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Synthesis and Reaction of 3-Aminotropone[1]

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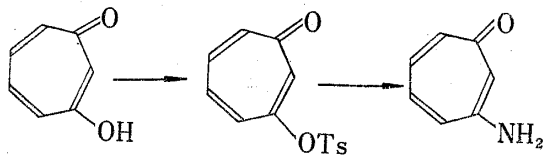
The synthesis of 3-aminotropone (III) which is one of the fundamental troponoid series aromatic compounds and has not never been synthesized was carried out, and optimal conditions of the ammonolysis of 3-tosyloxytropone (II) were taken in the following; solvent, isopropanol; reaction temperature, 45—50°; reaction time, about 80 min. It was found that bromination of III afforded 3-amino-2-bromotropone (IV) or known 2-bromo-3-hydroxytropone (V), depending on the conditions. The structure of IV was elucidated from a comparison of the NMR spectra of III and IV. Treatment of III with dimethyl sulfate gave 3-methoxytroponeimine (VI), which was isolated as picrate (VII). N-Acetyl derivative (VIII) of III was given by heating of III with acetic anhydride.

3-Aminotropone has been considered as one of the fundamental substances in the troponoid series aromatic compound, together with 2-,[3] 3-[4], and 4-hydroxytropone,[5] and 2-[6] and 4-aminotropone,[7] but its synthesis has never been carried out. In a previous work, 3-aminotropone was synthesized and its physical and chemical properties were reported as a brief communication.[8] The present paper is a detailed report on the synthesis of 3-aminotropone and its fundamental chemical reactions.

Synthesis of 3-Aminotropone

Reaction of 3-hydroxytropone (I) and tosyl chloride in pyridine at room temperature gives 3-tosyloxytropone (II) as colorless plates. In contrast to the facile formation of 2-aminotropone by ammonolysis of 2-methoxytropone,[3b,9] 3-methoxytropone[4] does not undergo ammonolysis. 3-Tosyloxytropone (II), because of its strong electron-attracting property, reacts with ammonia to form 3-aminotropone (III), though generally in a poor yield. This reaction is especially affected by reaction conditions and, therefore, examinations were made on the solvent,



I II III

Chart 1

1) A part of this work was reported at the Tohoku Local Meeting of the Pharmaceutical Society of Japan, Sendai, December 21, 1968.
2) Location: *Katahira-cho 75, Sendai.*
3) *a*) T. Nozoe, S. Seto, Y. Kitahara, M. Kunori, and Y. Nakayama, *Proc. Japan Acad.*, **26**, 38 (1950); *b*) J.W. Cook, A.R. Gibbs, R.A. Raphael, and A.R. Somerville, *J. Chem. Soc.*, **1951**, 503; *c*) R.D. Harworth and J.D. Hobson, *ibid.*, **1951**, 561; *d*) W. von E. Doering and L.H. Knox, *J. Amer. Chem. Soc.*, **72** 2305, (1950); *e*) J.D. Knight and D.J. Cram, *ibid.*, **73**, 4136, (1951).
4) R.B. Johns, A.W. Johnson, and M. Tisler, *J. Chem. Soc.*, **1954**, 4605.
5) T. Nozoe, T. Mukai, Y. Ikegami, and T. Toda, *Chem. Ind.* (London), **1955**, 66; R.B. Johns, A.W. Johnson, A. Langemann, and J. Murray, *J. Chem. Soc.*, **1955**, 309; R.S. Coffey and A.W. Johnson, *ibid.*, **1958**, 1741; J. Meinwald and O.L. Chapman, *J. Amer. Chem. Soc.*, **80**, 633, (1956).
6) T. Nozoe, S. Seto, H. Takeda, S. Morosawa, and K. Matsumoto, *Sci. Reports Tohoku Univ.*, **36**, 126, (1952); T. Nozoe, T. Mukai, and K. Takase, *ibid.*, **39**, 164, (1960).
7) K. Doi, *Bull. Chem. Soc. Japan*, **33**, 887, (1960).
8) S. Seto, H. Sugiyama, and H. Toda, *Chem. Commun.*, **1968**, 562.
9) T. Nozoe, S. Seto, T. Ikemi, and T. Arai, *Proc. Japan Acad.*, **27**, 102 (1951).

reaction temperature, and reaction time. 1) The solvent should be a polar solvent like alcohol but that of a small molecule like methanol brought about exchange of TsO group in 3-position with MeO group. Such exchange would not take place with *tert*-butanol but its polarity would be weak and a large amount of the tosylate was recovered. Isopropanol would have less of such defects and in fact it was found to be the most desirable solvent from the point of yield of the product and ease of handling. The product is obtained in a fairly good yield when the reaction is carried out in liquid ammonia as long as the tosylate concentration is very low but the yield falls drastically when the concentration increases. The reaction does not take place in benzene. 2) When the reaction temperature rises above 60°, the formed III itself undergoes change and the amount of structurally unknown oily substance increases. Below 35°, the reaction is extremely slow and yield of the product decreases. A reaction temperature of 45—50° seems to be optimal. 3) Since the reaction carried out on a large scale results in lower yield, initial concentration of ammonia is considered to have a great effect on the yield.

From the result of foregoing examinations, it was considered that the optimal conditions for this reactions would be ammonia-saturated isopropanol as a solvent, reaction temperature of 45—50°, and reaction time of about 80 min.

Reaction of 3-Aminotropone

2-Aminotropone is stable to acids but converts into tropolone when heated with alkali.[6] 3-Aminotropone (III) is also stable and only forms its hydrochloride when heated with 6N hydrochloric acid, but changes into 3-hydroxytropone (I) when heated with 6N sodium hydroxide at 100° for only 5 min.

III is considered to take the form of IIIa, since the high electron density at 2-position is caused by the resonance effect of the amino group and this was assumed with its nuclear magnetic resonance (NMR) spectrum (Fig. 1). It has been found that in the NMR spectra of 5-amino-2-methoxytropone derivatives, the signal of the proton at 4-position appears in the

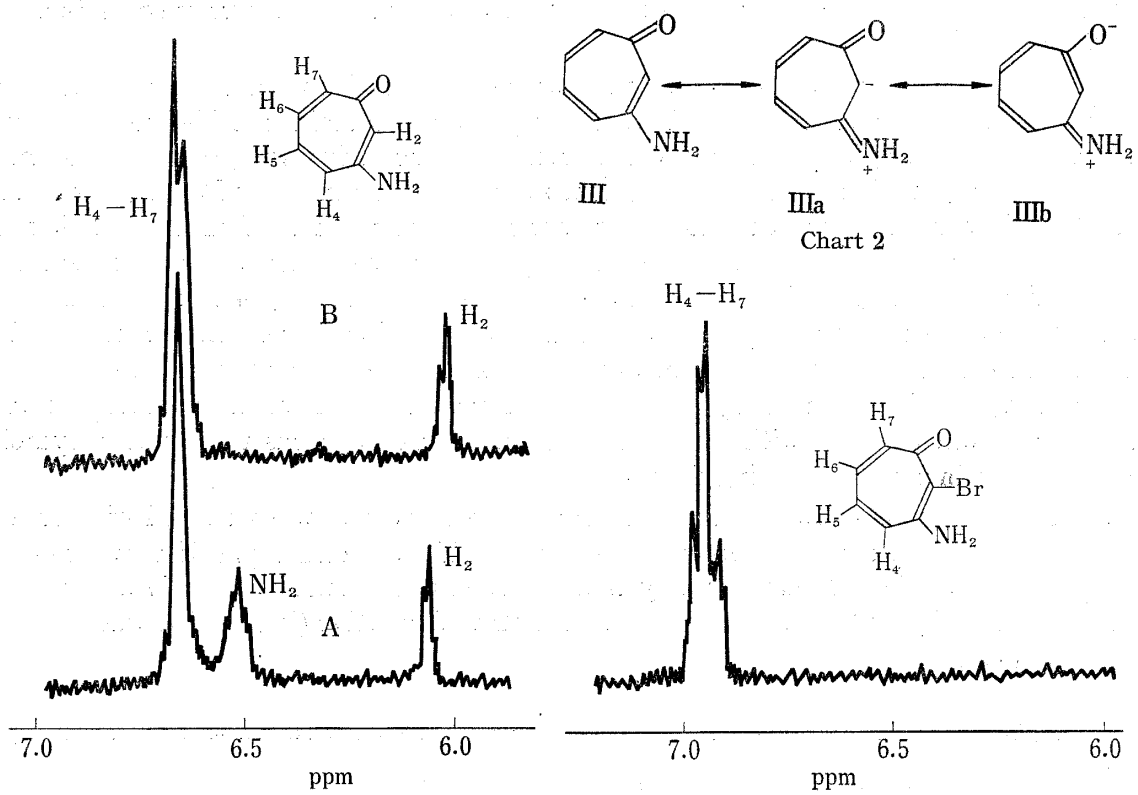


Fig. 1. NMR Spectra of III (60 Mc)
A: in DMSO-d_6 B: in D_2O

Fig. 2. NMR Spectrum of IV in DMSO-d_6 (60 Mc)

Chart 2

highest magnetic field among the ring protons.[10] In the case of III also, the proton at 2-position alone appears as a broad signal in the high field (6.07 ppm). The signal in the region of 6.5 ppm is due to the amino protons and this signal disappears when measured in deuterium oxide. These facts also suggest that a electrophilic substitution reaction in III would occur at 2-position of the tropone ring.

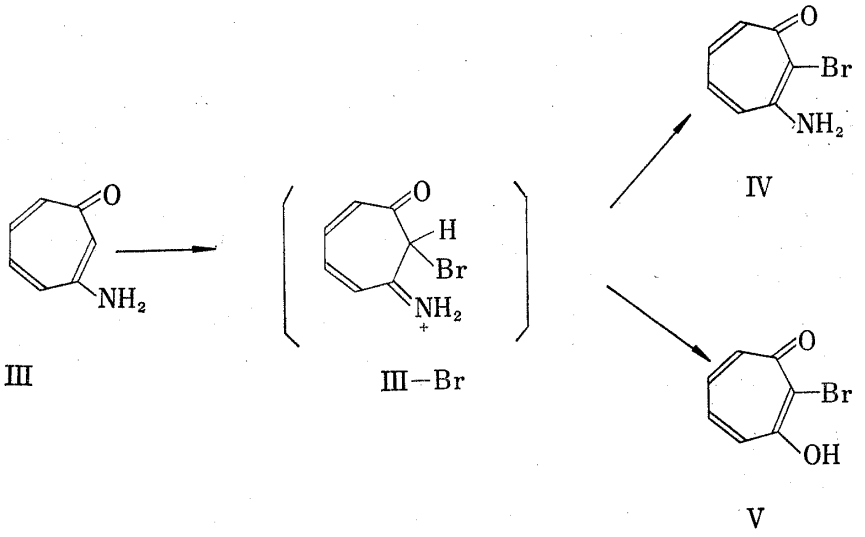


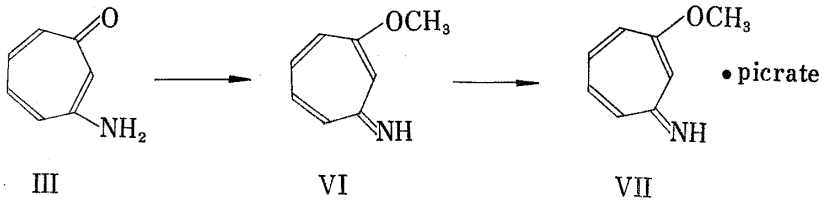
Chart 3

Reaction of III with bromine in ethanol gives a monobromo compound (IV) but changes in the reaction condition result in the forming of 2-bromo-3-hydroxytropone (V).[4,11] The NMR spectrum (Fig. 2) of the monobromo compound (IV) did not exhibit the signal corresponding to the proton in 2-position of III, although showed the complicated signals due to the four protons in 4-, 5-, 6-, and 7-positions, and IV was therefore determined as 3-amino-2-bromotropone.

The mechanism of the bromination of III whereby IV or V is formed can be explained by assuming the formation of an intermediate (III-Br). When bromine is added to the ethanolic solution of III at once, V is formed. When bromine is added dropwise, or when sodium carbonate is present, or when the reaction is carried out in chloroform, only IV is formed. These experimental evidences suggest the following as the mechanism for the formation of IV and V. (1) When water is not present in the reaction system, or even when water is present, if the concentration of the intermediate (III-Br) is low or a base is present, liberation of the proton at 2-position occurs preferentially and IV is produced. (2) When the concentration of III-Br increases temporarily in the presence of water, attack of water on carbon at 3-position occurs preferentially, and V is formed by liberation of ammonia. IV is stable enough to from its hydrochloride when heated with hydrochloric acid, so that V seems to be not a hydrolysis product of IV which formed during the reaction.

2-Aminotropone is known to form a troponeimine derivative when treated with dimethyl sulfate, as reported by Soma and others.[12] Reaction of III with dimethyl sulfate was examined in order to see whether III can actually take the resonance structure like IIIb. Treatment of III with dimethyl sulfate afforded the monomethyl derivative (VI), which was isolated as the picrate (VII).

10) S. Seto, K. Ogura, H. Toda (Sasaki), Y. Ikegami, and T. Ikenoue, *Bull. Chem. Soc. Japan*, **41**, 2696 (1968).
11) S. Seto, *Sci. Reports Tohoku Univ.*, **37**, 377, (1953).
12) N. Soma, J. Nakazawa, T. Watanabe, Y. Sato, and G. Sunagawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 457 (1965).



III VI VII

Chart 4

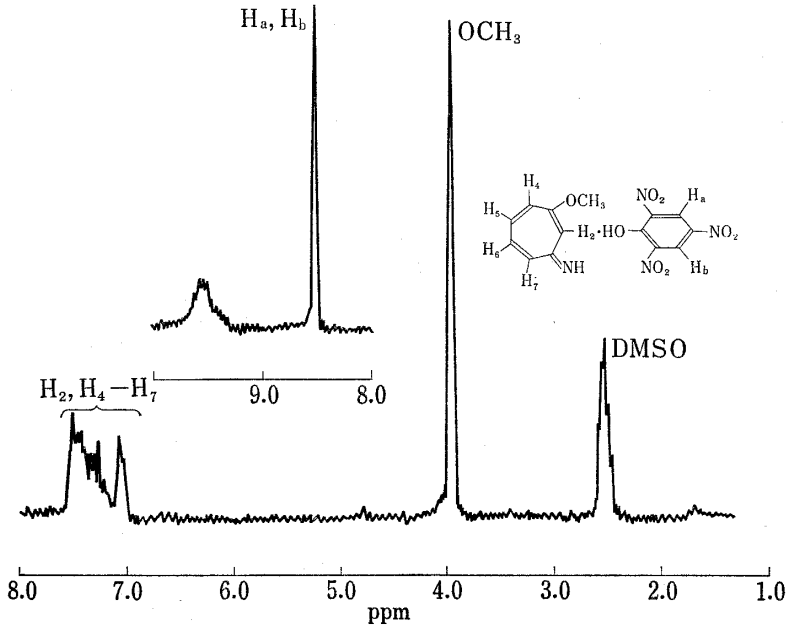


Fig. 3. NMR Spectrum of VII (60 Mc)

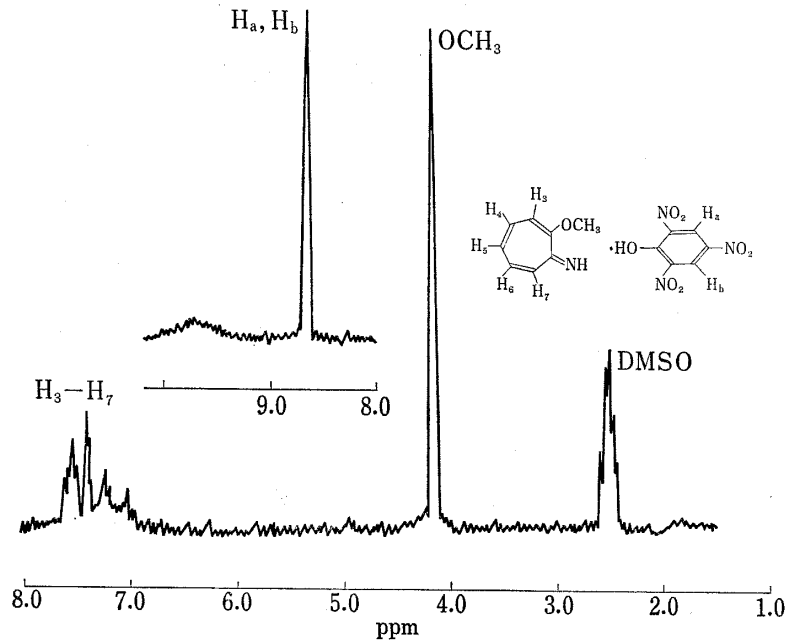


Fig. 4. NMR Spectrum of 2-Methoxytroponeimine picrate (60 Mc)

The NMR spectrum of VII (Fig. 3) indicated signals for the methoxyl protons at 3.89 ppm, aromatic protons (5H) of the seven-membered ring at 7.0—7.5 ppm, and aromatic protons (2H) of picric acid at 8.50 ppm. These data correspond well with the NMR spectrum (Fig. 4) of the picrate of 2-methoxytroponeimine obtained by the method of Soma and others.[12]

3-Methoxytroponeimine (VI) was so unstable that it could not be isolated but its formation was certain from the results of elementary analytical data and NMR spectrum of VII.

Heating of III with acetic anhydride resulted in formation of an N-acetyl compound (VIII). Azo coupling and diazotization of III in aqueous solution afforded a dark red powdery product in either case but their structure was not elucidated due to lability of the product and scarcity of the materials.

Experimental[13]

3-Tosyloxytropone (II)——Into a solution of tosyl chloride (2.5 g) in dry pyridine (20 ml), HBr salt of 3-hydroxytropone (I, 2.2 g) was added and the mixture was allowed to stand at room temperature overnight. Colorless crystals which were precipitated by addition of about 350 ml of water were filtrated, washed with water and recrystallized from methanol to give colorless plates. Yield, 2.0 g, mp 92—92.3°. *Anal.* Calcd. for $C_{14}H_{12}O_4S$: C, 60.85; H, 4.38. Found: C, 60.57, H, 4.59. UV λ_{max}^{MeOH} mμ (log ε): 227 (4.33), 293 (3.73). IR ν_{max}^{KBr} cm^{-1}: 1636, 1584, 1374, 1191, 1178, 1074, 747.

3-Aminotropone (III)——II (413 mg) was dissolved in 100 ml of isopropanol at 50—60°, and then gaseous ammonia was bubbled into this solution for 80 min at 45—50°. During the reaction, color of the solution changed to orange gradually and colorless crystals were separated out. After bubbling of ammonia was stopped, the reaction mixture was allowed to stand for 30 min at room temperature. The residual reaction mixture obtained by evaporation of the solvent at 30—40° was washed with 50 ml of dichloromethane several times, and the insoluble solid, NH_3 salt of *p*-toluenesulfonic acid, was removed. The pale yellow powder (III) which was obtained by gentle evaporation of the dichloromethane was collected as the first crop by quick filtration. The product seemed to change into brownish oily substance when filtration was continued long time. The yellow residue obtained by removal of the solvent from the filtrate was chromatographed on alumina with methanol after dichloromethane. Evaporation of the solvent from methanol eluate gave a pale yellow powder (III) as the second crop. The product (136 mg, 76%) was recrystallized from 0.5% ethanolic chloroform to give pure III, mp 188° (decomp.). *Anal.* Calcd. for C_7H_7ON: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.24; H, 5.73; N, 11.48. UV λ_{max}^{MeOH} mμ (log ε): 263 (4.49), 274 (4.43), 303 (3.81), 313 (3.79). IR ν_{max}^{KBr} cm^{-1}: 3340, 3120, 1645, 1580, 1540, 1505, 1480, 1285. pK_a: 3.33±0.02 (23°). Hydrochloride: mp 152—154°. *Anal.* Calcd. for $C_7H_8ONCl\cdot H_2O$: C, 47.88; H, 5.74; N, 7.98. Found: C, 47.94; H, 5.67; N, 7.73. Picrate: mp 184—185°. *Anal.* Calcd. for $C_{13}H_{10}O_8N_4$: C, 44.58; H, 2.88. Found: C, 44.85; H, 2.93.

Hydrolysis of 3-Aminotropone (III) with Alkali——III (0.825 mg) was heated with 6N NaOH (10 ml) at 80°. In every 10 minutes, 0.5 ml of the solution was diluted with 9.5 ml of water and then its UV spectrum was measured. Under these conditions, III changed to 3-hydroxytropone (I) in 20 min. It seems that higher concentration and temperature activate the reaction; that is, III (20 mg) in 6N NaOH (1 ml) changed to I at 100° within 5 min.

Bromination of 3-Aminotropone (III)——1) Formation of 3-Amino-2-bromotropone (IV): i) A solution of bromine (45 mg) in EtOH (2.5 ml) was added dropwise into a solution of III (30 mg) in EtOH (2.5 ml) under ice-cooling and the reaction mixture was allowed to stand for 1 hr at room temperature. The pale yellow residue which was obtained by removal of the solvent was dissolved in 8 ml of water and pH of the solution was adjusted to *ca.* 8 with Na_2CO_3. Pale yellow crystals which were separated out by concentration of this weak alkaline solution to about 0.5 ml of volume were filtrated, washed with water and recrystallized from EtOH. Yield, 35 mg (78%), mp 215—216° (decomp.). *Anal.* Calcd. for C_7H_6ONBr: C, 42.04; H, 3.00; N, 7.00. Found: C, 42.49; H, 2.66; N, 6.72. UV λ_{max}^{MeOH} mμ (log ε): 216 (4.06), 264 (4.33), 273 (4.30), 203 (3.68 ref.), 313 (3.71). IR ν_{max}^{KBr} cm^{-1}: 3360, 3240, 3140, 1634, 1534, 1492, 1450, 796. Hydrochloride: mp 221—222° (decomp.). *Anal.* Calcd. for $C_7H_7ONClBr$: C, 35.55; H, 2.98; N, 5.92. Found: C, 35.55; H, 2.99; N, 6.02. Hydrobromide: mp 130° (decomp.). ii) Into a mixture of III (100 mg), EtOH (7 ml) and Na_2CO_3 (150 mg), a solution of bromine (135 mg) in EtOH (3 ml) was rapidly added under ice-cooling and the reaction mixture was allowed to stand for 30 min at room temperature. A small amount of water was added to the residue obtained by evaporation of the solvent, and the formed insoluble crystals (IV) were collected by filtration and washed with water. Yield, 151 mg (91%). iii) Into a suspension of III (50 mg) in 3 ml of $CHCl_3$, a solution of bromine (70 mg) in $CHCl_3$ (2 ml) was added at once under ice-cooling. The yellow residue obtained by removal of the solvent was dissolved in 5 ml of water, and pH of the solution

13) All melting points were uncorrected. UV and IR spectra were measured by using a Cary model 14 spectrophotometer and Hitachi EPI-G 21 spectrophotometer, respectively. Decision of pK_a value was carried out by spectroscopic method,[14] using a Cary model 14 spectrophotometer and Hitachi-Horiba pH meter. The NMR spectra were taken on Varian A-60 and T-60 spectrometer with tetramethylsillan as internal standard.

14) A. Albert and E.P. Serjant, "Ion Teisu," ed. by S. Matsuura, Maruzen Co., Ltd., Tokyo, 1963, p. 63.

was adjusted to 8—9 with Na_2CO_3. Evaporation of water *in vacuo* gave pale yellow crystals (IV), 20 mg.

2) Formation of 2-Bromo-3-hydroxytropone (V): Into a solution of III (125 mg) in EtOH (6 ml), a solution of bromine (170 mg) in EtOH (3 ml) was dropped quickly under ice-cooling. The residual solid obtained by evaporation of the alcohol was dissolved in a large amount of water and a trace of insoluble substance was removed by filtration. Pale yellow crystals were separated out from a filtrate. Yield, 135 mg, mp 206—210°. Melting point and UV spectrum of V were in good agreement with them of the previous report.[9]

3-Methoxytroponeimine Picrate (VII)——A mixture of III (100 mg) and $(CH_3)_2SO_4$ (200 mg) in acetone (5 ml) was refluxed for 2 hr, and then the reaction mixture was allowed to stand at room temperature overnight. This mixture to which 2 ml of water was added was extracted with benzene. The separated water layer was neutralized with 1N NaOH. When ethanolic solution of picric acid was added to this neutral solution, yellow crystals were separated out. Recrystallization of the crystals from EtOH gave VII as yellow needles. Yield, 130 mg, mp 187° (decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_8N_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.33; H, 3.27; N, 15.24. UV λ_{max}^{MeOH} mμ (log ε): 214 (4.39), 253 (4.59), 260 (4.51 ref.), 304 (4.03 ref.), 316 (4.14), 350 (4.22). IR ν_{max}^{KBr} cm^{-1}: 3340, 3030, 1663, 1628, 1589, 1555, 1430, 1361, 1330, 1300, 1260, 1220, 1179.

Acetylation of 3-Aminotropone (III)——A mixture of III (30 mg) and acetic anhydride (2 ml) was heated at 80° for 1 hr. Pale brown crystals (VIII) obtained by evaporation of the excess acetic anhydride were collected by filtration and washed with MeOH. Yield, 35 mg, mp 172—173°. *Anal.* Calcd. for $C_9H_9O_2N$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.95; H, 5.34; N, 8.42. UV λ_{max}^{MeOH} mμ (log ε): 218 (4.16), 262 (4.60), 268 (4.57 ref.), 307 (3.92). IR ν_{max}^{KBr} cm^{-1}: 3250, 3050, 1711, 1643, 1610, 1546, 1522, 1250, 1212.

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