and dried. Yield was 4 g (20%) of compound VIII. UV spectrum (in ethanol), λ_{max} (log ε): 214.5 (4.41), 241 (4.46), 319 (4.03), 333 (4.03) nm. ^{1}H NMR spectrum (DMSO-d_6): 5-H 8.24 d; 6-H 7.51 t; 7-H 7.82 t; 8-H 7.7 d; Ph 7.64.

1-Ethyl-2-phenyl-3-nitro-4-oxo-1,4-dihydroquinoline (IX). A mixture of 1 g (0.0038 mole) of 2-phenyl-3-nitro-4-quinoline (VIII), 0.8 g (0.0058 mole) of calcined potash, and 18 ml of DMF was heated with agitation to 80°C, 1.16 g (0.0074 mole) of EtI was then added, the mixture was heated to 100°C for 3 h, 1.16 g (0.0074 mole) of EtI was added, and the mixture was heated at 100°C for a further hour and left overnight at room temperature. The DMF was distilled off under vacuum, the residue was diluted with 50 ml of water and extracted with CH_2Cl_2 (2 × 50 ml), the combined extracts were dried over Na_2SO_4, the solvent was evaporated, the oily residue was ground with isopropanol, and the precipitate was filtered off. Yield was 0.4 g (45%) of compound IX. UV spectrum (in ethanol), λ_{max} (log ε): 214 (4.47), 232 (4.48), 320 (4.13), 330 (4.13) nm. ^{1}H NMR spectrum (DMSO-d_6): 5-H 8.38 d; 6-H 7.63 t; 7-H 8.02 t; 8-H 8.01; Ph 7.62; Et: CH_2 4.08, CH_3 1.21.

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SYNTHESIS OF 3-ACYL-5-HYDROXYINDOLES AND 3-ACYL-5-HYDROXYBENZOFURANS. INFLUENCE OF SOLVENT ON THE COURSE OF THE NENITZESCU REACTION

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The Nenitzescu reaction, which is the interaction of quinones with enamines, is the most general method for the synthesis of 5-hydroxyindoles. In a number of cases, 5-hydroxybenzofurans are also formed, and depending upon the selected objectives and conditions of the process, one or the other direction of the reaction prevails [14].

The Nenitzescu reaction possesses unquestionable interest for the synthesis of compounds possessing high biological activity [1, 10]. In connection with this, an understanding of the mechanism of the reaction taking place upon interaction of quinones with different enamines, and an exploration of the possibility of the directed synthesis of both 5-hydrobenzofuran and 5-hydroxyindole derivatives in the synthetic and theoretical ratios is a timely challenge. One of the prospective directions is a study of the interaction of benzoquinone with enaminoketones, resulting in the preparation of derivatives of 5-hydroxy-3-acyl indole and -benzofuran.

The literature gives a series of examples of the application of enaminoketones, prepared by the reaction of acetylacetone with ammonia and aliphatic and aromatic amines, in this

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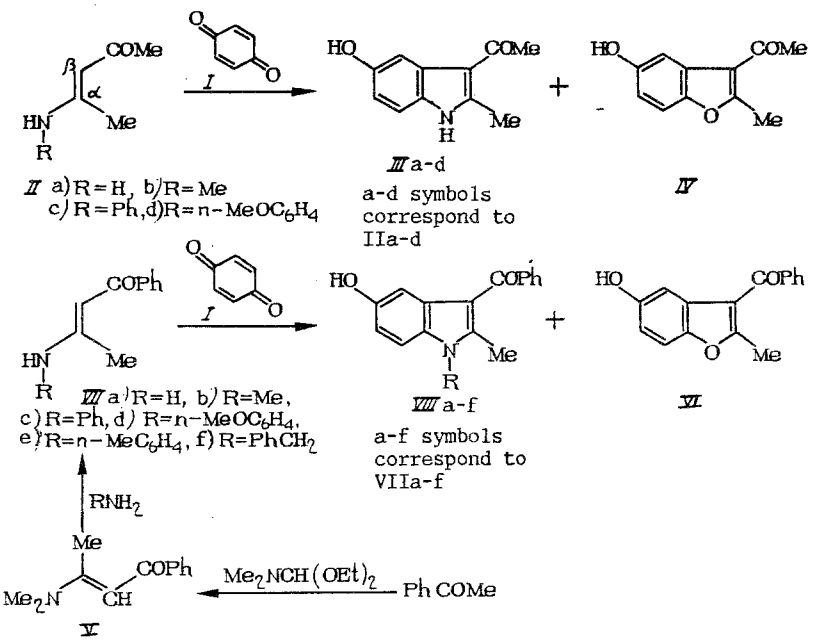
reaction. Thus the reaction of benzoquinone (I) with 1-acetyl-2-amino-1-propene (IIa) leads to a mixture of 2-methyl-3-acetyl-5-hydroxyindole (III, R = H) (IIIa) and -benzofuran (IV) [5], but the use of the N-methyl (IIb) and N-ethyl derivatives of enaminoketone IIa gave only the benzofuran IV [3]. Conversely, treatment of quinone I with the corresponding N-aryl analogs (IIc and IId) gave only the corresponding N-arylindoles (III, R = Ar)(IIIc and IIId) [4, 6].



Taking into account the relatively low yields of the Nenitzescu reaction, it is impossible to claim with confidence that the condensations of I with IIa-d take place unequivocally and that all the formed reaction products were isolated. However, in the indicated work, for this as well as other Nenitzescu reactions studied, the causes of the prevalence of or the other direction (indole or benzofuran cyclization) were not specifically examined.

Significantly less effort was dedicated to a study of the condensation of quinone I with enaminoketones having a benzoyl group in the β-position, probably as a result of the significantly lower accessibility of these enaminoketones.

Recently we showed that the tertiary enaminoketone 1-benzoyl-2-dimethylaminopropene (V) undergoes the Nenitzescu reaction with the formation of 2-methyl-3-benzoyl-5-hydroxybenzofuran (VI) [11]. It is known also that derivatives of 3-benzoyl-5-hydroxyindole are formed by condensation of quinone I with 2-benzoyl-1-R-aminostyrene [24] or 1-benzoyl-2,2-diaminoethylene [13], in the first case in yields of 7-30%, and in the second case the indole is accompanied by a benzofuran derivative. However consideration of the reason for the direction of the heterocyclization is absent from these works.

Tha aim of the present work is a study of the transformation of enaminoketones having acetyl (IIa-d) or benzoyl (VIIa-d) groups in the β-position under the conditions of the Nenitzescu reaction, while the basic emphasis is focused on the influence of solvent character on the course of the heterocyclization process.

The syntheses of the starting compounds IIa-d were carried out according to known methods [18-20]. For the preparation of β-benzoylenamines VIIIa-f, a transmination reaction was used.

The Nenitzescu reaction of benzoquinone I and enaminoketones II and VII was carried out under the usual conditions in different solvents, and the reaction mixture was analyzed by TLC, the crystalline products were separated by filtration, the mother liquor was concentrated, and the mixture thus obtained was studied by mass- and ^{1}H NMR spectroscopy; the latter was the primary instrumental method*, which allowed the accurate identification of

*Mass-spectra were used for determination of the molecular mass of the reaction products by analysis of the mixtures obtained after concentration of the mother liquor. Judging by this data, the mixtures contained indole and benzofuran derivatives, quinone and hydroquinone adducts, enamines, and substituted acetanilides.

TABLE 1. Significant Chemical Shifts (in ppm) in the ^1H NMR Spectra of Compounds IIIa-d, IV, VI, and VIIIb-d in DMSO-d_6

Compound	4-H	5-OH	6-H	7-H	2-CH_3	3-$COCH_3$ 3-COPh	1-CH_3 1-C_6H_5 1-$C_6H_4OCH_3$
IIIa	7,42* d	8,90 bs	6,61 qd	7,14 d	2,44 s	2,62 s	7,44 (1-NH)
IIIb	7,36**	8,98	6,68	7,30	2,48	2,67	3,66
IIIc		9,06	6,63	6,76	2,49	2,55	7,40—7,60
IIId	7,49	9,08	6,60	6,74	2,40	2,54	3,86 Center A_2B_2 7,26
IV	7,37	9,33	6,74	7,36	2,55	2,73	—
VI	6,80	9,27	6,75	7,39	2,40	7,52—7,78	—
VIIIb	6,74	8,87	6,67	7,32	2,37	7,50—7,62	3,68
VIIIc	6,90	8,98	6,64	6,84	2,20	7,34	7,74
VIIId	6,86	8,98	6,62	6,79	2,15	7,53—7,72	3,86 Center A_2B_2 7,29

*d = doublet, bs = broad singlet, qd = quadruplet, s = singlet. Splitting of the proton signals in positions 4, 6, and 7 in compounds IIIa-IIId, IV, VI, and VIIIb-d were analogous: $J_{4,6}$ = 3 Hz, $J_{6,7}$ = 9 Hz.
**Proton signals overlapped the PR signals.

TABLE 2. Mass Spectra by Electron Impact of the Synthesized Compounds

Compound	m/z(I_{rel}, %)
IIIb	203 (42) $[M]^+$; 189 (12); 188 (100); 131 (15); 130 (11); 117 (17); 115 (14); 94 (16); 77 (10)
VIId	267 (35) $[M]^+$; 268 (9); 162 (8); 147 (10); 108 (6); 105 (65); 91 (6); 77 (100)
VIIe	251 (23) $[M]^+$; 174 (100); 146 (23); 131 (60); 130 (37); 115 (18); 105 (12); 91 (29); 77 (89)
VIIIb	265 (76) $[M]^+$; 264 (100); 188 (65); 160 (5); 117 (9); 115 (8); 105 (7); 77 (9)
VIIIc	327 (92) $[M]^+$; 326 (100); 310 (7); 250 (76); 222 (8); 220 (17); 162 (10); 105 (16); 77 (18)
VIIId	357 (100) $[M]^+$; 356 (21); 280 (97); 250 (28); 248 (66); 220 (28); 209 (40); 208 (53); 192 (17); 180 (19); 169 (31); 154 (21); 153 (13); 148 (15); 77 (62)
VIIIe	341 (25) $[M]^+$; 340 (15); 264 (30); 222 (22); 221 (54); 193 (22); 171 (35); 105 (100); 91 (7); 77 (30)
VIIIf	341 (20) $[M]^+$; 340 (19); 250 (4); 220 (4); 105 (32); 91 (100); 77 (7)

TABLE 3. Influence of Solvent on the Nenitzescu Reaction of I with II and VII

Starting enamine	Solvent	Content of indole and benzofuran derivaties (^1H NMR)		Isolated product, yield, %
		crude product mixture	mother liquor*	
IIa	CH_3COOH	IV (~3 % III)	—	IV, 58
	CH_3NO_2	IIIa (very little IV)**	—	IIIa, 53
IIb	CH_3COOH	IV (~3 % III)	—	IV, 53
	CH_3NO_2	IIIb (~2 % IV)	IIIb:IV~1:1	IIIb, 30
IIc	CH_3COOH	IV	IIIc:IV~2:3	IV, 62
	CH_3NO_2	IIIc	IIIc:IV~1:4 (I and IIc present)	IIIc, 49
	Dichloroethane (DCE)	IIIc	IIIc:IV≈1:1 (contains I and IIc)	IIIc, 42
IId	CH_3COOH	IV (~5 % III)	IV:IIId (2:3)	IV, 70
	CH_3NO_2	IIId	IV	IIId, 40
	DCE	IIId (~20 % IV)	—	IIId, 38
VIIa	CH_3COOH	VI (~4 % VIII)	—	VI, 28
	CH_3NO_2	VIIIa (~10 % VI)	—,	VIIIa 31***
VIIb	CH_3COOH	VI (~2 % VIII)		VI, 43
	CH_3NO_2	VIIIb	VI:VIIIb=4:1	VIIIb, 15
VIIc	CH_3COOH	VI	$PhNHCOCH_3$	VI, 71
	CH_3NO_2	VIIIc	—	VIIIc, 18
	DCE	VIIIc	—	VIIIc, 12
VII	CH_3COOH	VI (~2 % VIIId)	VIId, I, VI:VIIId = 1:1	VI, 71
	CH_3NO_2	VIId:VIIId=1:1	—	VIIId, 27
	DCE	VIId, VIIId	VI absent, some VIId	VIIId, 8
	Acetone	VIId, much tarring	—	VIId, 50
	Ethanol	VIId, much tarring	—	VIId, 30
	CH_3COOH	VI	—	VI, 64
VIIe	CH_3COOH	VI	—	VI, 64
	CH_3NO_2	VIIIe	—	VIIId 5
VIIf	CH_3COOH	VI>VIIIf	—	VI, 1
	CH_3NO_2	VIIIf>VI	—	VIIIf, 9

*The spectra showed the signals of other products: benzoquinone, hydroquinone, in some cases (CH_3COOH) acetanilide, hydroquinone- and quinone adducts, starting enamines, other unidentified components.
**Also contains hydroquinone adduct (X, R = H, R' = Me).
***Yield is a mixture of VIIIa and VI.

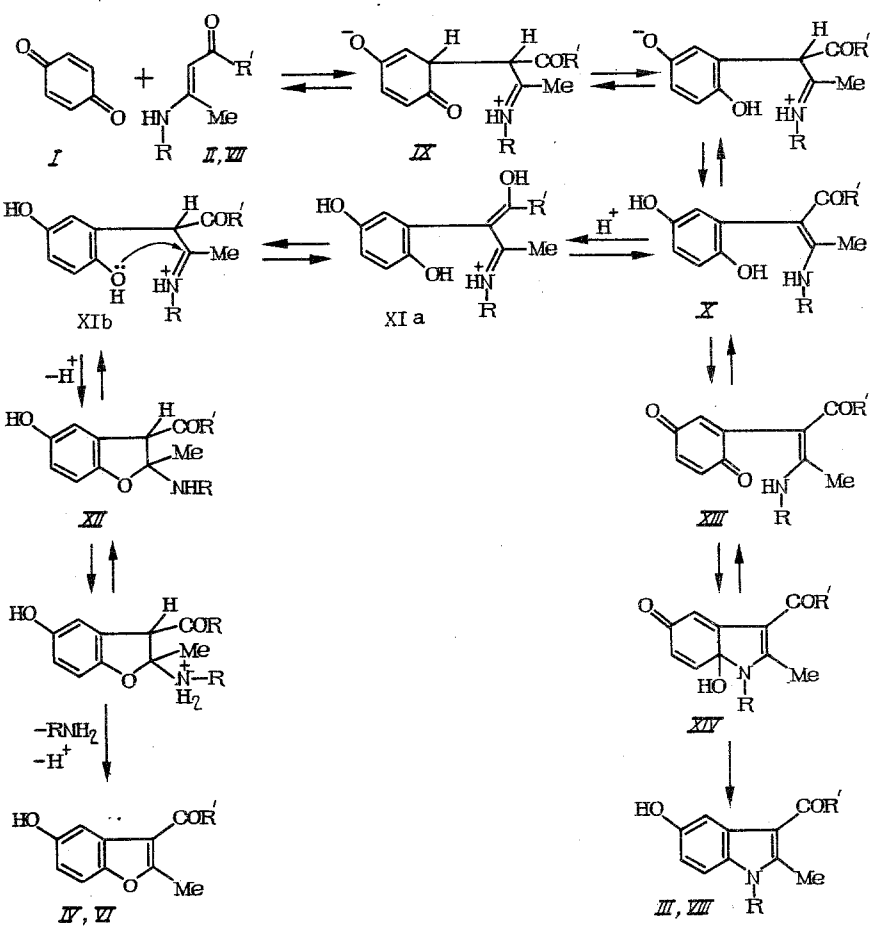
indole and benzofuran derivatives and the evaluation of their ratios. Analysis was carried out by the signals of the 2-CH_2 groups, which for the benzofurans was found at the lower field. The ^1H NMR spectral data for the subject compounds are included in Table 1, and the results of the mass spectral studies are given in Table 2.

The results obtained are presented in Table 3. As seen from these data, the ratio of heterocyclization products is determined to a significant extent by the use of solvents, among which were selected acetic acid, dichloroethane, acetone, ethanol, and also nitromethane, since the literature notes that the use of this solvent seems to result in diminished tar formation (in general a characteristic of the Nenitzescu reaction) and in some cases to an increased yield of 5-hydroxyindoles [23].*

The results (Table 3) indicate that the use of acetic acid as solvent directs the process towards the formation of 5-hydroxybenzofuran derivatives and that the use of dichloroethane and particularly nitromethane forms chiefly (and in some instances only) 5-hydroxyindole derivatives.

In order to interpret the data it follows that the general scheme for closing the indole or benzofuran ring in the course of the Nenitzescu reaction [21] should be examined along with the possibility of the participation of solvent in one or another stage of the process.

It should be noted that the spectral data obtained in the present work clearly indicate that the indole compounds formed are derivatives of 5-hydroxyindole (Table 1) and that the possible alternate mechanism involving the formation of the corresponding 6-hydroxyindoles by interaction of quinone I with enaminoketones is not realized,† and therefore the following scheme is concerned only with the possible route to the synthesis of derivatives of 5-hydryoxyindole and 5-hydroxybenzofuran.



*The possibility of 5-hydroxybenzofuran formation was not considered in this publication [23].

†In particular, the structure of 1,2-dimethyl-3-acetyl-5-hydroxyindole (IIIb) was rigorously proven by the use of the homonuclear Overhauser Effect; upon saturation of the N-methyl group signal at 3.66 ppm, the intensity of the signal δ 7.30 (d, J ≈ 9 Hz) increased by 18%, which clearly indicates the structure of this compound to be the 5-hydroxy derivative.

TABLE 4. Characteristics of the Synthesized Compounds

Empirical formula	Yield, %	mp, °C	Empirical formula
IIIb	30,3	245—7	$C_{12}H_{13}NO_2$
VIId	91,2	107—8	$C_{17}H_{17}NO_2$
VIIe	69,8	92—3	$C_{17}H_{17}NO$
VIIIb	14,7	272—5	$C_{17}H_{15}NO_2$
VIIIc	18,3	278—80	$C_{22}H_{17}NO_2$
VIIId	26,6	235—8	$C_{23}H_{19}NO_3$
VIIIe	5,3	242—4	$C_{23}H_{19}NO_2$
VIIIf	8,8	217—19	$C_{23}H_{19}NO_2$

*IIIb from CH_3OH; VIId and VIIe from iso-PrOH; VIIIb-f from CH_3COOH.

The first stage of the process is the Michael addition of the enaminoketone to the quinone with the formation of the zwitter-ionic intermediate IX, which is transformed through a series of proton shifts into the hydroquinone adduct X. In acidic medium such as acetic acid, this adduct is subject to rapid O-protonation (which is highly characteristic of enaminoketones [12]), whereupon the O-protonated form XIa equilibrates with the C-protonated XIb. The latter quite rapidly enters into reaction with nucleophilic reagents [2, 7] and probably is an immonium cation subject to the dominant benzofuran cyclization XIb → XII, although it is impossible to rule out certain contributions of the cyclization XIa → XII. It is entirely evident that the rate of the formation of the benzofuran is determined by the possibility of protonation related to the presence in the reaction mixture of an acidic agent (CH_3COOH) which accelerates the step of aromatization of the intermediates XII → IV and VI by means of protonation of the exocyclic amino group. On the other hand, the indole cyclization, involving the oxidation of the hydroquinone adduct X into the quinone adduct XIII, ought to be slowed down in acidic medium, since upon protonation of X the system becomes negatively charged, and the transfer of electrons to oxygen (for example to quinone I) is impeded. All the indicated factors act upon one side, which determines the prevalence of benzofuran over indole cyclization upon conducting the reaction in acetic acid.

In dichloroethane the situation is changed; the single and extremely weak protonating agent in this case is the hydroquinone adduct X. Accordingly, the rate of formation of 5-hydroxybenzofurans IV and VI is lowered, while the exchange of electrons from adduct X to the quinone I is accelerated in comparison with the reaction in CH_3COOH (the enamine fragment in the nonprotonated form is an electron donor). However, dichloroethane also is not an optimal solvent for carrying out the Nenitzescu indole synthesis. Actually, the oxidation of the hydroquinone adduct X to the quinone adduct XIII proceeds through the stage of formation of a cation-radical (for data on the quinone-hydroquinone pair, see [8]), and the stabilization of the latter by solvation may accelerate the process of oxidation of X → XIII. In so far as the oxidizing agent in the given case is the starting benzoquinone I, which itself is transformed into an anion-radical, protonation of the latter by weak acid (with minimization of protonation of the starting enaminoketone X) also ought to lead to an accelerated stage of oxidation. These conditions also are accomplished upon by the use the weakly acidic (pK_a 10.6 [15, 25]) nitromethane as solvent which is capable of solvating cations because of the presence of the nitro group. Thus, the use of nitromethane as solvent gives the possibility of avoiding protonation of the starting enaminoketones II and VIII and the hydroquinone adduct X and thereby checking the process of benzofuran cyclization, and on the other side, stabilizing materials originating from oxidation of the cation and anion intermediates and accelerating indole synthesis. The latter, of course, pertains to both to the X → XIII stage and a further oxidation-reduction process; the carbinol-amine XIV → indoles III and VIII. As a whole, the considerations presented above agree well with the experimentally-obtained data (Table 3) and therefore form the basis for a directed synthesis of 5-hydroxyindoles and 5-hydrobenzofurans by using nitromethane or acetic acid, respectively, for solvents in the Nenitzescu reaction.

The experimental data presented in Table 3 do not permit the fabrication of an unambiguous rule defining the influence of substituents in positions 1 and 3 of the enamine on the direction of the Nenitzescu reaction. In some cases, however, a review can determine definite tendencies. Thus, comparing the results of the reaction of I with IId and VIId in dichloroethane, it can be said that in the second case the benzofuran derivative is generally not formed, but IId gives a mixture with an indole IIId; benzofuran IV ratio of 80:20. Analogously, comparing the reaction of VIIa, b and d with quinone I in nitromethane shows that in the first and second cases the benzofuran VI is formed in appreciable quantities, but with VIId the reaction mixture did not contain VI. The indicated comparisons are similar in one way: upon passing from IId to VIId the volume of the substituent in position 3 of the enamine increases, and from VIIa and VIIb to VIId, the substituent volume in position 1 increases. Earlier we expressed the hypothesis that the structure of the intermediate XII plays an important role in the realization of the benzofuran synthesis as a result of the significant nonbonded interactions of substituents of the nonaromatic five-membered ring [9]. In so far as this interaction, apparently, grows upon transition from acetyl to benzoyl and from NH_2 and NHMe to the $NHC_6H_4OCH_3$-n groups, this is a possible cause for the decrease in the amount of benzofuran under the conditions examined.*

EXPERIMENTAL

The mass spectra were obtained on a Varian MAT-112 (70 eV) instrument with direct introduction of the sample into the ion chamber. The ^1H NMR spectra were determined with a Varian XL-200 spectrometer, using TMS as internal standard. Elemental analysis data agreed with the calculated values. The purity of the materials obtained was monitored by chromatography on Silufol UV-254 plates in the system benzoacetone = 9:1. Visualization was by UV light.

1-Acetyl-2-amino-1-propene (IIa), 1-acetyl-2-(N-methylamino)-1-propene (IIb), 1-acetyl-2-(N-phenylamino)-1-propene (IIc), and 1-acetyl-2-[N-(p-methoxyphenyl)-amino]-1-propene (IId) were obtained by earlier-described methods [18-20], and 1-benzoyl-2-dimethylamino-1-propene (V) by the method of [22].

The characteristics of the synthesized compounds are described in Tables 1, 2, and 4.

1-Benzoyl-2-amino-1-propene (VIIa). A mixture of 18.9 g (100 mmoles) of enamine V in 200 ml of CH_3OH, 20 ml of alcoholic solution containing 3.75% ammonia, and 17.2 g 100 mmoles) of p-toluenesulfonic acid was stirred for 5 h at room temperature. The reaction mixture was filtered and the solvent was evaporated. The residue was recrystallized from pentane to give 13.7 g of VIIa, mp 141-143°C (Lit. [16] mp 143°C).

Compound VIIb was prepared analogously (Lit. [17] mp. 74-75°C).

1-Benzoyl-2-(N-phenylamino)-1-propene (VIIc). To 18.9 g (100 mmoles) of enamine V in 150 ml of DMF was added 11 ml (120 mmoles) of aniline. The reaction mixture was boiled for 4-5 h until the disappearance of starting V. The reaction was monitored chromatographically on Silufol plates in benzene:acetone 9:1. The solvent was distilled and to the residue was added a small amount of iso-PrOH. The precipitate was filtered off and dried to give 20.5 g of VIIc, mp 110°C (Lit. [16] mp. 110°C).

Use of enamine V with benzylamine, p-anisidine, and p-toluidine in an analogous reaction gave the enamines VIId-f, respectively.

2-Methyl-3-acyl-5-hydroxybenzofurans IV and VI. To 10 mmoles of enamine IIa-d or VIIa in 10 ml of glacial acetic acid was added with stirring 0.01 mole of p-benzoquinone in 5 ml of glacial acetic acid at room temperature. The reaction mixture was kept overnight, the resulting crystals were filtered off, washed on the filter with 50% CH_3COOH, and dried to give IV and VI, the yields of which are given in Table 3.

1-Alkyl(aryl)-2-methyl-3-acyl-5-hydroxyindoles IIIb-d and VIII-f, a). To 10 mmoles of enamines IIc-d or VIIc-f in 10 ml of CH_3NO_2 was added 10 mmoles of p-benzoquinone in 5 ml of CH_3NO_2. After boiling for 3 h, an additional 5 mmoles of p-benzoquinone was added

*It is understood that in order to obtain accurate data supporting (or disproving) the proposal, it is necessary for special studies, since substituents in the enamine ought to be selected in such a way as to exclude complications by the effects of intramolecular H-bonds in the intermediates XII.

and boiling was continued for 3 h more. The reaction mixture was cooled in ice, the resulting crystals were filtered off, and washed on the filter with small amounts of CH_3COOH and ether.

In the cases of enamines IIa, IIb, VIIa, and VIIb, the reaction mixtures were stirred at 50-60°C for 1 h.

b). All reactions of enamines with p-benzoquinone in dichloroethane, acetone, and ethanol were carried out by methods described earlier [4, 6].

The yields and physicochemical characteristics of indoles VIIIb-f are presented in Tables 1, 2, and 4.

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