqueous NaOH solution, and then extracted with ether (2 × 75 ml). The aqueous layer was separated and acidified to pH 1; the precipitate was separated, washed with water to neutral reaction, dried over P_2O_5, and recrystallized from acetone. The characteristics of the acid IVf are listed in Table 1.

B. To 10 ml of a mixture of DMSO and water (9:1) and NaOH (0.8 g, 20 mmoles), 1.06 g (4 mmoles) of 1-phenacylindole-2,3-dione Ia was added; the reaction mixture was stirred for 2.5 h at 20°C; then 1.01 g (8 mmoles) of benzyl chloride was added, after which the synthesis followed the same procedure as in method A.

C. To 2 ml of water, 1.6 g (40 mmoles) of powdered NaOH was added, then 18 ml of DMSO and 1.06 g (4 mmoles) of the acid IIa; after 1 h, 1.01 g (8 mmoles) of benzyl chloride was added. After 3 h, the reaction mixture was poured into 200 ml of dilute (1:20) HCl; the subsequent treatment was the same as described in method A.

Syntheses of esters of acids VIa-h (characteristics of esters are listed in Table 2).

Methyl Ester of 1-Methyl-2-benzoylindole-3-carboxylic Acid (VIa). To 10 ml of anhydrous DMSO, containing 0.5 g (12.5 mmoles) of powdered NaOH, 1.06 g (4 mmoles) of the acid IIa was added, and the mixture was stirred for 45 min at 20°C, after which 1.78 g (12.5 mmoles) of CH_3I was added. After 1.5 h, the reaction mixture was poured into 100 ml of water; the precipitate was washed successively with 100 ml of cold water and 100 ml of hot water and then dried for 3 h at 115°C, obtaining VIa with a yield of 1.0 g (90%), mp 146-147°C (from hexane). When the DMSO was replaced by HMPA, the yield was 65%, mp 148-150°C.

The esters VIh and XII (Table 2) were obtained analogously.

Methyl Ester of 1-Methyl-(4-bromobenzoyl)indole-3-carboxylic Acid (VIb). In 2 ml of water, 0.5 g (12.5 mmoles) of NaOH was dissolved, and 6 ml of DMSO was added, after which 1.5 g (4.36 mmoles) of 4-bromophenacylindole-2,3-dione (Ic) was added while stirring. After 3 h, 12 ml of DMSO was added and the mixture was held for 1 h; then 1.86 g (13 mmoles) of CH_3I was added, and the mixture was stirred for an additional 2 h. The reaction mixture was diluted with 200 ml of water; the precipitate was separated, washed with water, air-dried, and then crystallized from petroleum ether (bp 60-100°C), obtaining VIb with a yield of 68%, mp 186-186.5°C. Mass spectrum: 374(17), 373(96), 372(21), 371(100), 349(26), 342(21),

341(30), 340(89), 339(38), 338(81), 312(32), 310(26), 293(17), 262(10), 261(34), 260(62), 251(23), 250(96), 248(91), 233(17), 232(26), 216(21), 185(26), 183(23), 158(19), 157(40), 155(39), 152(13), 151(40), 150(11), 149(45).

Synthesis of Esters of Acids VIa,c,d,f by Interfacial Catalysis Method. A. The diketone Ia (10 mmoles) was dissolved in an aqueous solution of 1.5 g NaOH in 33.5 ml of water, and the mixture was stirred for 3 h at 20°C; then the solution was chilled to +5°C, and 15 g of NaOH was added in small portions, so that the temperature did not exceed 20°C. After dissolving the caustic, 50-60 mmoles of the appropriate haloalkane was added, along with 50 ml of benzene and 10 mmoles of TEBA; the mixture was stirred vigorously for 24 h at 20°C, then diluted with 200 ml of water and extracted with benzene (3 × 100 ml); the combined benzene extract was washed with water (5 × 60 ml) and dried over Na_2SO_4; the benzene was evaporated to dryness, and the residue was crystallized from pentane. The yield of esters of the acids VIa,c,d,f was 60-70%. The constants of the substances were the same as those for the analogous compounds obtained in media A and B (Table 2).

B. The reaction was performed as with method A, except that all components were brought into reaction simultaneously.

Synthesis of 1-Alkyl-2-acylindole-3-carboxylic Acids IVa,c,d,e,g by Saponification of Their Esters, Previously Obtained in Medium A or B or Under IFC Conditions. To 10 ml of a mixture of DMSO and water (9:1) containing 20 mmoles of NaOH, 5 mmoles of one of the esters VIa,c,d,f,g was added; the mixture was stirred at 20°C for 1-2 h in the case of the allyl ester, 3 h for the methyl and ethyl esters, or 4 h for the n-propyl and n-butyl esters. The reaction mixture was poured into 100 ml of a 1.5% aqueous HCl solution; the precipitate of the acid IVa,c,d,e,g was separated, washed with water to neutral reaction, and dispersed in 150-200 ml of a 1% aqueous NaOH solution. After extraction with ether (3 × 50 ml), the aqueous layer was acidified to pH 1; the precipitate was washed with water and dried to constant weight over P_2O_5 (24-48 h). If necessary, the reaction product was further purified by recrystallization from 60-70% aqueous alcohol or diisopropyl ether, with the solution held for 24 h at −18°C. The yields and constants of the substances are given in Table 3.

1-(Tetradecyn-2-yl)-2-benzoylindole-3-carboxylic Acid (IVk). To a mixture of 2 ml of water and 6 ml of DMSO, containing 0.4 g (10 mmoles) of NaOH, 1.06 g (4 mmoles) of 1-phenacylindole-2,3-dione Ia was added, and the mixture was stirred for 2 h at 20°C. Then, 0.4 g (10 mmoles) of powdered NaOH and 12 ml of DMSO were added, and the stirring was continued for another 1.5 h, after which 1.09 g (4 mmoles) of 1-bromo-2-tetradecyne was added, and the mixture was held for 2 h. An oily residue collected on the bottom of the flask. The reaction mixture was diluted with 200 ml of a 1% aqueous NaOH solution. The aqueous layer was separated, and the oily residue was washed with ether (3 × 50 ml); the ether and aqueous layers were combined and shaken vigorously for several minutes. A brown-colored solution separated as a layer in 20-30 min. It was taken off, dried over Na_2SO_4, and chromatographed on 50 g of silica gel L 160/100μ in a benzene−acetone system (5:1). Recovered 0.85 g of the acid IVk, mp 134-136°C, along with 0.46 g of the acid IIa and 0.08 g of a mixture of the two acids. PMR spectrum of acid IVk (acetone-d_6): 0.91 (2H, t, J = 5.6, CH_3), 1.19-1.30 [18H, m, $(CH_2)_9$], 1.91 (2H, m, $C{=}C-CH_2$), 5.04 (2H, t, J = 2.20, CH_2-N), 7.34-8.21 (9H, m, H_{arom}), 14.37 ppm. (1H, s, COOH). Found, %: C 78.7, H 8.0, N 3.1. $C_{30}H_{35}NO_3$. Calculated, %: C 78.7, H 7.7, N 3.1.

1-(3-Chlorobuten-2-yl)-2-benzoylindole-3-carboxylic Acid (IVj). To 20 ml of a mixture of DMSO and water (9:1) containing 0.4 g (10 mmoles) of NaOH, 1.0 g (4 mmoles) of 1-phenacylindole-2,3-dione Ia was added. Then, 2 h after completion of its recyclization to the acid IIa, 0.96 g (24 mmoles) of NaOH was added; the reaction mixture was chilled to 0-5°C, and 3.78 g (30 mmoles) of freshly distilled 1,3-dichloro-2-butene was added. The darkened reaction mixture was left overnight at +5°C, after which 1.8 g (45 mmoles) of powdered NaOH was added, and the resulting ester of the acid IVj was hydrolyzed for 1 h. Then the solution was diluted with 200 ml of dilute (1:20) HCl; the white precipitate (1.17 g) was purified by reprecipitation by acid from 200 ml of a 1% aqueous NaOH solution and then further purified by crystallization from a mixture of methanol and water (6:4). Obtained 0.7 g of a substance with mp 211-212°C. From the mother liquor, after recrystallization, recovered another 0.19 g of a substance that was identical according to TLC with the substance just described, here with mp 207-211°C. Total yield of acid IVj 0.89 g (66%). Found, %: C 68.2, H 4.5, N 3.8, Cl 9.4. $C_{20}H_{16}ClNO_3$. Calculated, %: C 67.9, H 4.6, N 4.0, Cl 10.0. Mass spectrum: 356(4), 355(16), 354(12), 353(44), 337(8), 336(8), 335(24), 334(16), 301(20), 300(100), 299(16), 298(8), 272(12), 271(8), 247(7), 232(5), 230(7), 105(10), 89(6), 77(10).

Methyl Ester of 2-Benzoylindole-3-carboxylic Acid (VIIa). To 10 ml of a mixture of DMSO (or HMPA) and water (9:1) containing 0.8 g (20 mmoles) of NaOH, 1.33 g (5 mmoles) of 1-phenacylindole-2,3-dione Ia was added; the mixture was held for 3 h at 20°C, after which a stream of CO_2 was passed in until the caustic was neutralized; then 1.42 g (10 mmoles) of CH_3I was added, and the mixture was stirred for 4 h at the same temperature, after which it was poured into 100 ml of water. The aqueous layer was extracted with ether (3 × 100 ml); the combined extracts were washed with water (5 × 100 ml)

until the dissolved DMSO was completely removed, then dried with anhydrous Na_2SO_4. The ether solution was evaporated down to a volume of 30 ml, hexane was added until the solution became cloudy, and the mixture was then held for 24 h at −18°C. Yield of acid VIIa 70%, mp 178-179°C. PMR spectrum ($CDCl_3$): 3.37 (3H, s, CH_3), 7.25-822 (9H, m, H_{arom}), 9.62 ppm (1H, s, N−H). Found, %: C 73.4, H 4.4, N 4.9. $C_{17}H_{13}NO_3$. Calculated, %: C 73.1, H 4.7, N 5.0.

Other esters of the same acid were obtained analogously.

Ethyl ester (VIIb), yield 80%, mp 119-120°C. PMR spectrum ($CDCl_3$): 0.84 (3H, t, J = 7.3, CH_3), 3.89 (2H, d, J = 7.3, CH_2), 7.25-8.14 (9H, m, H_{arom}), 9.78 ppm (1H, s, N−H). Found, %: C 73.9, H 5.0, N 4.4. $C_{18}H_{15}NO_3$. Calculated, %: C 73.7, H 5.2, N 4.8.

n-Propyl ester (VIIc), yield 74%, mp 116-117°C. Found, %: C 73.8, H 5.4, N 4.5. $C_{19}H_{17}NO_3$. Calculated, %: C 74.3, H 5.6, N 4.6.

2-(3-Phenyl-1-oxopropenyl)indole-3-carboxylic Acid (Xa). In 10 ml of water, 0.3 g (7.5 mmoles) of NaOH was dissolved, and 5 ml of DMF and 0.5 g (2.5 mmoles) of 1-(2-oxopropyl)indole-2,3-dione was added. The mixture was held for 1.5 h at 20°C and then chilled to 10°C; to the 2-acetylindole-3-carboxylic acid VIII that was obtained, 0.5 g (12.5 mmoles) of NaOH was added. After the NaOH had dissolved, 1.5 g (14 mmoles) of freshly distilled benzaldehyde IXa was added; the mixture was stirred for 3.5 h, after which the flask was chilled with ice water, and the reaction mixture was acidified with concentrated HCl to pH 1. The precipitate was washed with water (50 ml), benzene (5 ml), and hexane (10 ml). Yield 0.65 g (91%), mp 225°C (decomp.). Found, %: C 74.7, H 4.7, N 4.8. $C_{18}H_{13}NO_3$. Calculated, %: C 74.2, H 4.5, N 4.8.

The acids listed below were obtained analogously.

2-[3-(3-Nitrophenyl)-1-oxopropenyl]indole-3-carboxylic Acid (Xb). Yield 70%, mp 220-226°C (decomp.). Found, %: C 63.8, H 3.6, N 8.1. $C_{18}H_{12}N_2O$. Calculated, %: C 64.3, H 3.6, N 8.3.

2-[3-(2-Furyl)-1-oxopropenyl]indole-3-carboxylic Acid (Xc), in the form of brown crystals. Yield 50%, mp 250-251°C. Mass spectrum: 281(28), 238(15), 237(72), 236(10), 208(12), 187(18), 185(28), 180(26), 170(26), 159(12), 157(12), 149(26), 144(54), 143(44), 129(30), 123(10), 121(15), 117(10), 116(21), 115(38), 114(23), 101(12), 98(15), 97(26), 96(15), 95(26), 94(12), 92(18), 90(23), 80(18), 88(24), 86(28), 85(21), 84(38), 83(21), 82(46), 80(12), 78(18), 77(12), 76(10), 75(24), 74(56), 72(41), 71(26), 70(79), 68(28), 66(31), 64(24), 63(15), 62(26), 61(85), 60(12), 59(13), 58(87), 57(46), 56(46), 55(92), 54(12), 53(15), 51(15), 46(15), 45(100). Found, %: C 66.3, H 3.9, N 4.8. $C_{16}H_{11}NO_4 \cdot 0.5\ H_2O$. Calculated, %: C 66.2, H 4.2, N 4.8.

2-(3-Phenyl-1-oxopropenyl)indole (XIa). In 50 ml of a mixture of DMF and water (1:1) containing 2.5 g of NaOH, 3 g of 2-(3-phenyl-1-oxopropenyl)indole-3-carboxylic acid Xa was dissolved, and the reaction mixture was heated for 3 h at 60-70°C. The solution was chilled to 2-5°C; the precipitate was separated, washed with water to neutral reaction, and dried over P_2O_5. Yield 90%, mp 226-227°C. Found, %: C 82.5, H 5.4, N 5.6. $C_{17}H_{13}NO$. Calculated, %: C 82.6, H 5.3, N 5.7.

2-[3-(3-Nitrophenyl)-1-oxopropenyl]indole (XIb) was obtained analogously. Yield 70%, mp 249-251°C. Found, %: C 69.5, H 4.2, N 9.3. $C_{17}H_{12}N_2O_3$. Calculated, %: C 69.9, H 4.1, N 9.6.

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