

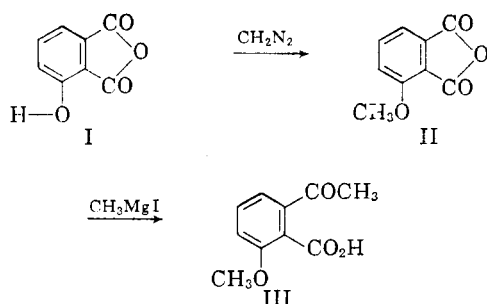
[CONTRIBUTION FROM THE INSTITUTE OF CHEMISTRY, THE UNIVERSITY, GLASGOW]

Reaction of Diazomethane with Some Anhydrides of *o*-Dicarboxylic AcidsASHARAM BHATI¹

Received October 9, 1961

Diazomethane gives, on reaction with substituted phthalic anhydrides, keto-lactones of the type XXV, and not the expected diazo-keto-esters. However, succinic anhydride and diazomethane lead to the normal product, XX. The mechanism of the reaction is described.

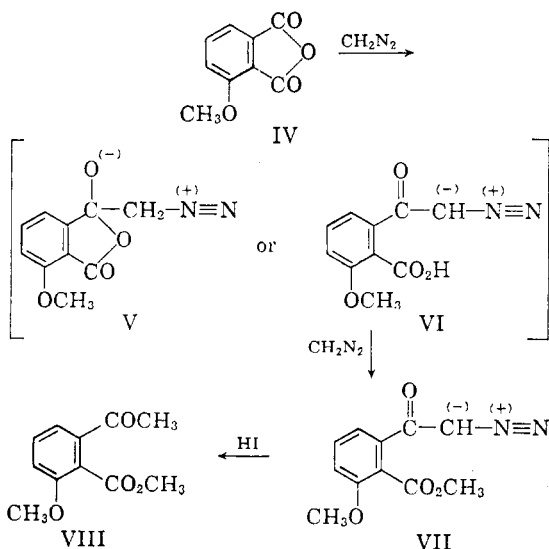
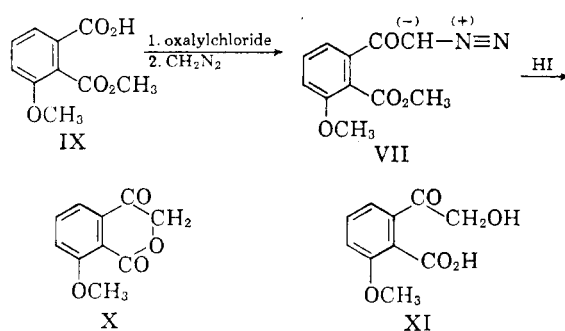
During the study of tetracyclic antibiotics the author attempted to prepare the methyl ether III of one of the degradation products of terramycin, according to the following scheme:



However, the methylation of *o*-hydroxyphthalic anhydride I with diazomethane gave a mixture containing an unstable nitrogenous by-product. A reference to the literature revealed that diazomethane reacts with carboxylic anhydrides; e.g., in 1930 Bradley and Robinson² had obtained α -diazoacetophenone and methyl benzoate from the reaction of diazomethane with benzoic anhydride. Recently, Tarbell and Price³ have reported the formation of diazo ketones from mixed carboxylic-carbonic anhydrides. By analogy to these examples one would expect *o*-methoxyphthalic anhydride to give (2-carbomethoxy-3-methoxy)- α -diazoacetophenone which on treatment with hydriodic acid⁴

could give the methyl ester VIII of the desired product III as outlined previously.

Hence the reaction of diazomethane with *o*-methoxyphthalic anhydride was closely studied. The reaction, which was fairly slow, yielded a crystalline solid along with the expected diazo keto ester VII. The crystalline compound, which is free from nitrogen, reduced Fehling's solution in the cold and gave analysis agreeing with $\text{C}_9\text{H}_5\text{O}_4$. It shows in the infrared (CHCl_3) two strong CO bands at 1725 cm^{-1} (aryl ester or lactone) and 1680 cm^{-1} (aryl ketone), 1285 cm^{-1} (aryl ester or lactone $-\text{C}-\text{O}-$), and in the ultraviolet ($\text{C}_2\text{H}_5\text{OH}$) maxima at $223\text{ m}\mu$ (ϵ 22,400), $254-258\text{ m}\mu$ (ϵ 5138) and $338\text{ m}\mu$ (ϵ 4148). These data suggested that the compound is 8-methoxy-1,4-isochroman-dione (X), which is the lactone of 6-glycolyl-*o*-anisic acid (XI).⁵ The same compound was obtained in the following way, which represents its synthesis.



As treatment of the diazo keto ester VII led to the keto lactone X and not the expected keto ester VIII, the stated aim of the investigation could not be achieved. The failure is to be attributed to the preferential reaction of the intermediate carbonium ion XII with the carbomethoxyl oxygen. Similar carbonium ion reactions must be involved

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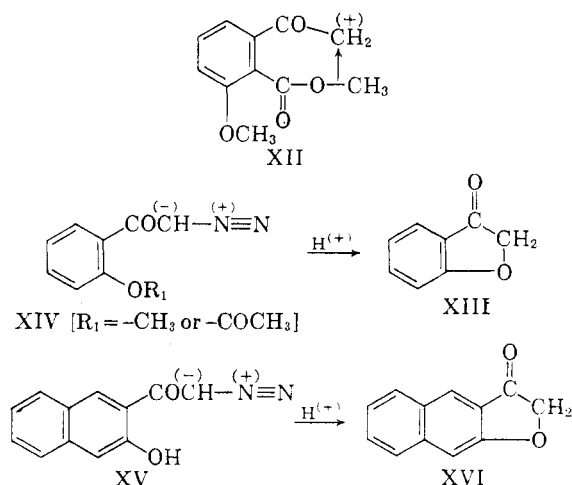
(2) W. Bradley and R. Robinson, *J. Am. Chem. Soc.*, **52**, 1558 (1930).

(3) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).

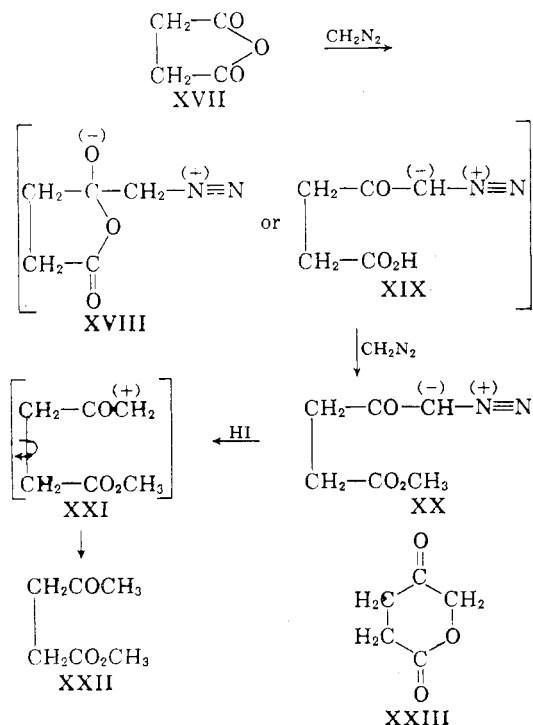
(4) M. L. Wolfrom and R. L. Brown, *J. Am. Chem. Soc.*, **65**, 1516 (1943).

(5) I am grateful to the nomenclature director (Dr. Leonard T. Capell) of *Chemical Abstracts* for naming this and other similar compounds mentioned in this paper.

in the formation of coumaranone⁶ (XIII) from (*o*-methoxy- or *o*-acetoxy)- α -diazooacetophenone (XIV); and naphthofuran-3-one (XVI) from α -diao(3-hydroxy-2-)acetophenone (XV). From *o*-nitrophthalic anhydride and diazomethane the 8-nitro-1,4-isochromandione along with the expected (2-carbomethoxy-3-nitro)- α -diazooacetophenone was isolated. Evidence has been collected to show that simple phthalic anhydride behaves similarly.

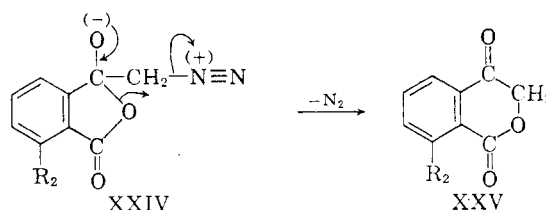


Among other factors, the steric environment and the rigidity of the molecule indeed govern the course of this reaction. Thus in the reaction of succinic anhydride the intermediate carbonium ion XXI, by virtue of the inherent free rotation about the bond connecting the two methylene groups, can to some extent⁸ avoid reaction with its



carbomethoxy oxygen. The normal product (XXII) has been isolated by treating the diazo keto ester XX with hydriodic acid. Diazomethane has been found to be indifferent toward *dl*-camphoric anhydride.

The origin of the 8-methoxy- and 8-nitro-1,4-isochromandione from the corresponding substituted phthalic anhydrides and diazomethane alone (*i.e.*, without the use of any proton source, *e.g.*, HI) shows that the primary reaction product (XXIV. $R_2 = OCH_3$ or NO_2) eliminates a nitrogen molecule and directly leads to these compounds (XXV. $R_2 = OCH_3$ or NO_2) as shown:



EXPERIMENTAL

Freshly sublimed anhydrides were used. The diazomethane was prepared from nitrosomethylurea and aqueous alkali in pure ether. The ethereal solution was dried (potassium hydroxide) and then distilled. The amount of diazomethane in the distillate was estimated by reaction with benzoic acid in the known way. All melting points are uncorrected. The ultraviolet measurements were done on a Unicam SP 500 spectrophotometer and the infrared measurements on a Perkin-Elmer Infracord. The carbon-hydrogen estimations are by the departmental microanalyst, Mr. Cameron and his staff to whom the author is grateful.

(a) *Reaction of diazomethane with o-methoxyphthalic anhydride.* To *o*-methoxyphthalic anhydride (3.6 g.) dissolved in dry tetrahydrofuran (150 ml.), diazomethane (2.53 g.) in 93 ml. of ether was added at 0°. There was no visible reaction. The homogeneous solution was allowed to stand at 0–5° for about a week. The yellowish white crystals which had separated were removed, washed with a little petroleum ether b.p. (40–60°) and then dried at 40–50°/0.1 mm., m.p. 165–167°.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.17. Found: C, 62.34; H, 4.17.

The mother liquor, left after the removal of the crystals, was freed from the solvents and excess diazomethane *in vacuo* at $\sim 20^\circ/4$ mm., and the residual yellow oily gum, containing some solid (unchanged anhydride from its melting point and infrared spectrum) was treated with ice-cold anhydrous ether and the supernatant solution was decanted. The yellow oil, obtained on removal of ether, showed in the infrared (film), among others, the following characteristic absorption bands: 2100 cm^{-1} (strong, $-N\equiv N-$), 1840 and 1770 cm^{-1} (strong, $-CO-O-CO-$, contaminating anhy-

(6) E. R. Marshall *et al.*, *J. Org. Chem.*, **7**, 444 (1942); N. Pailt and J. N. Chatterjea, *Sci. and Culture* (Calcutta), **17**, 345 (1952); U. S. Seth and S. S. Deshapande, *J. Ind. Chem. Soc.*, **27**, 429 (1950); P. Pfeiffer and E. Enders, *Ber.*, **84**, 247 (1951); A. K. Bose and P. Yates, *J. Am. Chem. Soc.*, **74**, 4703 (1952).

(7) H. Kerzickalla and B. Eistert, *J. prakt. Chem.*, **143**, 55 (1935). See also G. Haberland and H. Siegert, *Ber.*, **71**, 2619 (1938).

(8) As the reaction product (*cf.* experimental part of ref. 2) reduces Fehling's solution there is reason to believe that compound XXIII is also formed.

dride), 1715 cm^{-1} (strong, aryl ester CO), 1620 cm^{-1} (strong, diazoketone CO),¹¹ 1280 cm^{-1} (strong, aryl ester C—O—).

(b) *Synthesis of 8-methoxy-1,4-isochromandione.* To 2-carbomethoxy-3-methoxybenzoic acid (IX) (1.34 g.) [prepared by the partial hydrolysis of dimethyl *o*-methoxyphthalate with alkali], dry tetrahydrofuran (5 ml.), and oxalyl chloride (8 ml.) were added at 0°. After the brisk evolution of the gases had ceased the mixture was allowed to stand at room temperature for 40 hr. The solvent and excess oxalyl chloride were removed at $\sim 45^\circ/1$ mm. and the acid chloride, [which showed two strong CO bands at 1770 cm^{-1} (acid chloride) and 1720 cm^{-1} (aryl ester), dissolved in dry tetrahydrofuran (15 ml.)], was added in 30 min. to diazomethane solution (5.1 g. of diazomethane in 300 ml. of ether) under cooling with a freezing mixture. The mixture was allowed to stand in a "dry-cold" bath for 1 hr. A very small amount of a white solid (Compound X, from its melting point and infrared spectrum) which had separated was filtered off, and the filtrate freed from the solvents and excess diazomethane at $\sim 25^\circ/1$ mm. The residue comprised a small amount of *o*-methoxyphthalic anhydride and the expected diazo keto ester VII. The infrared spectrum was identical with that of the yellow oil mentioned under (a). The anhydride, which is difficultly soluble in ether, was removed by treatment with cold ether. The yellow oil so obtained was taken up in chloroform (30 ml.) and the solution shaken with 48% hydriodic acid (2.5 ml.) until the evolution of nitrogen ceased. The dark red chloroform solution was successively washed with water, 5% sodium thiosulfate, and water, dried, and the chloroform distilled off *in vacuo*. The resultant solid was identical in melting point, mixed melting point, infrared and ultraviolet spectra, with the crystalline compound X mentioned under (a).

(c) *Reaction of diazomethane with *o*-nitrophthalic anhydride.* To *o*-nitrophthalic anhydride (1.79 g.), dissolved in dry tetrahydrofuran (25 ml.) was added ethereal diazomethane (43.8 ml., containing 1.26 g. of diazomethane) at 0°. A crystalline compound and the expected diazo keto ester were isolated in the same way as described under (a). The crystalline solid, m.p. 172–175° dec. showed in the infrared potassium chloride disk no band at 2100 cm^{-1} (absence of —N≡N—) but it possessed, among others, two strong CO bands at 1725 cm^{-1} (aryl ester or lactone), 1690 cm^{-1} (aryl ketone), 2900 and 1460 cm^{-1} (—CH₂—), 1540 cm^{-1} (NO₂), and 1285 cm^{-1} (aryl ester C—O—). In the ultraviolet (C₂H₅OH) it exhibits a maximum at 250 μ (ϵ 5995). It reduces Fehling's solution in the cold.

Anal. Calcd. for C₉H₅O₅N: C, 52.18; H, 2.47. Found: C, 52.59; H, 2.76.

The diazo keto ester, obtained from the mother liquor, possessed among others the following bands in the infrared (film): 2090 cm^{-1} (strong, —N≡N—), 1725 cm^{-1} (strong, aryl ester CO), 1625 cm^{-1} (medium, diazo ketone CO),¹¹ 1525 cm^{-1} (strong, NO₂) and 1280 cm^{-1} (strong, aryl ester C—O—). This diazo compound, like the other similar ones mentioned in this paper, was unstable. It could not, therefore, be purified and consequently no analysis is given.

On the whole the reaction was faster than that with *o*-methoxyphthalic anhydride.⁹

(d) *Reaction of diazomethane with phthalic anhydride.* To phthalic anhydride (4.7 g.) dissolved in dry tetrahydrofuran (40 ml.) was added diazomethane (4.7 g.) solution in ether (150 ml.) at 0° and the mixture was left at 0–5°. No free crystalline solid separated as in the previous two cases. After 56 hr. a portion of the reaction mixture was freed from the solvents and excess diazomethane by distillation *in vacuo* at $\sim 40^\circ/0.2$ mm. The residual product consisting of a solid

(unchanged anhydride) and a yellow oil which showed in the infrared (film), among others, the following bands (all strong): 2100 cm^{-1} (—N≡N—), 1850 and 1770 cm^{-1} (unchanged anhydride), 1725 cm^{-1} (CO of aryl ester), 1620 cm^{-1} (CO of diazo ketone),¹¹ 1280 cm^{-1} (aryl ester C—O—). The infrared spectrum was almost identical with that of the diazo keto ester prepared from methyl hydrogen phthalate in the same way as described under (b). This reaction mixture, dissolved in chloroform (25 ml.), was treated with hydriodic acid (1 ml.) and the resultant product (0.435 g.), isolated, as described under (b), was still found to contain the unchanged anhydride. On chromatography over silica gel a fraction, m.p. 95–115°, was obtained. This showed in the infrared (Nujol) the characteristic bands of the adhering anhydride along with two strong CO bands at 1725 (aryl ester or lactone) and 1680 cm^{-1} (aryl ketone) and at 1280 cm^{-1} (aryl ester C—O—). The product reduced Fehling's solution in the cold. Attempts to remove the anhydride by converting it into the methyl hydrogen phthalate by boiling with absolute methanol and then washing with alkali did not give promising results.

*Reaction of diazomethane with succinic anhydride.*¹⁰ (a) To the freshly sublimed anhydride (3.90 g.), dissolved in dry tetrahydrofuran (100 ml.), the potassium hydroxide-dried ethereal diazomethane solution (775 ml., containing 2.15 molar equivalents of diazomethane) was added at 0°, and the reaction mixture was protected with a calcium chloride guard tube and allowed to stand at $\sim 5^\circ$. There was no immediate reaction. As even after 3 days no appreciable reaction had taken place (as seen by the infrared spectrum of a part of the reaction mixture), the mixture was allowed to stand at the same temperature for about a fortnight, at the end of which a colorless solution containing a fluffy material (polymethylene) was obtained. The mixture was filtered and the filtrate was freed from the solvents, the residue consisting of a solid (unchanged anhydride) and a slightly yellowish liquid, showed in the infrared the following characteristic bands: 2100 cm^{-1} (weak) (—N≡N—); 1860 and 1775 cm^{-1} (strong) (anhydride), 1730 cm^{-1} (strong) (ester CO), 1640 cm^{-1} (weak) (diazo ketone CO).¹¹ The major product was dimethyl succinate which was obtained by fractionating the reaction product, and it was identified from its boiling point, and from its infrared spectrum which was identical with that of an authentic sample.

(b) In this experiment the concentrations of the reactants were kept as high as possible. To the freshly sublimed succinic anhydride (3.03 g.), dissolved in dry tetrahydrofuran (50 ml.), the thoroughly dried and distilled solution of diazomethane (about 3.1 molar equivalents in 275 ml. of ether) was added at 0°. Some of the anhydride was precipitated from the solution. The heterogeneous mixture was allowed to react at $\sim 5^\circ$. After 6 days the solvents and excess of diazomethane were removed at $\sim 20^\circ/40$ mm. The residual semi-solid mass was treated with ice-cold anhydrous ether (2 × 250 ml.) and the supernatant yellow solution was freed from the insoluble solid (1.1 g., m.p. $\sim 122^\circ$, mostly the unchanged anhydride from its melting point and infrared spectrum). The supernatant yellow ethereal solution was passed through a silica gel column (15 cm. × 1 sq. cm.) and eluted with pure ether. Four fractions (~ 200 ml. each) were collected. In the infrared spectra, all the fractions showed weak anhydride bands at 1860 and 1775 cm^{-1} , but there was a strong diazo band at 2100 cm^{-1} , an ester CO at 1720 cm^{-1} , and a diazo ketone CO band¹¹ at 1630 cm^{-1} , indicating no separation. Hence the four fractions were combined and the yellowish mobile oil (2.0 g.), so obtained, was taken up in chloroform

(10) This reaction was carried out by using (a) ethereal diazomethane which was just dried over caustic potash (b) an absolutely dried and distilled solution of diazomethane. The aim of these two experiments and the bearing of the results will be described later in a communication entitled, "The Reaction of Diazomethane with Water."

(11) P. Yates *et al.*, *J. Am. Chem. Soc.*, **79**, 5756 (1957).

(9) This inference is based on a spectroscopic study of the two reaction mixtures—*e.g.*, by comparing the time of appearance of the diazo-band in the infrared, and also by the comparison of the peak heights of this band at regular intervals.

(75 ml.) and then shaken with constant boiling hydriodic acid (10 ml.). When the evolution of nitrogen had ceased, the resultant dark red chloroform solution was removed and successively washed with water (3 × 50 ml.), saturated sodium thiosulfate solution (50 ml.), saturated sodium bicarbonate solution (50 ml.), and again with water (50 ml.). On drying (Na_2SO_4) and removal of the solvent, a yellowish white mobile oil (1.70 g.) was obtained. It no longer showed the diazo, the diazocarbonyl or the anhydride bands. The infrared spectrum is in fact a composite picture of dimethyl succinate and methyl levulinate. In this connection it is interesting to note that the carbonyl CO and the ester CO of an authentic sample of methyl levulinate (prepared from levulinic acid and diazomethane) show in the infrared (film) spectrum only a single band (strong and somewhat broad) at 1725 cm^{-1} . The above oil gave a 2,4-dinitrophenylhydrazone, (0.21 g., crude: m.p. $\sim 130^\circ$) which crystallized from ethanol into shiny orange-yellow platelets,

m.p. 133° , mixed melting point with the authentic sample of the 2,4-D.N.P. of methyl levulinate was the same. The infrared spectra of the two dinitrophenylhydrazones are also identical. The material left after the removal of the 2,4-D.N.P. was worked up in the usual way and dimethyl succinate was isolated. The remaining products of reactions were not examined.

As the investigation was only incidental to the author's main work on the tetracyclines, and as it did not yield the desired results, the study was not further pursued. For the same reason yields of the reaction products are not specified.

Acknowledgment. The author thanks the University Court and Professor R. A. Raphael for the award of a Pfizer Research Fellowship.

GLASGOW W. 2., SCOTLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

α -Halo Ketones. I. The Reaction of 2 α ,4 α -Dibromocholestan-3-one with *N,N*-Dimethylaniline¹

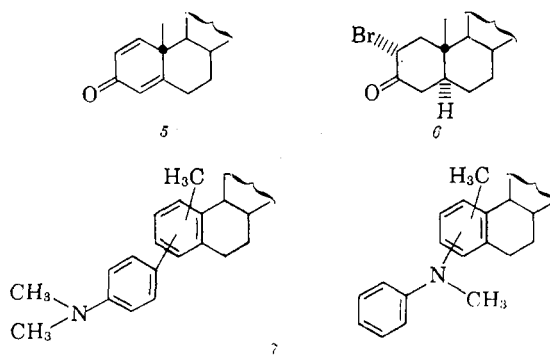
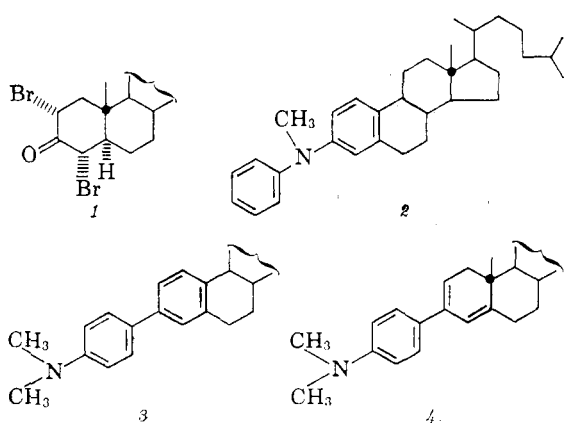
E. W. WARNHOFF AND PAETONG NANONGGAI²

Received November 20, 1961

The product obtained earlier from reaction of the title compounds at *ca.* 200° has been shown to be the conjugated indole (17). The first step in the reaction sequence is apparently dehydrobromination to 2 α -bromo- Δ^4 -cholesten-3-one (23) and dimethylaniline hydrobromide which reacts with dimethylaniline to give *N*-methylaniline and phenyltrimethylammonium bromide. The indole (17) could result from reaction of *N*-methylaniline with (23) or one of its transformation products. Several indoles incorporating the steroid nucleus have been prepared and evidence for their structures is presented.

In 1937 Schwenk and Whitman³ while studying the dehydrobromination of bromo-3-keto steroid derivatives refluxed 2 α ,4 α -dibromocholestan-3-one (1) with *N,N*-dimethylaniline (b.p. 193°). A crystalline product, m.p. 230 – 232° , whose analysis corresponded to $\text{C}_{33-34}\text{H}_{47-49}\text{N}$, was isolated in small

yield. The compound in alcohol-acetic acid solution was reported to give a red color with *p*-nitrobenzenediazonium ion and was presumed to be an amine for which three structures 2, 3, and 4 were tentatively suggested. Although dehydro-



(1) Taken in part from a thesis presented by Paetong Nanonggai to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree Master of Science.

(2) On leave of absence from Chulalongkorn University, Bangkok, Thailand.

(3) E. Schwenk and B. Whitman, *J. Am. Chem. Soc.*, **59**, 949 (1937).

bromination of 1 would give dimethylaniline hydrobromide, a fairly strong acid in refluxing dimethylaniline, the loss of an angular methyl group required by 2 or 3 seemed unlikely under the relatively mild reaction conditions. From experience with the acid-catalyzed and thermal reactions of $\Delta^{1,4}$ -3-keto dienones (5), loss of a methyl group is observed only under pyrolysis at 325 – 600° .⁴ Formula 4 or a double bond isomer was more reasonable since Schwenk and Whitman also observed