The Base-catalyzed Condensation of o-Nitroacetophenone. II. The Ozonolysis of Methyl Ether of Compound A, a Condensation Product, and the Structure of Compound B, Another Product

By Takeo SAKAN, Kousuke KUSUDA[1] and Toshio MIWA

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The base-catalyzed condensation of *o*-nitroacetophenone has been reported to give an orange-red product, $C_{17}H_{14}O_5N_2$, named compound A.[2] In order to elucidate the structure of this compound, its methyl ether was ozonolyzed. The ozonolysis of compound A methyl ether yielded a colorless neutral compound, $C_{10}H_{11}O_3N$, along with *o*-nitrobenzoic acid, *o*-nitroacetophenone and formaldehyde.

The measurement of the *C*-methyl number of the C_{10}-compound gave a value of 0.64; a positive alkoxyl group test[3] showed the presence of an alkoxyl group. This compound gave negative reactions both with a ferric hydroxamate test[4] and with various carbonyl reagents, indicating the absence of either an ester or a keto function. On the other hand, it gave positive results with the Millon and Folin-Dennis reactions.[5] After hydrolysis,

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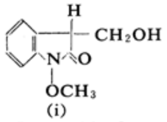
[1] Present address: Research Institute of Atomic Energy, Osaka City University, Kita-ku, Osaka.

[2] T. Sakan, K. Kusuda and T. Miwa, This Bulletin, 37, 1678 (1964).

[3] N. D. Cheronis, "Micro and Semimicro Methods," Interscience Publisher, New York (1954), p. 454.

[4] Ibid., p. 460.

[5] Since the oxindoles with no hydrogen atom at their β-position had generally given a negative Folin-Dennis reaction, formula i was assigned to this compound (The 11th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1958). Later this formula was found to be false by the confirmation of the presence of a *C*-methyl group. A color test with ammonium phosphomolybdate is more specific to the presence of the β-hydrogen of oxindole derivatives (T. Tokuyama, The 12th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1959); the C_{10}-compound gave a negative reaction with this reagent.



(i)

followed by diazotization and coupling with β-naphthol, it developed an orange color. The vapor of the zinc-dust distillation gave a violet spin-splinter reaction. These color reactions,[6] associated with the features of the ultraviolet spectrum[7] (Fig. 1), suggested the presence of an oxindole system in this compound. The carbonyl bond (1715 cm^{-1}) of the infrared spectrum of the compound can be assigned to the oxindole carbonyl. The *N*-unsubstituted oxindoles usually exhibit a broad band near 3200 cm^{-1}.[8] The absence of any bands above 3000 cm^{-1} of the infrared spectrum of the compound, except for a sharp band at 3410 cm^{-1}, indicated that the postulated oxindole nucleus can be substituted at the nitogen atom.

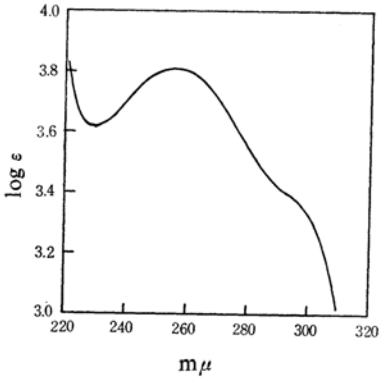


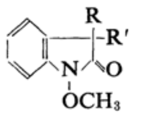
Fig. 1. Ultraviolet spectrum of the C_{10}-compound (I) in ethanol.

The acylation of the C_{10}-compound by acetic anhydride or *p*-nitrobenzoyl chloride in the presence of pyridine gave the corresponding *O*-acyl derivatives, as is indicated by their infrared spectra (see Experimental section). The disappearance of the 3410 cm^{-1} band in these spectra demonstrated that the band of the original compound should be attributed to a hydroxyl group.

On the basis of these results, the C_{10}-compound may be considered to be an *N*-substituted oxindole derivative with a hydroxyl, a methoxyl and a methyl group as substituents. The neutral property of the compound excluded the possibility that it might be a hydroxamic acid. Therefore, this compound was assumed to be 1-methoxy-3-methyldioxindole (I).

The treatment of the C_{10}-compound with thionyl chloride and pyridine produced a chloride II, which was hydrogenated in the presence of palladium-on-carbon and sodium acetate to a chlorine-free oil considered to be 1-methoxy-3-methyloxindole (III).

On the other hand, 1-methoxyoxindole (IV)[9] was formylated with ethyl formate in the presence of sodium ethoxide.[10] The formylation product, V, was hydrogenated over palladium-on-carbon to compound III. Both the compound from the ozonolysis and that from the synthetic path showed quite identical infrared spectra. The oily oxindole, III, was characterized by bromination to a crystalline monobromine atom of which was tentatively located at the position 5 of the oxindole system.



I, R=CH_3, R'=OH
II, R=CH_3, R'=Cl
III, R=CH_3, R'=H
IV, R=R'=H
V, R, R'=CHOH

Interestingly, the hydrogenation of V over Raney nickel caused a further reduction to 3-methyloxindole.

In order to confirm whether the *O*-methyl group of the C_{10}-compound had been introduced by the methylation of compound A, the ethyl ether of the latter was ozonolyzed. From ethyl ether of latter was ozonolyzed. From the neutral fraction two unknown compounds besides *o*-nitroacetophenone were isolated. One of the unkonwn compounds, $C_{19}H_{11}O_5N_2$, was supposed to be dehydro-compound A[2] ethyl ether on the basis of its ultraviolet spectrum.

The other unknown product, $C_{11}H_{13}O_3N$, was assigned the 1-ethoxyoxindole structure I (OEt for OMe) by analogy with the above-mentioned C_{10}-compound; this assignment was confirmed by its ultraviolet and infrared spectra, which were similar to those of the latter. Consequently, it is apparent that the hydroxyl group of weak acidity in compound A is not an enolic one, but one attached to a nitrogen atom, as in an oxime or in a hydroxamic acid. Hence, compound A contains an *N*-hydroxyindoline and an *o*-nitrophenyl moiety in its molecule.

The base-catalyzed condensation of *o*-nitroacetophenone using a large excess of sodium acetylide yielded no compound A, but formed a faintly yellow product, compound B.[2]

Contrary to the weakly acid compound A, this compound was basic and soluble in dilute hydrochloric and. It was recovered as precipitates from the acid solution when it was made alkaline with aqueous ammonia. It was insoluble in aqueous sodium bicarbonate. Hot aqueous alkali dissolved it gradually, with the

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[6] H. Wieland and B. Witkop, *Ann.*, **543**, 171 (1940).

[7] For the ultraviolet spectra of oxindoles see, e. g., J. W. Cornforth, C. E. Dargliesh and A. Neuberger, *Biochem. J.*, **48**, 598 (1951).

[8] J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, **1957**, 4789.

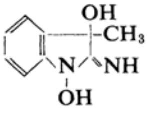
[9] W. B. Wright, Jr., and K. H. Collins, *J. Am. Chem. Soc.*, **78**, 221 (1956).

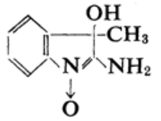
[10] P. L. Julian, J. Pikel and F. E. Wentz, ibid., **57**, 2026 (1935).

evolution of ammonia. The vapor of zinc-dust distillation gave a violet pine-splinter reaction, indicating the formation of the indole derivative. The green color developed with alcoholic ferric chloride quickly turned yellow. Aqueous ferric chloride gave the pale blue color characteristic of α-aminopyridine *N*-oxides.[11]

The attempted methylation of compound B by treatment with dimethyl sulfate and potassium carbonate afforded a compound melting at 134~135°C and with the evolution of ammonia. This compound was shown to be identical with the C_{10}-compound I obtained above by the ozonolysis of the compound A methyl ether.

On the basis of these results compound B may be represented by either of the following tautomeric structures, VIa or VIb:


VIa


VIb

Experimental[12]

The Ozonolysis of Compound A Methyl Ether. 1-Methoxy-3-methyldioxindole (I). — *a) Oxidative Decomposition.*—A solution of 1.31 g. (3.88 mmol.) of compound A methyl ether[2] in 40 cc. of ethyl acetate, which had been chilled in an ice-bath, was saturated with ozone and allowed to stand in an ice-bath overnight. The solvent was then removed by distillation under reduced pressure in the cold, and the remaining red oil was added to a mixture of 0.4 g. of sodium dichromate in 40 cc. of acetic acid to cause a violent reaction, with foaming. The mixture, diluted with water, was extracted continuously with ether, and the extract washed with aqueous sodium bicarbonate. The acid fraction (469 mg., 72%) was recrystallized from benzene-petroleum benzine to give crystal melting at 145~147°C. No depression was observed in a mixed melting point determination with *o*-nitrobenzoic acid.

The removal of the solvent in vacuo from the ethereal solution left a viscous oil, which deposited a small amount of crystals when left standing. The residue in benzene was adsorbed on active alumina. Four fractions taken with benzene gave a yellow oil weighing 61 mg., 60 mg., 63 mg. and 37 mg. respectively. The first three of them (184 mg. in total, 30%) showed identical infrared (ν_{max} 1695 (C=O), 1522, 1348 (NO_2)) and ultraviolet (λ_{max} 259) spectra. The combined oil was then converted to a 2,4-dinitrophenylhydrazone melting at 164~165°C, which was identified with that of *o*-nitroacetophenone by a mixed melting point determination.

Elution with benzene containing some ethanol yielded 38 mg. (5.1%) of crystals, which, after recrystallization from benzene-ligroin, melted at 134~136°C. λ_{max} 257 (3.81). ν_{max} 3410 (OH), 1715 (C=O).

Found: C, 62.37; H, 6.06; N, 7.47; *C*-methyl, 0.62. Calcd. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25%.

A solution of 5 mg. of the C_{10}-compound in one drop of pyridine was treated with about 5 mg. of *p*-nitrobenzoyl chloride under ice-cooling, and the mixture was allowed to stand overnight. The removal of the pyridine under reduced pressure, followed by washing successively with two portions of water, 5% aqueous sodium carbonate and water, gave a *p*-nitrobenzoate, which melted at 107~109°C after recrystallization from ethanol. ν_{max} 1745, 1730 (C=O).

A solution of 51 mg. of the C_{10}-compound in 15 drops of pyridine, cooled with ice, was treated with 4 drops of acetic anhydride. After being kept for 6 hr. at room temperature, the mixture was decomposed by the addition of water. The resulting oil was washed with N hydrochloric acid, water and aqueous sodium carbonate, and then taken into benzene. The benzene solution, after drying, was filtered through a short column of active alumina. The removal of the solvent left an oily acetate. ν_{max} 1745 (shoulder), 1739 (C=O).

b) Decompsition with Water. — Compound A methyl ether (623 mg., 1.83 mmol.), dissolved in ethyl acetate, was saturated with ozone. The resulting ozonide, as a solution, was decomposed by the addition of water. The organic layer was separated from the aqueous layer, which was extracted with ether. The extract, combined with the original organic layer, was worked out as described in a). The acid fraction gave 279 mg. (91%) of crude *o*-nitrobenzoic acid. The neutral fraction was adsorbed on alumina. A yellow oil (100 mg.) was eluted by benzene. Elution with benzene containing a small amount of ethanol gave 98 mg. (28%) of a crude C_{10}-compound.

c) Reductive Decomposition.—After a solution of 308 mg. (0.91 mmol.) of compound A methyl ether in 20 cc. of ethyl acetate had been saturated with ozone, the solution was shaken saturated sulfurous acid and worked out as described in a). From the acid fraction, 96.5 mg. (63.9%) of crude *o*-nitrobenzoic acid was obtained. The removal of the solvent from the neutral fraction immediately gave 124 mg. (71.1%) of crystals, which after, recrystallization from benzene-ligroin, melted at 136°C. The chromatography of the mother liquor of recrystallization gave a small amount of oil. It was assumed to be *o*-nitroacetophenone because of a positive reaction with 2,4-dinitrophenylhydrazine.

d) In Carbon Tetrachroride. — A solution of 429 mg. of compound A methyl ether in 80 cc. of carbon tetrachloride, chilled with ice, was saturated with ozone. After it had been allowed to stand overnight, the solution deposited a resinous material on the wall of the flask. The resinous material

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[11] G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, **1949**, S133; W. Sharp and F. S. Spring, ibid., **1951**, 932; J. D. Loudon and G. Tennant, ibid., **1960**, 3466.

[12] All melting points are not corrected. Unless otherwise noted, ultraviolet spectra were taken in ethanol and infrared spectra in Nujol mull; they are expressed in λ_{max} mμ (log ε) and in ν_{max} cm^{-1}, respectively.

was dissolved by the addition of ethyl acetate, and the ozonide was decomposed by the addition of 70 cc. of water. The aqueous solution gave a positive reaction with 2,4-dinitrophenylhydrazine and chromotropic acid (formaldehyde).[13] The aqueous solution was then distilled, and 35 cc. of the distillate was treated with 12 cc. of a saturated aqueous methone solution and allowed to stand, thus depositing small needles melting at 183~185°C, which did not depress the melting point of the methone derivative of formaldehyde.

3-Formyl-1-methoxyoxindole (V). — Into a hot sodium ethoxide solution prepared from 1.0 g. (44 mmol.) of sodium and 13 cc. of dry ethanol was added a mixture of 4.4 g. (27 mmol.) of 1-methoxyoxindole[9] and 3.0 g. (40 mmol.) of ethyl formate, the reaction mixture solidifying into a pink cake with heat evolution. The cake was dissolved with 120 cc. of water, and the solution was acidified with hydrochloric acid to separate yellowish brown precipitates, which were collected by filtration, washed with 50% aqueous ethanol and recrystallized from ethanol to give 2.9 g. (56%) of V decomposing at 190°C. ν_{max} 2650 (OH), 1658 (C=O).

Found: C, 62.84; H, 4.75; N, 7.51. Calcd. for $C_{10}H_9O_3N$: C, 62.82; H, 4.75; N, 7.33%.

1-Methoxy-3-methyloxindole (III).—*a) From 1-Methoxy-3-methyldioxindole (I).*—A solution of 62 mg. (0.32 mmol.) of the C_{10}-compound in 1 cc. of pyridine was treated with 35 mg. (0.42 mmol.) of thionyl chloride. After being kept at room temperature for 18 hr., the mixture was diluted with ether and washed with water. The removal of the ether by distillation left 47 mg. of crystals, m. p. 78~102°C, which showed positive in a Beilstein test. The filtration of a benzene solution of the crystals through a short column of alumina gave 16 mg. of the chloride II. ν_{max} 1739 (C=O).

A solution of 45 mg. (0.21 mmol.) of the chloride II in ethanol was hydrogenated in the presence of 17.5 mg. (0.21 mmol.) of sodium acetate and 20 mg. of 5% palladium-on-carbon. Within 40 min. 7.9 cc. (14°C) of hydrogen was absorbed. After the removal of the catalyst by filtration, followed by the evaporation of the solvent in vacuo, the residue, as a benzene solution, was filtered through a short column of alumina to give 35 mg. of an oil. The oil showed an infrared spectrum (ν_{max} 1736~1721 (C=O)) quite identical with that of 1-methoxy-3-methyloxindole synthesized below.

b) From 3-Formyl-1-methoxyoxindole (V). — A solution of 170 mg. (0.89 mmol.) of the formylation product V in 10 cc. 95% ethanol was hydrogenated in the presence of 80 mg. of 5% palladium-on-carbon. Within 2 hr. 5.6 cc. (13°C) of hydrogen was absorbed. Work-up in a way similar to that described in a) gave III as an oil, which was characterized as a bromide. The elution of the alumina with benzene containing a little ethanol yielded crystals melting at little ethanol yielded crystals melting at 110~125°C. The hydrogenation of V over Raney nickel in ethanol also gave crystals, m. p. 118~120°C, as a sole product. They were assumed to be 3-methyloxindole (reported m. p. 123°C[14]).

5(?)-Bromo-1-methoxy-3-methyloxindole. — Into seven-tenths of a solution of 120 mg. (0.77 mmol.) of bromine and 140 mg. (1.54 mmol.) of potassium bromide in 5 cc. of water, 95 mg. (0.54 mmol.) of oily oxindole III was added, and the mixture was left to stand overnight. The mixture was then extracted with ether. The evaporation of the ether produced 94 mg. (48%) of pale yellow crystals, which, after filtration, as a benzene solution, through alumina, followed by recrystallization from benzene-ligroin, melted at 90~92°C.

Found: C, 46.91; H, 4.18; N, 6.21. Calcd. for $C_{10}H_{10}O_2NBr$: C, 46.89; H, 3.94; N, 5.47%.

The Ozonolysis of Compound A Ethyl Ether.—A solution of 492 mg. (1.39 mmol.) of the ethyl ether[2] in 36 cc. of ethyl acetate was saturated with ozone, and the ozonide was decomposed with saturated aqueous sulfurous acid. Work-up in a way similar to that described in the ozonolysis of the methyl ether c) gave 125 mg. (54%) of *o*-nitrobenzoic acid and 260 mg. of the neutral fraction. The latter, dissolved in benzene, was adsorbed on alumina. The first crop eluted with benzene gave 27 mg. of an oil, which was identified with *o*-nitroacetophenone by derivation to its 2,4-dinitrophenylhydrazone. The second crop eluted with the same solvent gave 27.5 mg. of crystals, which, after recrystallization from benzene-ligroin, melted at 130~131°C. On the basis of the elementary analysis, the compound was assumed to be dehydro-compound A ethyl ether.

Found: C, 64.58; H, 4.56. Calcd. for $C_{19}H_{16}\cdot O_5N_2$: C, 64.77; H, 4.58%.

Elution with benzene containing a little ethanol yielded 79 mg. of crystals, which were recrystallized from benzene-ligroin; m. p. 80~81°C. λ_{max} 259 (3.59). ν_{max} 3344 (OH), 1704 (C=O).

Found: C, 63.51; H, 6:45; N, 6.97. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76%.

The Attempted Methylation Compound B.—A mixture of 104 mg. of compound B, 5 cc. of acetone, 183 mg. of dimethyl sulfate and 200 mg. of potassium carbonate was heated under reflux for 5 hr. During the heating, the evolution of ammonia was observed (detected by the Nessler reaction and with litmus paper). After the removal of inorganic substances and of recovered compound B by filtration, followed by the evaporation of the solvent in vacuo, the remaining residue was dissolved in 100 cc. of benzene containing 3 drops of ethanol and the solution was filtered through a short column of alumina. The evaporation of the solvent left 37 mg. of crystals, which, after recrysallization from benzene-ligroin, melted at 134~135°C. This compound was identified with the 1-methoxy-3-methyldioxindole (I) obtained above by the ozonolysis of compound A methyl ether by a mixed melting point determination. By treating the insoluble material of the reaction mixture with water, 57 mg. of compound B remained undissolved.

Faculty of Science
Osaka City University
Sumiyoshi-ku, Osaka

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[13] F. Feigl, "Spot Tests," Vol. II, Elsevier Publ., New York (1954), p. 240.

[14] K. Brunner, *Monatsh.*, **18**, 533 (1897).