The Base-catalyzed Condensation of o-Nitroacetophenone. I. Some Properties of the Condensation Products

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The reaction of nitrobenzene with phenylmagnesium bromide is known to yield diphenylamine.[2] However, Newman and Smith[3] have found that *m*-nitrobenzaldehyde reacts smoothly with phenylmagnesium bromide at the low temperature of −70°C to give *m*-nitrobenzhydrol, while the reaction gives only a tarry product at room temperature. This technique has been applied also to *o*-nitrobenzaldehyde.[4]

It seemed interesting to see what the reactions would be to the action of sodium acetylide upon *o*-nitroacetophenone at such a low temperature.

The treatment of *o*-nitroacetophenone with sodium acetylide in liquid ammonia at −70°C yielded an orange-red crystalline compound, m. p. 171~172°C of a weak acidity (pK_a ca. 5.9) in a moderate yield, along with *o*-nitrobenzoic acid. A series of following papers will report on the elucidation of the structure and the reactions of this product, which will be referred to as compound A throughout this series.

The elementary analysis of compound A did not afford a constant result; rather, the results depended upon the kind of solvents from which it was recrystallized (see Experimental section). The analytical results agreed approximately with the $C_{17}H_{14}O_5N_2$ composition, which was supported by analyses of some of its derivatives (see below). The measrement of the *C*-methyl number gave a value of 0.72. The absence of a distinct absorption in the carbonyl region of the infrared spectrum of compound A suggests that the weak acidity of this compound may be due to an enolic group, to which a band near 3300 cm^{-1} can be assigned (Fig. 1). The absorption bands at 1535 and 1355 cm^{-1} correspond to the nitro group.

When compound A was treated with diazomethane or dimethyl sulfate and potassium carbonate, a yellow methyl ether, $C_{18}H_{16}O_5N_2$, was obtained. Similarly, the treatment of compound A with diethyl sulfate and potassium carbonate produced an ethyl ether, $C_{19}H_{18}O_5N_2$. These derivatives had lost the acidity as well as the absorption band near 3300 cm^{-1} of the original compound; these facts seem to support the speculation that the acidity of compound A may be attributed to an enolic function. The methyl ether has a weak absorption band at 3000 cm^{-1} which is shifted to 3250 cm^{-1} with an increase in its intensity in the carbon tetrachloride solution. Another conspicuous difference in the infrared spectrum of the methyl ether from that of compound A is the appearance of a new band, of a medium intensity, at 1616 cm^{-1}.

The ultraviolet spectra of compound A and its alkyl ethers possess a characteristic intense band near 380 mμ. The position of the band of compound A is shifted to ca. 400 mμ and the intensity of the band is increased when the compound is dissolved in aqueous alkali. On the other hand, such behavior is not observed in the case of its alkyl ethers.

The molecular formula of compound A, $C_{17}H_{14}O_5N_2$, was confirmed by elementary analyses of its alkyl ethers and by the determination of the molecular weight of the methyl ether by the Barger method. With this composition, compound A was assumed to be formed by the dehydrogenative condensation of three moles of *o*-nitroacetophenone with the simultaneous cleavage of one mole of *o*-nitrobenzoic acid.[5]

$$3\,C_8H_7O_3N \rightarrow C_{17}H_{14}O_5O_2 + C_7H_6O_4N + H_2$$

If this condensation proceeds according to the stoichiometry of the equation and is terminated by the formation of the stable salts of both the products, the best yield compound A can be expected on the use of two gram atoms of sodium per three moles of *o*-nitroacetophenone;[6] this is indeed the case, as Table I

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2) H. Gilman and R. McCracken, *J. Am. Chem. Soc.*, **51**, 821 (1929).

3) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

4) D. H. Hey and R. D. Mulley, *J. Chem. Soc.*, **1952**, 2276.

5) Although a pair of reagents, liquid ammonia and sodium, sounds like the conditions of the Birch reduction, the coexistence of a nitro compound and a strong base, sodium amide or acetylide, may produce oxidizing circumstances similar to those of the nitrobenzene and alkali pair.

6) Strictly speaking, the consumption of the nitro compound by reduction during the reaction is neglected.

TABLE I. BASE-CATALYZED CONDENSATION OF *o*-NITROACETOPHENONE

Per mole of *o*-nitroacetophenone		Compd. A	Compd. B	*o*-Nitrobenzoic acid	Recovered
Liq. NH_3 l.	Sodium g. atom	%[a]	%[b]	%[a,b]	%
1.3	0.57	37	—	121	49
2.1	0.63	54	—	31	30
1.0	0.67	50	—	70	c)
1.0	0.67	62	—	50	c)
3.2	1.04	34	—	53	45
6.6	3.45	—	26	71	58
1.0[d]	0.67	46	—	c)	c)
0.8[e]	0.67	45	—	c)	c)

a) The yield was calculated using the Eq. 1. The recovered ketone, if weighed, was reduced from the starting material on the calculation.

b) The yield of compound B was calculated by postulating that the compound had been formed according to the following equation:

$$2\ C_8H_7O_3N + NH_3 \rightarrow C_9H_{10}O_2N_2 + C_7H_5O_4N + H_2$$

c) The amount was not recorded.

d) Sodium amide was used in stead of sodium acetylide.

e) The reaction was carried out under an atmosphere of nitrogen.

shows. Without the introduction of acetylene, which might be unnecessary for the reaction, a comparative yield of compound A was obtained, and the reaction was rather violent. The fact that a similar result was obtained under an atmosphere of nitrogen excluded the possibility of the dehydrogenation by atmospheric oxygen.

When the condensation was carried out with a large excess of sodium, compound A was not formed, but a colorless product, $C_9H_{10}O_2N_2$, named compound B was obtained in a low yield.

The oxidation of compound A with alkaline hydrogen peroxide gave a weakly acidic substance, $C_{17}H_{12}O_5N_2$, m. p. 226~227°C. This compound was also obtained when the reaction mixture of the condensation had been allowed to stand in air for a long time before acidification. This substance is named dehydro-compound A.

Dehydro-compound A was methylated with dimethyl sulfate and potassium carbonate in a way similar to that used in the methylation of compound A to give a neutral methyl ether, $C_{18}H_{14}O_5N_2$. The methyl ether was obtained also by the oxidation of compound A

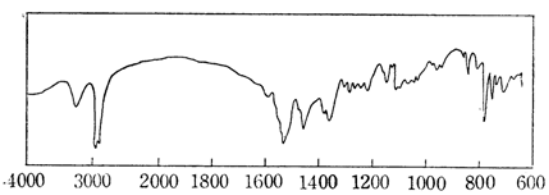

Fig. 1. Infrared spectrum of compound A (Nujol mull).

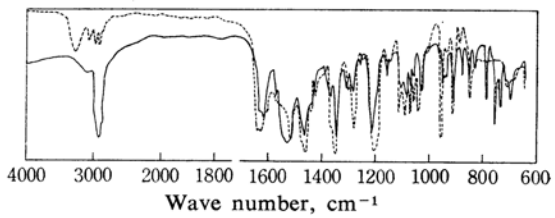

Fig. 2. Infrared spectrum of compound A methyl ether. (—— Nujol mull; ---- 0.06 M CCl_4 solution).

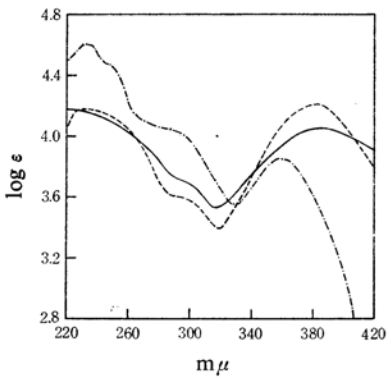

Fig. 3. Ultraviolet spectra (in ethanol) of compound A (——), compound A methyl ether (----) and dehydro-compound A (-·-·-).

methyl ether with periodic acid in dioxane. The ozonization of compound A ethyl ether produced a small amount of dehydro-compound A ethyl ether.[7] It should be pointed out that the dehydrogenation of compound A or its

7) See Part II: T. Sakan, K. Kusuda and T. Miwa, This Bulletin, 37, 1681 (1964).

alkyl ethers took place very readily with a variety of oxidizing agents.

In the ultraviolet spectra of dehydro-compound A and its methyl ether, the characteristic band near 380 mμ of the compound A series disappeared and a new band showed up near 350 m. This striking change in the spectrum suggests that a major reaction had occurred during the dehydrogenation.

Experimental[8]

The Condensation of *o*-Nitroacetophenone by Sodium Acetylide. *a) Compound A.*—Into 100 cc. of liquid ammonia saturated with acetylene, 1.5 g. (0.065 g. atom) of sodium was added in small pieces. After all the sodium had been added, 16.5 g. (0.1 mol.) of *o*-nitroacetophenone in 20 cc. of dry ether was stirred in one portion at −70°C. A violent exothermic reaction (the temperature of the reaction mixture reached −50°C) took place, giving a dark red mixture. The mixture was then kept at −50∼−60°C for one hour, 4.0 g. (0.075 mol.) of ammonium chloride was added, and the liquid ammonia was allowed to evaporate while about 50 cc. of ether was added. When the reaction mixture had reached the room temperature, a further amount of ether and some water were added. The separated ethereal solution was extracted with several portions of a 10% sodium hydroxide solution, and the aqueous extracts were added to the original aqueous layer. (From the ethereal solution, after concentration followed by distillation in vacuo, *o*-nitroacetophenone was recovered.) The combined aqueous solution, dark red in color, was washed with ether, acidified with hydrochloric acid, and extracted with ether. The ethereal solution was washed with a sodium bicarbonate solution until the washing became reddish.[9] The concentration of the ethereal solution gave orange-red needles, which, after recrystallization from ethanol, melted at 170∼171°C. Recrystallization from non-polar solvents gave somewhat yellowish crystals of the same melting point. The pK_a value (ca. 5.9) in an aqueous solution was not accurate because of the poor solubility of this compound in water. λ_{max} 382∼384 (4.05). ν_{max} 3286 (OH), 1535, 1355, 844 (NO_2).

Found: (a) From benzene-ligroin: C, 63.10; H, 4.46; N, 7.52. (b) From chloroform: C, 62.52; H, 4.22; N, 8.08. (c) From ethanol: C, 62.68; H, 4.17; N, 8.48. *C*-Methyl group[10]: 0.72. Calcd. for $C_{17}H_{14}O_5N_2$: C, 62.57; H, 4.32; N, 8.59%. The results of the condensation under various conditions, are listed in Table I.

b) Compound B.—*o*-Nitroacetophenone (10.0 g., 0.061 mol.) was subjected to condensation with sodium acetylide prepared from acetylene 5.0 g. (0.22 g. atom) of sodium in 400 cc. of liquid ammonia, and the reaction mixture was worked up in a way similar to that described in a). There was obtained 0.4 g. of a crystalline substance insoluble both in the ethereal and alkaline aqueous layers. From the neutral fraction, 5.8 g. of an oil boiling at 146°C/2.5 mmHg was obtained. The 2,4-dinitrophenylhydrazone of the oil, m. p. 166∼167°C, was identified as that of *o*-nitroacetophenone. The acid fraction gave 1.0 g. of crude *o*-nitrobenzoic acid. The insoluble material was dissolved in N hydrochloric acid, and the solution was treated with active carbon and then made alkaline with aqueous ammonia to give faintly brown plates decomposing at 236°C. λ_{max} 230 (4.18), 291 (3.92). ν_{max} 3280 (OH), 2860∼2500 (NH or OH[6]), 1672 (C=O).

Found: C, 60.82; H, 5.78; N, 15.69. Calcd. for $C_9H_{10}O_2N_2$: C, 60.66; H, 5.66; N, 15.72%.

Compound A Methyl Ether. — *a) With Diazomethane.*—A solution of 400 mg. (1.22 mmol.) of crude compound A in a little methanol was treated with an ethereal solution of diazomethane prepared from 4.0 g. (40 mmol.) of nitrosomethylurea. A benzene solution of the crude product was adsorbed on a small amount of active alumina. Benzene eluted 342 mg. (82%) of yellow crystals, which, after recrystallization from petroleum benzine, melted at 114∼115.5°C. λ_{max} 230 (4.17), 383 (4.21). ν_{max} 1533, 1347, 851 (NO_2).

Found: C, 63.58; H, 4.77; N, 8.36. Mol. wt. (Barger) 325±25. Calcd. for $C_{18}H_{16}O_5N_2$: C, 63.52; H, 4.74; N, 8.23%. Mol. wt. 340.

Elution with 50 cc. of benzene containing one drop of ethanol gave 44 mg. of dehydro-compound A methyl ether m. p. 127°C (see below).

b) With Dimethyl Sulfate and Potassium Carbonate.—A mixture of 1.6 g. (4.7 mmol.) of crude compound A, 1.0 g. (7.9 mmol.) of dimethyl sulfate, and 1.1 g. (8.0 mmol.) of potassium carbonate in 20 cc. of acetone was refluxed for 20 min. The insoluble substances were then removed by filtration, and the acetone was evaporated under reduced pressure to give a viscous oil.[11] The oil was purified in the way described in a) to give a quantitative yield of the methyl ether m. p. 113∼115°C and a trace of dehydro-compound A methyl ether, m. p. 127°C.

Compound A Ethyl Ether.—A mixture of 3.3 g. (10 mmol.) of crude compound A, 1.6 g. (10 mmol.) of diethyl sulfate, and 1.4 g. (11 mmol.) of potassium carbonate in 50 cc. of acetone was refluxed for one hour. The reaction mixture was worked out in a way similar to that described in methylation b). Chromatographic purification gave 3.4 g. (94%) of the ethyl ether, which was recrystallized from ether m. p. 117∼118°C.

8) All melting points are uncorrected. Unless otherwise noted, ultraviolet spectra were taken in ethanol and infrared spectra, in Nujol mull; Peak positions and intensities are expressed in λ_{max} mμ (log ε) and in ν_{max} cm^{-1}, respectively. The authors are much indebted to Mr. Jun'ichi Gōda and his associates for their elementary analyses and to Mrs. Michino Butsugan and Miss Hiromi Tokuda for their infrared determinations for this series of papers.

9) A considerable amount of compound A was extracted by aqueous sodium bicarbonate because of its acidity.

10) E. J. Eisenbraun, S. M. McElvain and B. F. Aycock, *J. Am. Chem. Soc.*, **76**, 607 (1954). The measurement was carried out by Dr. Akira Fujino, to whom the authors are indebted.

11) Superheating during the evaporation caused a severe resinification that made it impossible to obtain the methyl ether.

Found: C, 64.13; H, 4.89; N, 8.16. Calcd. for $C_{19}H_{18}O_5N_2$: C, 64.40; H, 5.12; N, 7.91%.

Dehydro-compound A.—To a warm solution of 4.0 g. (12 mmol.) of crude compound A in 150 cc. of a 2% sodium hydroxide solution was added 20 cc. of 30% hydrogen peroxide. The mixture was then stirred well and allowed to stand overnight to from a yellowish gel. The crystal-cake formed on acidification with 20% hydrochloric acid was crushed, collected by filtration, washed successively with water and ethanol, and then dried. Dehydro-compound A (3.5 g.) was recrystallized from chloroform and ligroin to give faintly grayish prisms melting at 226~227°C. This compound is rather unstable to light. λ_{max} 234 (4.60), 358 (3.85). ν_{max} 3145 (OH), 1675, 1600 (C=O), 1517, 1340 (NO_2).

Found: C, 63.44; H, 3.78; N, 8.79. Calcd. for $C_{17}H_{12}O_5N_2$: C, 62.96; H, 3.73; N, 8.64%.

Dehydro-compound A Methyl Ether.—A mixture of 470 mg. (1.44 mmol.) of dehydro-compound A, 0.2 g. (1.5 mmol.) of dimethyl sulfate, and 0.22 g. (1.6 mmol.) of potassium carbonate in acetone was refluxed for one hour. The removal of the insoluble material by filtration, followed by the evaporation of the solvent in vacuo, left crystals, which were then chromatographed on a short column of active alumina in benzene to give a quantitative yield of the methyl ether. After recrystallization from benzene-ligroin, it melted at 129.5~130°C. λ_{max} 230~231 (4.58), 285~287 (4.05), 350~352 (3.78). ν_{max} 1684, 1647 (C=O), 1534, 1355 (NO_2).

Found: C, 63.94; H, 4.25; N, 8.34. Calcd. for $C_{18}H_{14}O_5N_2$: C, 63.90; H, 4.17; N, 8.28%.

The Periodic Acid Oxidation of Compound A Methyl Ether.—A mixture of 500 mg. (1.47 mmol.) of compound A methyl ether, 380 mg. (1.42 mmol.) of sodium periodate, and 1.44 mg. of sulfuric acid in 9 cc. of dioxane was left to stand at room temperature for six days. The addition of water, followed by the evaporation of the solvent under reduced pressure, was repeated to remove the dioxane. The resulting aqueous solution was then extracted with ether-benzene, and the extract was washed with aqueous sodium bicarbonate and dried. The evaporation of the solvent under reduced pressure and the chromatography of the residue on active alumina gave 188 mg. of dehydro-compound A methyl ether, which, after recrystallization from benzene-ligroin, metled at 129.5~130°C. A mixed melting point determination with an authentic samle of the methyl ether showed no depression.

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