The Base-catalyzed Condensation of *o*-Nitroacetophenone. III. The Structure of Compound A, a Condensation Product

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In a previous paper,[2] compound A,[3] $C_{17}H_{14}O_5N_2$, an orange-red product of the base-catalyzed condensation of *o*-nitroacetophenone, has been shown to contain *o*-nitrophenyl and *N*-hydroxyindoline moieties.

The reduction of compound A methyl ether, $C_{18}H_{16}O_5N_2$, with sodium borohydride gave a colorless product, dihydro-compound A methyl ether, $C_{18}H_{18}O_5N_2$. The infrared absorption spectrum of this compound indicated that the nitro group of the original compound had survived during the reduction. The dihydro-compound, on acetylation with acetic anhydridepyridine, gave a monoacetyl derivative, $C_{20}H_{20}O_6N_2$. The infrared absorption spectrum

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[2] T. Sakan, K. Kusuda and T. Miwa, This Bulletin, **37**, 1681 (1964).

[3] T. Sakan, K. Kusuda and T. Miwa, ibid., **37**, 1678 (1964).

of the latter has a peak at 3435 cm^{-1}, which should be assigned to a tertiary hydroxyl group of the indoline nucleus.[2] The formation of an acetylable hydroxyl group by the reduction seems to imply the presence of a carbonyl group in the original compound.

The catalytic hydrogenation of dihydro-compound A methyl ether in the presence of palladium-on-carbon gave an amine, $C_{17}H_{18}ON_2$. The ultraviolet absorption of the amine indicated the presence of an indole nucleus in it. The amine, on brief heating with acetic anhydride, was transformed into a monoacetyl derivative, whereas it was converted into an *O*, *N*-diacetyl derivative by treatment with acetic anhydride-pyridine. The latter derivative was obtained in the crystalline state with a molecule of benzene as a solvent of crystallization. The series of reductions will be represented by partial structures in Chart 1.

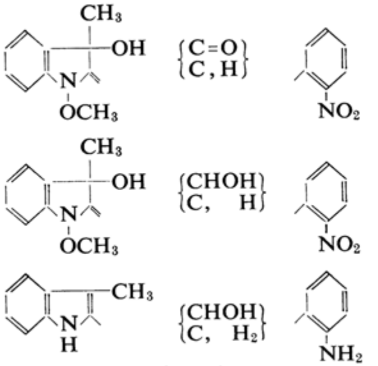
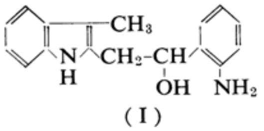


Chart 1

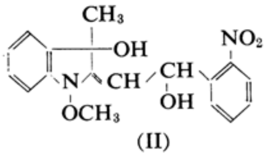
The fact that the catalytic hydrogenation of compound A methyl ether over Raney nickel at a high temperature and high pressure gave the same indole-amine confirmed that no skeletal change had occurred during the above reductions.

The indole-amine on alkali-fusion was cleaved to give 2, 3-dimethylindole and anthranilic acid in fairly good yields. The latter product was isolated as the *N*-acetyl derivative. Hence, structure I was assigned to the indole-amine.

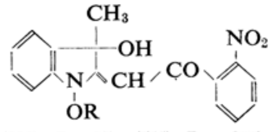


(I)

Consequently, dihydro-compound A methyl ether, compound A and its methyl ether possess structures, II, III and IV respectively.



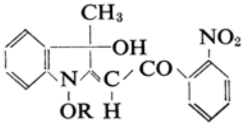
(II)



(III) R=H, (IV) R=CH$_3$

Loudon and Wellings[4] reported that the *O*-acetyl derivatives of cyclic hydroxamic acids exhibit an intense absorption near 1800 cm^{-1}. Interestingly, the acetyl derivative of compound A, a vinylog of hydroxamic acid, has a strong peak at 1796 cm^{-1}. The acetyl derivative decomposed gradually on being kept at room temperature for a long time.

The infrared spectra of compound A methyl ether and acetate give information on the stereochemistry around the double bond in these compounds. Both of the compounds in the solid state possess a very weak band near 3100 cm^{-1} as a result of the tertiary hydroxyl group. The low wave number of the band is probably due to an intermolecular hydrogen bonding, for the band is shifted to about 3300 cm^{-1} when the compounds are dissolved in carbon tetrachloride. The fact that this band of the methyl ether remains at 3300 cm^{-1}, even in a very dilute solution (3.4×10^{-4} M in carbon tetrachloride), suggests the presence of an intramolecular hydrogen bonding between the tertiary hydroxyl and the carbonyl of this compound, thus locating these groups on the same side of the double bond as shown in V. Compound A itself has the same configuration, for the mild conditions of the methylation should not change the stereochemistry around the double bond.



(V)

The carbonyl stretching absorption of compound A is quite obscure, as has been stated in a previous paper.[3] The infrared spectra of the methyl ether and the acetate also show quite unusual features in the region. Although they have a band of medium intensity at 1626 and 1632 cm^{-1} respectively, it appears that these should be assigned to the double bond rather than to the carbonyl bond, the stretching band of the latter being considered to be shifted to about 1500 cm^{-1} from the following reasons: (1) The bands at 1626 and 1632 cm^{-1} are rather weak for the carbonyl bond; (2) the 1500 cm^{-1} bands of these compounds are much broader than those of dihydro-compound A derivatives; (3) the 1500 cm^{-1} bands show a shoulder near 1560 cm^{-1} in a carbon tetrachloride solution. The unusual shift of the carbonyl absorption of compound A derivatives may be due to an intense interaction between

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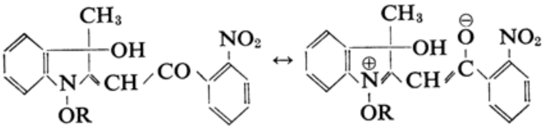
[4] J. D. Loudon and I. Wellings, *J. Chem. Soc.*, **1960**, 3463.

the tertiary hydroxyl group and the carbonyl oxygen atom, which possesses a high electron density produced by the mesomerism VI ↔ VII.



(VI) (VII)

The characteristic ultraviolet spectra³⁾ of compound A and its alkyl ethers correspond to those of β-amino-α, β-unsaturated ketones.⁵⁾

The base-catalyzed condensation of the homologous *o*-nitrophenyl ketones is currently being investigated. The mechanism for the formation of compound A will be discussed in a later paper.

Experimental⁶⁾

The Sodium Borohydride Reduction of Compound A Methyl Ether. Dihydro-Compound A Methyl Ether (II). — To a solution of 1.70 g. (5 mmol.) of compound A methyl ether³⁾ in 60 cc. of methanol 0.5 g. (13 mmol.) of sodium borohydride was added. The mixture was heated on a water bath for five minutes and diluted with 10 cc. of water, and the solvent was removed by distillation. The residue was then triturated with water, filtered, washed with water, and dried. The crude material weighed 1.25 g. (73%). A small portion of the material was recrystallized from aqueous methanol for analysis. A pure compound melts at 155°C. IR 3304, 3240 (OH), 1529, 1350, 855 (NO_2).

Found: C, 63.09; H, 5.83; N, 7.86. Calcd. for $C_{18}H_{18}O_5N_2$: C, 63.15; H, 5.30; N, 8.18%.

Dihydro-Compound A Acetate. — A mixture of 320 mg. (0.93 mmol.) of dihydro-compound A methyl ether, 1.5 cc. of acetic anhydride, and 7 drops of pyridine was shaken for three hours, left to stand overnight, and decomposed with water. The separated crystals were then filtered, washed with water, and dried. Crude acetate (m. p. 140.5—142°C) weighed 340 mg. (95%). Recrystallization from ethanol gave pure acetate melting at 145°C. IR 3435 (OH), 1718 (CO), 1522, 1355, 855 (NO_2).

Found: C, 62.33; H, 5.64; N, 7.34. Calcd. for $C_{20}H_{20}O_6N_2$: C, 62.49; H, 5.24; N, 7.29%.

2-[2-(*o*-Aminophenyl)-2-hydroxyethyl]-3-methylindole (I).—*The Catalytic Hydrogenation of Dihydro-Compound A Methyl Ether.* — Dihydro-compound A methyl ether (1.13 g., 3.3 mmol.) in 100 cc. of methanol was hydrogenated in the presence of 0.5 g. of 5% palladium-on-carbon. After the removal of the catalyst, the methanol was distilled and the residue dissolved in a small amount of hot benzene. On cooling, 0.63 g. (64%) of the indoleamine was obtained. The amine (m. p. 151—152°C) was found to be identical with the sample described below by an admixture test and by infrared spectroscopy.

The High Pressure Hydrogenation of Compound A Methyl Ether.—A solution of 1.0 g. (2.9 mmol.) of compound A methyl ether in 50 cc. of ethanol was hydrogenated over 1.0 g. of Raney nickel at a hydrogen pressure of 75 atm. and 125—145°C for three hours. The hydrogenation mixture was worked up as described above to give 0.2 g. of the amine melting at 146—148°C. The amine, after recrystallization from benzene, melted at 149.0—149.5°C. λ_{max} 229—230 (4.61), 286 (4.02), 293 (3.99). IR 3390 (NH and OH).

Found: C, 76.60; H, 6.99; N, 10.30. Calcd. for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81; N, 10.52%.

***N*-Acetyl Derivative.**—A mixture of 0.46 g. (1.6 mmol.) of the amine and 0.8 cc. of acetic anhydride was heated to the boiling point, immediately cooled with water, and decomposed with 5 cc. of water. The separated solid was then filtered, washed with water, and dried. The acetate, after recrystallization from ethanol, melted at 154.5—155.5°C. IR 3400 (OH), 3210 (NH), 1645 (CO).

Found: N, 9.06. Calcd. for $C_{19}H_{20}O_2N_2$: N, 9.09%.

***O, N*-Diacetyl Derivative.**—To a solution of 240 mg. (0.8 mmol.) of the amine in 1 cc. of pyridine, 0.3 cc. of acetic anhydride was added at room temperature. The mixture was left to stand overnight and diluted with water, and the separated oil was triturated with 1 N hydrochloric acid until it became solid. The dried solid was recrystallized from benzene. The pure diacetyl derivative melts at 108°C. IR 3340 (NH), 1728, 1663 (C=O).

Found: C, 75.62; H, 6.64; N, 6.07. Calcd. for $C_{21}H_{22}O_3N_2\text{-}C_6H_6$: C, 75.67; H, 6.59; N, 6.54%.

The Alkali-fusion of the Indole-amine I. — A solution of 0.8 g. of the amine and 1.0 g. of potassium hydroxide in 3 cc. of methanol was heated under nitrogen to 180°C; at that temperature effervescence occurred. The mixture was kept at the temperature for a few minutes until the foaming subsided; then it was cooled and taken into water and ether. The aqueous layer was neutralized with 1 N hydrochloric acid until the solution had become slightly turbid, treated with two portions of 1 cc. of acetic anhydride each, acidified with hydrochloric acid to Congo red, and extracted with ether. The ether was then evaporated and the residue treated with benzene and petroleum ether to yield about 30 mg. of precipitates, which on recrystallization from water melted at 185.5°C. This material was identified with *N*-acetylanthranilic acid, m. p. 186—187°C, by the mixed melting point test with an authentic sample and by infrared spectroscopy. The original ethereal layer, on concentration, gave 180 mg. of crystals melting at 104—108°C. The crystals, after sublimation followed by recrystallization from petroleum benzine, melted at 107—108°C. This compound was identified as 2,3-dimethylindole, m. p. 106.5—107°C, by mixed melting point determination and by infrared spectral comparison.

Compound A Acetate.—An aqueous-alkaline solution of compound A was treated with acetic anhydride under ice-cooling. The precipitates formed

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5) N. H. Cromwell and J. C. David, *J. Am. Chem. Soc.*, **82**, 2046 (1960).

6) All melting points are uncorrected. Unless otherwise noted, the ultraviolet spectra were taken in ethanol and the infrared spectra in Nujol mull; they are expressed in λ_{max} mμ (log ϵ) and in IR cm^{-1} respectively.

were dissolved in aqueous ethanol and the solution was condensed in a desiccator to give yellow crystals decompositing at 108—109°C. IR (in CCl_4) 3300 (OH), 1818 (C=O), 1525, 1346 850 (NO_2).

Found: C, 62.10; H, 4.57; N, 7.63. Calcd. for $C_{19}H_{16}O_6N_2$: C, 61.95; H, 4.38; N, 7.61%.

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