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The Reaction of Aminotropones with Diketene. II. The Structure of the By-product in the Reaction of 5-Aminotropolone with Diketene

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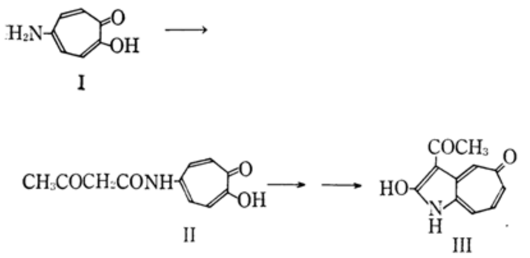
The reaction of 5-aminotropolone with diketene gave a minor product and 5-aceto acetamidotropolone, which had previously been described (K. Ogura et al., This Bulletin, **38**, 306 (1965)). This unknown compound was obtained as a main product when 5-acetoacetamidotropolone was treated with diketene in the presence of triethylamine. From its oxidative degradation and its NMR spectrum, this compound was proved to be 3-acetyl-4-hydroxy-6-methyl-1-(tropolon-5′-yl)pyridone-2. Furthermore, for the sake of the structural determination, 3-acetyl-4-hydroxy-6-methylpyridone-2 and its deacetylated product were prepared.

In the previous paper of this series, it was reported that the reaction products of aminotropones with diketene were useful for the synthesis of 3-acetyl derivatives of 1-azaazulan-2-one and their related compounds. For example, the reaction of 5-aminotropolone (I) with diketene gave 5-acetoacetamidotropolone (II), which could then be converted into 3-acetyl-2-hydroxycyclohepta-[b]pyrrol(1*H*)-5-one (III).¹⁾



I

II

III

The present authors have since examined the reaction of I with diketene in more detail, and found that another product, IV, was a by-product in this reaction. This paper will concern the structure of the compound IV.

The mixture of the reaction products obtained by the treatment of I with a large excess of diketene was separated by recrystallization into II and IV, the yields of which were 65 and 10% respectively. The compound IV was considered to be a *N*, *N*-disubstituted derivative of I from the fact that its ultraviolet absorption spectrum is of the *N*-acylaminotropolone type and from its infrared absorption spectrum. It shows a broad band at 3200 cm^{-1} due to the hydroxyl group and two bands at 1660 and 1625 cm^{-1} for the carbonyl groups in the chloroform solution. The NMR spectrum of IV in deuterochloroform exhibits signals for a methyl group attached to the double bond (2.04), an acetyl group (2.61), aromatic protons of the tropolone ring (near 7.2), and two signals for hydroxyl groups at 9.00 and 16.10 p.p.m. (with tetramethylsilane as a standard). The signal at the lower field (16.10) can be attributed to the enolic hydroxyl group, which is strongly chelated with the carbonyl group, while the higher one (9.00 p.p.m.) corresponds to the hydroxyl group of tropolone.

The treatment of IV with diazomethane gave a monomethyl ether (V). In the NMR spectrum of V, a new signal, at 3.97 p.p.m., for the methoxyl

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1) K. Ogura, H. Sasaki and S. Seto, This Bulletin, **38**, 306 (1965).

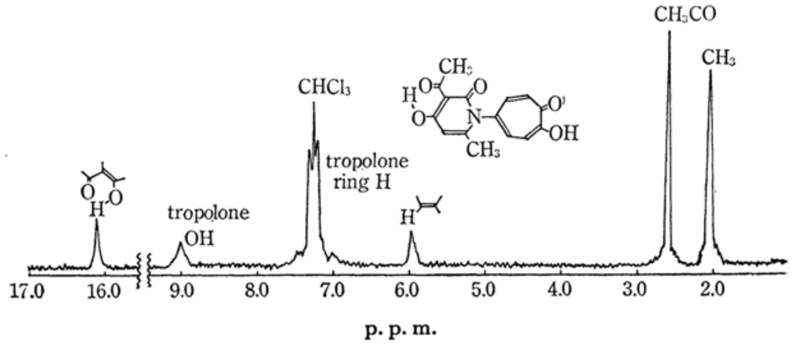
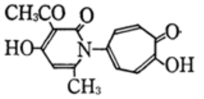


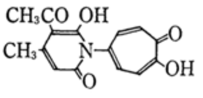
Fig. 1. NMR spectrum of IV in $CDCl_3$.

group appears instead of the hydroxyl group of tropolone in IV, while the signal for the enolic hydroxyl group is still observed at 15.90 p. p. m., indicating that V is the 2-methoxytropone derivative.

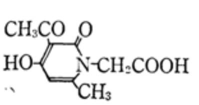
These facts and the elemental analysis of IV corresponding to $C_{15}H_{13}O_5N$ suggest that IV has a pyridone moiety formed by the addition of II to another molar equivalent of diketene, followed by dehydration. Two kinds of pyridone derivatives, the 4-hydroxy type (IVa) and the 6-hydroxy type (IVb), can be expected, according to the manner of addition. Garatt and Shemin reported that the reaction of glycine with diketene in the alkaline solution gave no *N*-acetoacetylglycine, but it did give 3-acetyl-1-carboxymethyl-4-hydroxy-6-methylpyridone-2 (VI).²⁾ Kato also obtained the corresponding pyridone derivative from 4-aminopyridine.³⁾



IVa



IVb



VI

Our spectral data for compound IV mentioned above correspond well with those for VI obtained by Garatt; IV seems to be 3-acetyl-4-hydroxy-6-methyl-1-(tropolon-5′-yl)pyridone-2 (IVa) by analogy. These data alone, however, can not exclude another structure (IVb), so the following experiments were carried out in order to determine the structure precisely.

The oxidation of IV with potassium permanganate gave colorless needles (VII). The fact that VII has an absorption maximum at 326 mμ indicates that VII is no longer a tropolone derivative, but a pyridone derivative which is probably a key compound for the structural determination of IV. The same compound VII could be obtained by the reaction of acetoacetamide with diketene in the presence of triethylamine. The infrared spectrum exhibits complicated bands in the region 3200—2500 cm⁻¹ and ν_{CO} bands at 1670 and 1625 cm⁻¹. The NMR spectrum of VII in deuterodimethylsulfoxide indicates the existence of an enolic hydroxyl group (15.65) which chelates strongly with the acetyl group (2.50 p.p.m.).

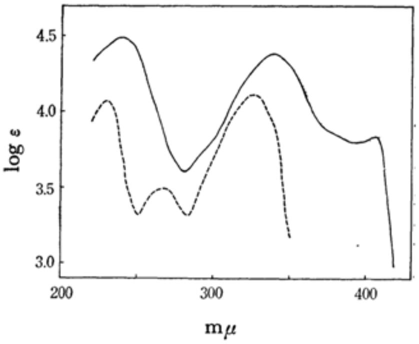


Fig. 2. Ultraviolet spectra of IV (——) and VII (----) in methanol.

The ultraviolet spectrum and the chemical behavior of both 4-hydroxy- and 6-hydroxypyridone-2 are known through the literature,⁴,⁵⁾ but no data on their acyl derivatives have yet been reported. It is also known that the treatment of dehydroacetic acid (VIII) with ammonia gives 4-lutidone (IX) and that 4-hydroxy-6-methylpyrone-2 (X) obtained from VIII, on treatment with ammonia, is converted into the corresponding pyridone derivative XI.⁶,⁷⁾ The present authors examined these reactions and obtained compound XI, whose structure was confirmed by

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2) S. Garatt and D. Shemin, *J. Org. Chem.*, **28**, 1372 (1963).

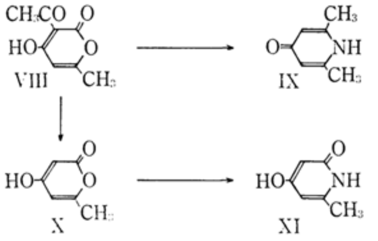
3) T. Kato, H. Yamanaka, T. Niitsuma, K. Wagatsuma and M. Oizumi, *Chem. Pharm. Bull.*, **12**, 910 (1964).

4) H. J. den Hertog and D. J. Buuman, *Rec. Trav. Chim.*, **75**, 257 (1956).

5) L. Gattermann and A. Skita, *Ber.*, **49**, 495 (1916).

6) R. C. Elderfield, "Heterocyclic Compounds," John Wiley & Sons, New York and London (1959), p. 528.

7) M. A. Butt and J. A. Elvidge, *J. Chem. Soc.*, **1963**, 4483.



a study of its ultraviolet, infrared and NMR spectra. Thus, the removal of the acetyl group from the compound VII was desirable for the elucidation of the structure.

The deacetylation of VII was successful in affording colorless crystals, crystals which a comparison of the ultraviolet and infrared absorption spectra showed to be quite identical with IX. The compound XI shows an absorption maximum at 283 mμ in methanol and at 265 mμ in the acidic solution.

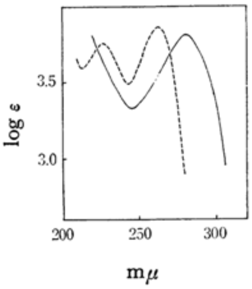


Fig. 3. Ultraviolet absorption spectra of XI in methanol (——), and in 0.1 N HCl - methanol (----).

The NMR spectrum of XI in deuterodimethylsulfoxide exhibits a doublet (*J*, 2.5 c.p.s.) at 5.34 p.p.m. for the proton in the 3-position and a multiplet at 5.58 p.p.m. for the proton in the 5-position.

This identification undoubtedly indicates that the by-product IV is 3-acetyl-4-hydroxy-6-methyl-1-(tropolon-5′-yl)pyridone-2 (IVa). Furthermore,

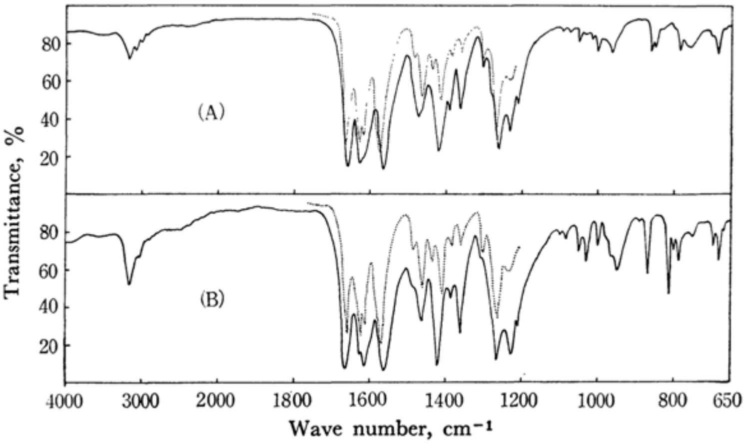


Fig. 4. Infrared absorption spectra of IV (crystals A and B) in KBr disk (——) and in chloroform solution (----).

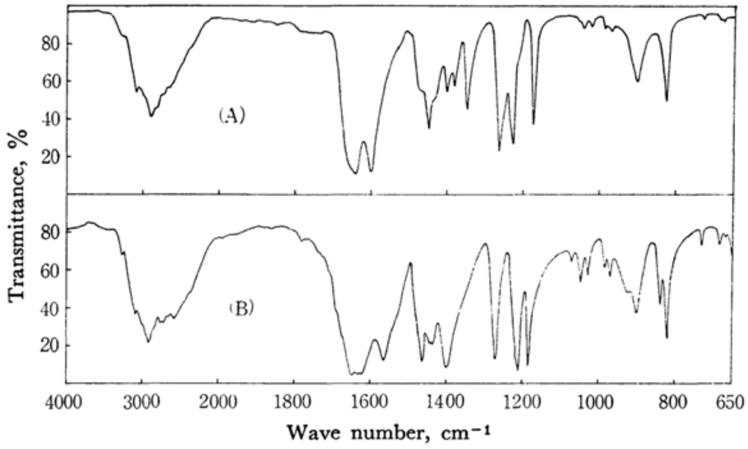
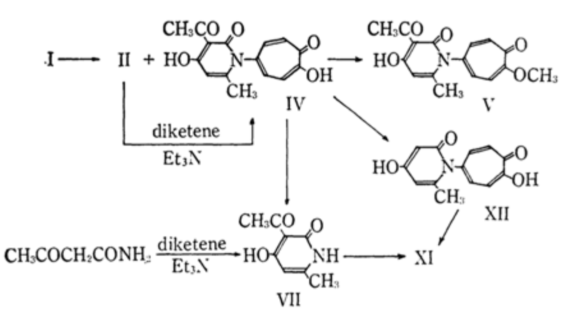


Fig. 5. Infrared absorption spectra of XI (crystals A and B) in KBr disk.

it was found that the treatment of IV with sulfuric acid gave the deacetylated compound XII, from which XI was also obtained, though in such a low yield that identification was possible only by a means of comparison of the ultraviolet absorption spectrum in both methanolic and acidic solutions.

The treatment of II with an equivalent amount of diketene in benzene resulted only in the recovery of II. However, IV could be obtained in a good yield when a small amount of triethylamine was added to the above reaction mixture. The reaction of I with diketene in the presence of triethylamine gave IV directly and exclusively. These facts suggest that, in the reaction of I and diketene in the absence of triethylamine, 5-aminotropolone (I) itself acts as a catalyzer to give a small amount of IV.



The compound IV has two crystalline forms (A and B), which are convertible into one other. These two forms exhibit slightly different infrared absorption spectra in the solid state, as is shown in Fig. 4, but their spectra in the solution, as well as their ultraviolet and NMR spectra, are quite identical. Analogous phenomena are observed also in the case of the compound XI. The infrared spectra of the two forms (A and B) of XI are shown in Fig. 5.

Experimental*

3-Acetyl-4-hydroxy-6-methyl-1-(tropolon-5′-yl)-pyridone-2 (IV).—a) A solution of I (4 g.) in diketene (20 ml.) was heated at 80°C for 1 hr. The yellow crystalline mixture that separated out on cooling was then collected. The recrystallization of this mixture from methanol-chloroform gave a major product, II (4.2 g.), which had been already reported in our previous paper,1) and pale yellow crystals (IV). Yield, 850 mg. The repeated recrystallization of IV from methanol-chloroform gave two forms of crystals, A (globules) and B (prisms). Both A and B decomposed at 250 °C, and no depression of the mixed melting point was observed. The crystals A, when recrystallized from their methanol-chloroform solution by adding tiny crystals of B as seed, were converted into crystals B. The crystals B, however, were easily changed again to A by the acidification of the alkaline solution of B.

b) A suspension of I (500 mg.) in dry benzene (10 ml.), with a catalytic amount of triethylamine added, was stirred at 80°C, while a solution of diketene (680 mg.) in dry benzene (5 ml.) was being dropped into the suspension over a 30 min. The mixture was then kept at the same temperature while being stirred for 1 hr. During this reaction the crystals of I gradually dissolved, and orange crystals newly appeared. The crystals were collected and recrystallized from methanol-chloroform to give IV. Yield, 300 mg.

c) A suspension of II (550 mg.) in dry benzene (10 ml.), with one drop of triethylamine added, was heated at 80°C and stirred, while a solution of diketene (450 mg.) in dry benzene (5 ml.) was being added, drop by drop, to the suspension over a 1 hr. Then the mixture was stirred at 80°C for 2 hr. The crystals that separated out on cooling were collected and recrystallized from methanol-chloroform to give IV. Yield, 500 mg. λ_{max}^{MeOH} mμ (log ε): 240(4.49), 340(4.39), 405(3.85).

Found: C, 62.55; H, 4.78; N, 4.11. Calcd. for $C_{15}H_{13}O_5N$: C, 62.71; H, 4.65; N, 4.56%.

3-Acetyl-4-hydroxy-6-methylpyridone-2 (VII). — a) To a mixture of IV (100 mg.) and a potassium hydroxide solution (potassium hydroxide, 70 mg.; water, 1 ml.), a potassium permanganate solution (potassium permanganate, 580 mg.; water, 15 ml.) was added slowly. After the addition of potassium permanganate solution had been completed, the manganese dioxide was removed by filtration. This filtrate was acidified with hydrochloric acid, adjusted to pH 3. After the water had been completely removed under reduced pressure, the residue was extracted with acetone. The evaporation of the acetone afforded colorless crystals, which were then collected and recrystallized from acetone to give colorless needles, m. p. 256°C (decomp.).

b) A suspension of acetoacetamide (1 g.) in dry benzene (20 ml.), with a catalytic amount of triethylamine added, was heated at 80°C while being stirred. After a solution of diketene (1.3 g.) in dry benzene (10 ml.) had been slowly added, the mixture was stirred at 80—85°C for an additional 1.5 hr. The precipitate that separated out on cooling was collected and recrystallized from acetone-methanol to give colorless needles (m. p. 256°C (decomp.)). Yield, 500 mg. λ_{max}^{MeOH} mμ (log ε): 260(4.07), 263(3.49), 326(4.11).

Found: C, 57.68; H, 5.30; N, 8.38. Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38%.

The Methylation of IV.—After ethereal diazomethane had been added to a suspension of IV (100 mg.) in methanol (10 ml.) until portions of the solution were no longer colored with ferric chloride, the mixture was allowed to stand at room temperature for 2 hr. The pale yellow crystals that separated out were collected and recrystallized from methanol to give V (225°C (decomp.)). Yield, 45 mg. λ_{max}^{MeOH} mμ (log ε): 230(4.52), 330(4.30).

Found: C, 63.51; H, 4.31; N, 4.91. Calcd. for $C_{16}H_{15}O_3N$: C, 63.78; H, 5.02; N, 4.65%.

The Deacetylation of IV.—A mixture of IV (500

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* All melting points are uncorrected. The microanalyses were carried out by Misses Yoko Endo and Noriko Matsukawa of this Institute, to whom the authors are indebted. The measurements of the ultraviolet and infrared absorption spectra were made with a Cary recording spectrophotometer model 14 and with a Hitachi EPI-S2 spectrophotometer respectively. The NMR spectra were measured in a deuterochloroform or deuterodimethylsulfoxide solution, using tetramethylsilane as an internal standard, on a Varian A-60 spectrometer.

mg.) and sulfuric acid (2 ml.) was heated at 200°C for 30 min.; then the mixture was poured into ice water. The colorless precipitate thereby obtained was recrystallized from methanol to give colorless crystals, m. p. 284—285°C (decomp.). Yield, 270 mg. $\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 206(4.55), 240(4.49), 290(3.81), 340(4.09).

Found: C, 63.75; H, 4.49; N, 4.93. Calcd. for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.52; N, 5.71%.

4-Hydroxy-6-methylpyridone-2 (XI).—a) After a mixture of VIII (2.0 g.) and 93% sulfuric acid (6 g.) had been allowed to stand at room temperature for 1 hr., the mixture was heated at 130°C for 7 min. When cracked ice was added into the reaction mixture, a pale yellow precipitate was immediately deposited. The recrystallization of this precipitate gave pale yellow crystals of X (1.9 g.), m. p. 183—184°C. A solution of X (350 mg.) in a 28% ammonium hydroxide solution (4 ml.) was heated on a water bath. The removal of an excess of ammonium hydroxide gave colorless crystals, which were then recrystallized from water to afford colorless needles, m. p. 320°C (decomp.). Yield, 50 mg.

b) A mixture of VII (200 mg.) and concentrated sulfuric acid (0.4 ml.) was heated at 180°C for 7 min. After it had been cooled, the mixture was poured into ice water and neutralized with a barium hydroxide solution. The barium sulfate that separated out was removed by filtration. When the filtrate was concentrated under reduced pressure, colorless needles of XI were obtained.

c) To a solution of XII (120 mg.) in a potassium hydroxide solution (potassium hydroxide, 90 mg.; water, 2 ml.), a potassium permanganate solution (potassium permanganate, 790 mg.; water, 20 ml.) was added slowly. After this addition had been completed, the manganese dioxide that precipitated out was removed by filtration and the filtrate was acidified with hydrochloric acid, adjusted to pH 3. After the water from the filtrate had been completely removed under reduced pressure, the residue was extracted with acetone. The evaporation of the acetone gave colorless crystals in a very poor yield. $\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 280(3.82). $\lambda_{max}^{\mathrm{MeOH-HCl}}$ mμ (log ε): 225(3.75), 263(3.86).

Found: C, 57.40; H, 5.42; N, 11.34. Calcd. for $C_6H_7O_2N$: C, 57.59; H. 5.64; N, 11.20%.

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