LACTAM AND ACID AMIDE ACETALS.

71.* NEW SYNTHESIS OF 3-NITRO-6-HYDROXYINDOLE DERIVATIVES

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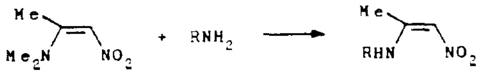
Previously unknown 3-nitro-6-hydroxyindole derivatives were synthesized by condensation of p-benzoquinone with secondary β-nitro enamines.

We have previously [2] developed a new method for the synthesis of 3-nitro-5-hydroxybenzofurans based on the reaction of p-benzoquinone with tertiary nitro enamines, viz., 1-nitro-2-dimethylaminoethylene and 1-nitro-2-dimethylaminopropylene, under the conditions of the Nenitzescu reaction. The presence of dimethylamino groups in the β position of these enamines excluded the possibility of an alternative pathway to give indole structures. Because of this, it seems of interest to study the condensation of benzoquinone with nitro enamines having, in the β position, a primary or secondary amino group with substituents of different character attached to the nitrogen atom. To synthesize enamines of this type in the present research we studied the transamination of 1-nitro-2-dimethylaminopropylene (I) with ammonia, methyl- and benzylamine, and substituted anilines. We found that the best conditions for obtaining enamines IIa, b are transamination of enamine I at room temperature in ether or chloroform, while the best conditions for obtaining enamine IIc are transamination in 2-propanol. The transamination by arylamines proceeds best in DMF in the presence of an equimolar amount of p-toluenesulfonic acid.

Thus the transamination of enamine I is a convenient preparative method for the synthesis of β-amino, β-alkyl(aralkyl)amino, and β-arylamino nitro enamines IIa-g. As a rule, IIa-d were previously synthesized in extremely low yields by a less convenient synthetic method,† viz., by the reaction of nitroacetone with amines in the presence of titanium tetrachloride [3].



I   II a-g

II a R=H, b R=Me, c R=CH_2Ph, d R=Ph, e R=$C_6H_4CH_3$-*p*, f *R*=$C_6H_4OCH_3$-*p* g R=C_6H_4Cl-*p*

The PMR spectra of starting enamines IIa, c, f, g contain singlet signals of protons of methyl groups (1.96-2.03 ppm) and CH groups (6.50-6.66 ppm). Signals of protons the NH groups in secondary enamines IIc, f, g are observed at 10.75-11.49 ppm, while in the case of primary enamine IIa there are two singlet signals at 9.22 and 7.92 ppm. This constitutes evidence for the existence of the hindered rotation about the C—N single bond that is quite often observed for various enamine systems. The signals of the protons of the benzene ring in IIc, f, g are observed in the form of multiplets centered at 6.99-7.34 ppm. The PMR spectrum of IIc also contains a singlet signal of the protons of the methylene group of a benzyl substituent (4.63 ppm).

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*See [1] for Communication 70.

†It is evident that the use of enamine I, which is readily formed in the reaction of nitromethane with dimethylacetamide diethylacetal [4], is preparatively more convenient than the use of the less accessible nitroacetone.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C*	Yield, %	Compound	Empirical formula	mp, C*	Yield, %
IIa	$C_3H_6N_2O_2$	100...101 (98...99 [3])	64	IVc	$C_{16}H_{14}N_2O_3$	265...268 (dec.)	16
IIb	$C_4H_8N_2O_2$	59...60 (65...66 [3])	81	IVd	$C_{15}H_{12}N_2O_3$	275...276 (dec.)	38
IIc	$C_{10}H_{12}N_2O_2$	83 (86...87 [3])	92	IVe	$C_{16}H_{14}N_2O_3$	271...272 (dec.)	39
IId	$C_9H_{10}N_2O_2$	87 (86...87 [3])	96	IVf	$C_{16}H_{14}N_2O_4$	265...266 (dec.)	52
IIe	$C_{10}H_{12}N_2O_2$	93	92	IVg	$C_{15}H_{11}ClN_2O_3$	285...287	36
IIf	$C_{10}H_{12}N_2O_3$	85...87	75	Va	$C_{18}H_{16}N_2O_4$	99	97
IIg	$C_9H_9ClN_2O_2$	95	59	Vb	$C_{18}H_{16}N_2O_5$	247...248	99
III	$C_9H_7NO_4$	191..192 (191...193 [2])	67	VI	$C_{21}H_{21}N_3O_5$	189...191	76
IVb	$C_{10}H_{10}N_2O_3$	256...258 (dec.)	7	VII	$C_{20}H_{20}N_2O_3$	199...200	93

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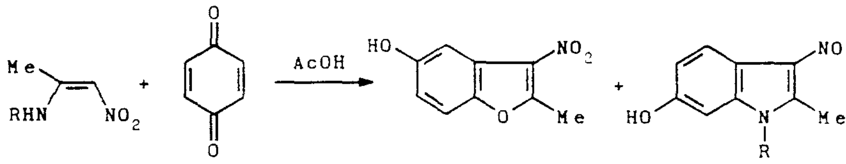
*The compounds were recrystallized: IIa-g from 2-propanol, IVb from dioxane—petroleum ether (2:1), IVc from dioxane, IVd, e, g and Va from alcohol, IVf and Vb from acetic acid, VI from ethyl acetate, and VII from benzene.

Nitro enamines IIa-g were subjected to reaction with p-quinone under the conditions that we developed for the synthesis of nitrobenzofurans [2], viz., in acetic acid in the presence of acetic anhydride. Since only one study of the reaction of quinones with enamines with a nitro group in the β position is known (the authors of this study carried out the Nenitzescu reaction with substituted β,β-diamino- or β-amino-β-methylmercaptonitroethylenes, and, consequently, the indole and benzofuran derivatives they obtained have methylmercapto or R-amino groups in the 2 position [5]), it seemed necessary to make a detailed study of the structures of the synthesized compounds. In fact, although the usual pathway of the Nenitzescu reaction involves the production of 5-hydroxyindoles [6], the production of 6-hydroxy derivatives is also known [7, 8]; this anomalous course of the reaction is observed when one uses N-aryl enamines as the starting compounds in acetic or propionic acid.

According to the data in [8], in a number of cases not only does indole cyclization occur, but benzofuran cyclization also takes place in the reaction of quinones with primary and secondary enamines; the reasons for one or another reaction pathway have not yet been discussed in detail. As a consequence of this, the results of the reaction of p-quinone and enamines IIa-g are useful not only in a synthetic respect but also for a deeper understanding of the complex processes that are characteristic for the Nenitzescu reaction.

In fact, the condensation of benzoquinone with primary amine IIa leads exclusively to the formation of the previously [2] synthesized 2-methyl-3-nitro-5-hydroxybenzofuran (III) in 57% yield; indole IVa is not formed in this case. Two compounds, viz., benzofuran III (in 67% yield) and indole derivative IVb (in 7% yield), were isolated in a similar reaction with the participation of N-methyleneamine IIc. The PMR spectrum of IVb in $CDCl_3$ contains singlet signals of 1-CH_3 and 2-CH_3 groups at 2.83 and 3.68 ppm, respectively, a doublet at 6.80 ppm (1H, J = ≈2 Hz), a quartet at 6.90 ppm (1H, J_1 = ≈2 Hz, J_2 = ≈9 Hz), and a doublet at 8.0 ppm (1H, J = ≈9 Hz). A 12% increase in the intensity of the signal at 6.80 ppm due to the nuclear Overhauser effect is observed when the signal of the 1-CH_3 group is saturated. Since this signal can be ascribed only to a 7-H indole proton (only this proton is spatially close to the N-methyl group), the data obtained demonstrate unequivocally that 1,2-dimethyl-3-nitro-6-hydroxyindole (IVb) is formed in this case, i.e., the reaction for indole IVc, synthesized from N-benzylideneamine IIc. In this case the benzofuran:indole ratio is shifted to favor an increase in the amount of the latter (the yields of the isolated III and IVc are ≈50% and 16%, respectively), although benzofuran cyclization still prevails.

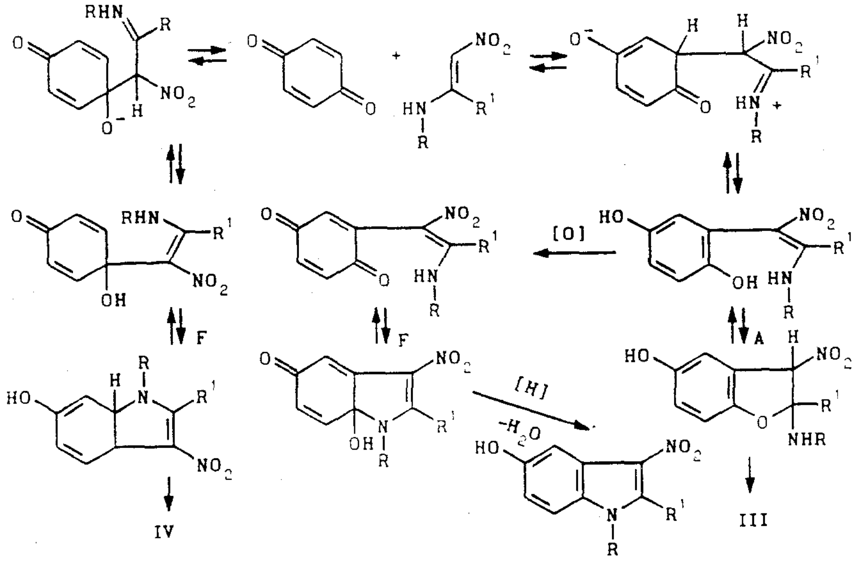
A further increase in the indole:benzofuran ratio to favor 3-nitro-6-hydroxyindole compounds IV is observed when N-aryl enamines IIId-g are used. Despite the fact that the yields of the isolated indoles IVd-g are not too high (36-52%), a chromatographic study of the reaction mixtures shows that the relative amounts of indoles in these cases are relatively greater than when N-alkyl enamines IIb, c are used, although the presence of benzofuran III is also detected in all cases. For more precise information regarding the compositions of the reaction mixtures obtained in the reaction of the quinone with enamines IIa-c, f we investigated the PMR spectra of solutions in CD_3COOD. It was found that an N-unsubstituted indole actually is not formed in the reaction of primary enamine IIa with the quinone; the presence of benzofuran III is detected from signals of 4- and 7-H protons (7.44 and 7.34 ppm) and a $2\text{-}CH_3$ group (2.86 ppm). When enamines IIb, c, f are used, the indole:benzofuran ratio increases on passing from the N-methyl to the N-benzyl and then to the N-p-methoxyphenyl enamine and is, respectively, 0.07:1 (for IIb) and 0.32:0.68 (for IIf), i.e., the results obtained on the basis of the yields of the isolated reaction products were confirmed. The formation of indoles IVb, c, f was detected from the presence of a signal of a 4-H proton (7.92-8.04 ppm) in the PMR spectrum.



IIa-g IV a-g

IVa R=H, b R=Me, c $R=PhCH_2$, d R=Ph, e $R=p\text{-}MeC_6H_4$, f $R=p\text{-}MeOC_6H_4$, g $R=p\text{-}ClC_6H_4$

The data obtained make it possible to draw several preliminary conclusions regarding the principles of the occurrence of the processes observed during the Nenitzescu reaction. Starting from the usual concepts [6] of the condensation of quinones and enamines, the principal scheme of the reactions can be represented in the form



In other words, the first step in the reaction is addition of the β-carbon atom of the enamine to the 2 position of the quinone, as a result of which benzofurans and (or) 5-hydroxyindoles are formed, or addition of this position of the enamines directly to the carbonyl group of the quinone, which leads to 6-hydroxyindole derivatives; the alternative possibility of the synthesis of 6-hydroxyindoles via the initial addition of the NH-enamine fragment to the 2 position of the quinone can be rejected on the basis of recent studies [9, 10].

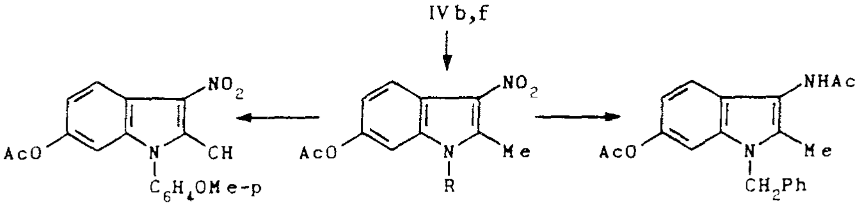
Both of these pathways are realized in the reactions of nitro enamines with the quinone investigated in the present research. A peculiarity consists in the fact that the first pathway leads only to benzofuran derivative III, while 5-hydroxyindoles are not formed at all. Regardless of which process (the formation of 5- or 6-hydroxyindoles) proceeds simultaneously with the benzofuran synthesis in accordance with the scheme presented above, the rate of formation of benzofuran III should depend substantially on the volume of the substituents in the 1, 2, and 3 positions of the starting enamines.

In fact, if one assumes that precisely equilibrium A includes a step that determines the rate of formation of benzofuran III, the development of two sp^3-hybridized atoms in the five-membered dihydrofuran ring determines the existence of nonbonding interactions between the substituents in the ring 2 and 3 positions [11]. These interactions are more significant, the more bulky the substituent attached to the enamine nitrogen atom (with the same substituent in the 3 position — a nitro group in our case), which leads to a decrease in the rate of benzofuran cyclization. In conformity with this, on passing from the unsubstituted nitro enamine to the N-substituted analogs the yields of benzofurans decrease, as was shown above. It might be assumed that this conclusion is not limited to this special case and that steric characteristics are a substantial factor that determines the direction (to give indoles or benzofurans) in which the Nenitzescu reaction may primarily proceed.

It is substantially more difficult to establish the reasons for the formation of 6-hydroxyindoles rather than 5-hydroxyindoles in this case. The experimental data obtained in the present research do not provide an answer to this question. However, in our opinion, attention should be directed to a number of considerations that are essential for an understanding of the general problems associated with the Nenitzescu indole synthesis. First, the process takes place in acetic acid [7, 8, 12], and the active particle is possibly the O-protonated quinone, which significantly levels out the differences in the rates of addition of the enamine to the 2 or 1 position that are associated with the lower steric accessibility of the latter. Second, the oxidation step necessary for obtaining 5-hydroxyindoles is slowed down markedly because of the presence of a nitro group, while a step involving oxidation is absent in the production of 6-hydroxyindoles. Finally, the powerful joint electron-acceptor effect of the nitro group and the quinonyl substituent also hinders step B, while this is less important for step F because of the absence of a second (in addition to a nitro group) β substituent having a negative mesomeric effect. Of course, the further accumulation of data on the effect of various factors on the composition and ratio of products formed in the reaction of enamines and quinones under the conditions of the Nenitzescu reaction is required for more definite conclusions.

Within the framework of this research we have also demonstrated the possibility of obtaining a number of other derivatives on the basis of the synthesized indoles IVc, f. Thus the acylation of nitro indoles IVc, f leads to the corresponding 5-O-acetyl derivatives Va, b. The reaction of indole Vb with DMF acetal takes place at the 2-CH_3 group, activated by the adjacent 3-nitro group, to give indolyl enamine VI. In the case of indole Va we established the fundamental possibility of reducing the nitro group with zinc in acetic acid. As a result, 3-acetylaminoindole derivative VII was obtained in high yield.

The PMR spectra of indoles IVc, e are presented in the experimental section.



VI

Va,b

Va R=CH_2Ph, b R=C_6H_4OMe-p

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were obtained with a Varian XL-200 spectrometer with tetramethylsilane (TMS) as the internal standard. Monitoring of the progress of the reactions and the individuality of the substances was accomplished by chromatography on Silufol UV-254 plates in a benzene—methanol (9:1) system with development in UV light.

The results of elementary analysis were in agreement with the calculated values.

The characteristics and yields of the compounds are presented in Table 1.

1-Nitro-2-amino-1-propene (IIa). A 50-ml sample of a saturated alcohol solution of ammonia was added with stirring at 20°C to a solution of 5.2 g (40 mmole) of I in 75 ml of chloroform, after which the mixture was allowed to stand for 30 min at the same temperature and then evaporated to dryness. The residue was recrystallized from isopropyl alcohol to give 2.6 g of IIa.

Compounds IIb, c. These compounds were similarly obtained In obtaining IIc starting enamine I was dissolved in isopropyl alcohol.

1-Nitro-2-phenylamino-1-propene (IId). A 17.2-g (100 mmole) sample of p-toluenesulfonic acid and 27.9 g (300 mmole) of aniline were added with stirring at 20°C to a solution of 13.0 g (100 mmole) of I in 5 ml of DMF, after which the reaction mixture was stirred at the same temperature for 2 h and then diluted with 700 ml of water. The resulting precipitate was removed by filtration, washed with water, and dried to give 17.0 g of IId.

Compounds IIe-*l*. These compounds were similarly obtained.

1,2-Dimethyl-3-nitro-6-hydroxyindole (IVb) and 2-Methyl-3-nitro-5-hydroxybenzofuran (III). A 1.74-g (15 mmole) sample of enamine IIb was added with stirring at 20°C to a solution of 1.08 g (10 mmole) of p-benzoquinone in a mixture of 20 ml of acetic acid and 2.0 ml of acetic anhydride, after which the reaction mixture was allowed to stand at the same temperature for 36 h and then diluted with water. The resulting precipitate was removed by filtration, washed with water, dried, and dissolved in ethyl acetate. The solution was chromatographed with a column packed with silica gel by elution with ethyl acetate—petroleum ether (2:1) to give 1.3 g of III and 0.15 g of IVb.

1-Benzyl-2-methyl-3-nitro-6-hydroxyindole (IVc). A 1.6-g (8.35 mmole) sample of enamine IIc was added with stirring at 20°C to a solution of 0.72 g (6.7 mmole) of p-benzoquinone in a mixture of 15 ml of acetic acid and 1.5 ml of acetic anhydride, after which the reaction mixture was allowed to stand at the same temperature for 36 h. The resulting precipitate was removed by filtration, washed successively with acetic acid and water, and dried to give 0.3 g of IVc. PMR spectrum: 2.80 (s, 2-CH_3), 5.12 (s, CH_2), 6.85-7.35 (m, 6-H, 4-H, C_6H_5), 7.93 (d, 7-H), 9.85 ppm (s, OH).

The acetic acid mother liquor was diluted with water, and the precipitate was removed by filtration, washed with water, dried, and recrystallized from dichloroethane to give 0.5 g (30%) of III.

1-Phenyl-2-methyl-3-nitro-6-hydroxyindole (IVd). A 23.5-g (132 mmole) sample of enamine IId was added with stirring at 20°C to a solution of 9.5 g (88 mmole) of p-benzoquinone in a mixture of 190 ml of acetic acid and 19 ml of acetic anhydride, after which the reaction mixture was allowed to stand at the same temperature for 36 h. The resulting precipitate was removed by filtration, washed successively with acetic acid and water, and dried to give 9.0 g of IVd. Workup of the acetic acid mother liquor gave 0.05 g (7%) of III.

1-(p-Tolyl)-2-methyl-3-nitro-6-hydroxyindole (IVe). A 5.76-g (30 mmole) sample of enamine IIe was added with stirring at 20°C to a solution of 2.16 g (20 mmole) of p-benzoquinone in a mixture of 40 ml of acetic acid and 4.0 ml of acetic anhydride, after which the reaction mixture was allowed to stand at the same temperature for 36 h. The resulting precipitate was removed by filtration, washed successively with acetic acid and water, and dried to give 2.2 g of IVe. PMR spectrum: 2.46 (s, CH_3 in $CH_3C_6H_4$), 2.57 (s, 2-CH_3), 6.89 (q, 6-H), 6.38 (d, 4-H), 7.45 A_2B_2 (C_6H_4), 7.96 (d, 7-H), 9.52 ppm (s, OH).

Compounds IVf, g. These compounds were similarly obtained.

1-Benzyl-2-methyl-3-nitro-6-hydroxyindole (Va). Two drops of concentrated H_2SO_4 were added to a suspension of 2.82 g (10 mmole) of indole IVc in 50 ml of acetic anhydride, and the mixture was stirred until the solid had dissolved. The reaction mixture was then cooled, and the resulting precipitate was removed by filtration, washed successively with acetic acid and water, dried, and recrystallized from alcohol to give 3.16 g of Va.

Compound Vb. This compound was similarly obtained.

1-(p-Methoxyphenyl)-2-(2-dimethylaminovinyl)-3-nitro-6-acetoxyindole (VI). A 7.35-g (5 mmole) sample of DMF diethylacetal was added to a suspension of 1.7 g (5 mmole) of indole Vb in 25 ml of DMF, after which the mixture was heated until a solution formed. The solution was then cooled and diluted with water, and the precipitated crystals were removed by filtration, washed with water, and dried to give 2.5 g of VI.

1-Benzyl-2-methyl-3-acetylamino-6-acetoxyindole (VII). A 6.5-g (100 mmole) sample of zinc dust was added in portions with stirring to a refluxing solution of 3.24 g (10 mmole) of Vb in a mixture of 100 ml of acetic acid and 2 ml of acetic anhydride until the solution became colorless. The reaction mixture was filtered hot, and the precipitate on the filter was washed with hot acetic acid (3 × 25 ml). The combined mother liquors were evaporated to a volume of 30 ml, the concentrate was diluted with water, and the precipitate was removed by filtration, washed with water, and dried to give 3.1 g of VII.

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