The Reaction of 3-Carboxy- and 3-Cyanotropolone with Hydrazine

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It has been known that tropolones generally do not react with the ketonic reagents, with a few exceptions, such as nitro-,[1] nitroso-[2,3] and arylazotropolone[3]. In our previous studies, however, it has been found that 3-carboxytropolone reacts with *o*-phenylenediamine to form cyclohepta[b]quinoxaline (benzo[b]tropazine).[4] The present authors have now carried out some studies of 3-carboxy- and 3-cyanotropolone and found that these tropolones react easily with hydrazine to give hydrazinotropone derivatives. Furthermore, 2-cyano- and 2-carboxytropone have been derived from 3-cyanotropolone by utilizing this reaction.

When 3-carboxytropolone (I) was heated with hydrazine in ethanol, 2-hydrazinotropone (II)[5] was obtained. Since tropolone itself does not react with hydrazine under these conditions, it is clear that the formation of II from I is not due to the reaction of hydrazine on tropolone, which would be formed by the decarboxylation of I, but to the decarboxylation of 2-carboxy-7-hydrazinotropone (III) (or its isomer; 3-carboxy-2-hydrazinotropone) formed as an intermediate.

3, 5-Dibromo-7-carboxytropolone (IV)[6] also reacted with hydrazine, but no decarboxylation occurred in this case; 3,5-dibromo-7-carboxy-2-hydrazinotropone (V) (or its isomer, 5, 7-dibromo-3-carboxy-2-hydrazinotropone) was obtained. The structure of V was confirmed from its analytical value, the similarity of its ultraviolet spectrum to that of II, and the formation of IV by its hydrolysis with 75% sulfuric acid.

In the reaction of 3-cyanotropolone (VI) and hydrazine in ethanol, the hydrazine salt of VI was first formed; this was changed by heating to afford a hydrazinotropone derivative (VII). The ultraviolet spectrum of VII is similar to that of II. The hydrolysis of VII with concentrated hydrochloric acid afforded

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1) T. Nozoe, *Science of Drugs*, **3**, 191 (1949); *Sci. Repts. Tohoku Univ.*, **I**, **34**, 225 (1950); T. Nozoe, Y. Kitahara, K. Doi and T. Arai, *Bull. Chem. Research Inst. Non-Aqueous Solns., Tohoku Univ.*, **7**, 13 (1957).

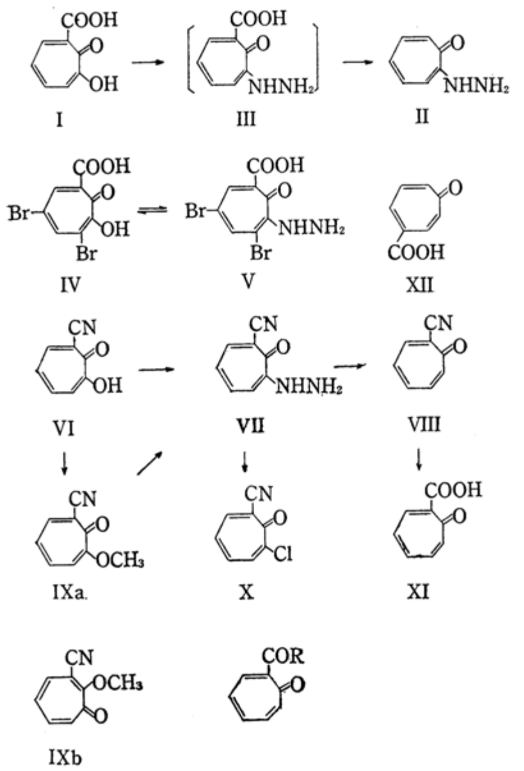
2) T. Nozoe, M. Sato and K. Matsui, *Sci. Repts. Tohoku Univ.*, **I**, **37**, 407 (1953); S. Ito, ibid., **42**, 236 (1958); **43**, 216 (1959).

3) T. Nozoe, S. Ito, S. Suzuki and K. Hiraga, *Proc. Japan Acad.*, **32**, 344 (1956).

4) T. Nozoe, Y. Kitahara, K. Takase and M. Sasaki, ibid., **32**, 349 (1956).

5) T. Nozoe, S. Seto, H. Takeda, S. Morosawa and K. Matsumoto, ibid., **28**, 192 (1952); *Sci. Repts. Tohoku Univ.*, **I**, **36**, 126 (1952).

6) Y. Kitahara, ibid., **I**, **40**, 74 (1956).



XIII : R=OCH_3
XIV : R=$NHC_6H_4CH_3$
XV : R=$NHNHCOC_6H_5$

VI, and the oxidative decomposition of VII in acetic acid with cupric sulfate afforded 2-cyanotropone (VIII).[7] This evidence suggests that VII is 7-cyano-2-hydrazinotropone. The methylation of VI with diazomethane afforded two methyl ethers, 2-cyano-7-methoxytropone (IXa) and 3-cyano-2-methoxytropone (IXb); one of these, IXa, gave VII when treated with hydrazine, thus establishing the structures of these methyl ethers. When VII was oxidatively decomposed in concentrated hydrochloric acid with cupric sulfate, 2-chloro-7-cyanotropone (X) was obtained.

The above-mentioned results show that the tropolonic hydroxyl group of I and VI is substituted with hydrazine to the hydrazino group. This is, presumably, due to the electron-withdrawing nature of the carboxyl or cyano group, by which the tropolone nucleus is more liable to the attack of hydrazine than is usual tropolone.

The hydrolysis of 2-cyanotropone (VIII) by heating it in 75% sulfuric acid gave 2-carboxytropone (XI) in a good yield. The isomeric 4-carboxytropone (XII) has only been synthesized by Johnson et al.;[8] therefore, the XI obtained here is of interest as one of the fundamental troponoids. Its ultraviolet absorption spectrum in methanol (maxima at 231 and 316 mμ; log ε, 4.25 and 3.85 respectively) is similar to those of the usual tropones, and its pK_a value, 3.73,[9] is smaller than those of acetic acid or benzoic acid. The bromination of XI afforded an oily substance which gave 2, 7-dibromotropone[10] when heated. Methylation with diazomethane gave an oily methyl ester (XIII), while treatment with thionyl chloride afforded an unstable acid chloride. *p*-Toluidide (XIV) and benzoylhydrazide derivative (XV) of the acid XI were derived through this methyl ester or acid chloride.

Experimental[11]

The Reaction of 3-Carboxytropolone (I) with Hydrazine.—A mixture of I (330 mg.) and 80% hydrazine hydrate (300 mg.) in ethanol (10 ml.) was refluxed for 5 hr. The solvent was then evaporated, and the residue sublimed under reduced pressure. The sublimate (130 mg.) was recrystallized from benzene to give yellow needles (110 mg.); m. p. 92~93°C, which was undepressed on admixture with 2-hydrazinotropone (II).[5] λ_{max}^{MeOH} mμ (log ε); 246 (4.37), 338 (4.09), 406 (4.05).

3, 5-Dibromo-7-carboxy-2-hydrazinotropone (V).—A mixture of 3, 5-dibromo-7-carboxytropolone (IV) (160 mg.) and 80% hydrazine hydrate (50 mg.) in ethanol (20 ml.) was refluxed for 24 hr. The removal of the solvent and recrystallization from ethanol afforded V (150 mg.) as yellow needles, m. p. 216°C (decomp.)

λ_{max}^{MeOH} mμ (log ε); 268 (4.37), 352 (4.05), 431 (3.96).

Found: N, 8.29. Calcd. for $C_8H_6O_3N_2Br_2$: N, 8.55%.

The hydrolysis of V by heating it with 75% sulfuric acid afforded IV in a good yield.

2-Cyano-7-hydrazinotropone (VII).—*From 3-Cyanotropolone (VI).*—To a hot solution of VI (600 mg.) in ethanol (20 ml.), 80% hydrazine hydrate (800 mg.) was added; hydrazine salt of VI was then crystallized out as yellow needles, m. p. 166~168°C (Found: N, 23.27. Calcd. for $C_8H_9O_2N_3$: N, 23.45%). This mixture was refluxed for 3 hr., and the crystals thereby obtained were recrystallized from ethanol to give VII (550 mg.) as orange needles, m. p. 205°C (decomp.).

λ_{max}^{MeOH} mμ (log ε); 214 (4.22), 252 (4.14), 268 (4.08), 355 (3.87), 438 (4.24). Found: C, 59.52; H, 4.71; N, 26.13. Calcd. for $C_8H_7ON_3$: C, 59.62; H, 4.38; N, 26.08%.

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[7] T. Nozoe, S. Seto and S. Matsumura, *Proc. Japan Acad.*, **28**, 483 (1952).

[8] J. R. Bartels-Keith, A. W. Johnson and A. Langemann, *J. Chem. Soc.*, **1952**, 4461.

[9] N. Tanaka, I. T. Oiwa, T. Kurosawa and T. Nozoe, This Bulletin, **32**, 92 (1959).

[10] T. Nozoe, S. Seto and S. Matsumura, *Proc. Japan Acad.*, **28**, 483 (1952); T. Nozoe, T. Mukai, K. Takase and T. Nagase, ibid., **28**, 477 (1952); S. Seto, *Sci. Repts. Tohoku Univ.*, **I**, **37**, 275 (1953).

[11] All melting points are uncorrected.

From 2-Cyano-7-methoxytropone (IXa). — To a suspension of IXa (150 mg.) in methanol (10 ml.), 80% hydrazine hydrate (100 mg.) was added; when the mixture was then allowed to stand for 2 hr. at room temperature, it gave VII (110 mg.) as orange needles, m. p. 205°C (decomp.).

The heating of VII in concentrated hydrochloric acid for 3 hr. gave VI.

The Acetate of VII; m. p. 260°C, yellow needles (from ethanol).

λ_{max}^{MeOH} mμ (log ε); 215 (4.12), 247 (4.22), 273 (4.12), 345 (3.87), 430 (4.27).

Found: C, 59.32; H, 4.73; N, 20.69. Calcd. for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.46; N, 20.68%.

2-Cyanotropone (VIII).—To a hot solution of VII (200 mg.), in a mixture of glacial acetic acid (6 ml.) and water (6 ml.) a 10% cupric sulfate solution (12 ml.) was added in one lot. After it has been heated for 15 min., the mixture was diluted with water and extracted with chloroform. The solvent was removed, the residue was sublimed under reduced pressure at 130°C, and the sublimate (60 mg.), m. p. 132~137°C, was recrystallized from benzene to give VIII as yellow needles, m. p. 136~137°C (decomp.), which was identified by mixed melting point and by a comparison of its infrared spectrum with that of an authentic specimen.[7] λ_{max}^{MeOH} mμ (log ε); 238 (4.32), 305 (3.71), 320 (3.73), 340 (3.70).

2-Cyano-7-methoxytropone (IXa) and 3-Cyano-2-methoxytropone (IXb).—Into a suspension of VI (2.0 g.) in methanol (40 ml.), an ethereal solution of diazomethane was added under cooling; the mixture was then allowed to stand overnight. The crystals which separated out were collected by filtration and recrystallized from water to give IXa (530 mg.) as pale yellow needles, m. p. 173.5~174.5°C.

λ_{max}^{MeOH} mμ (log ε); 250 (4.31), 311 (3.68), 327 (3.73).

Found: C, 66.54; H, 4.45. Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.38%.

The crystalline material (1.53 g.) obtained by the removal of the solvent from the mother liquor was dissolved in benzene and chromatographed on an aluminum column. From the first effluent, IXb was obtained as pale yellow scales, m. p. 141~142°C, after recrystallization from methanol.

λ_{max}^{MeOH} mμ (log ε); 234 (4.23), 331 (3.82).

Found: C, 66.89; H, 4.69. Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.38%.

7-Chloro-2-cyanotropone (X).—To a mixture of VII (500 mg.) and concentrated hydrochloric acid (6 ml.), a 30% cupric sulfate solution (6 ml.) was added in one lot, the mixture was then heated for 5 min. The crystals which were precipitated were collected and sublimed under reduced pressure to give X (410 mg.), m. p. 155~158°C, which was recrystallized from ethanol to afford yellow needles, m. p. 162~162.5°C.

Found: C, 58.13; H, 2.86; N, 8.79. Calcd. for C_8H_4ONCl: C, 58.02; H, 2.43; N, 8.46%.

2-Carboxytropone (XI).—A mixture of VIII (220 mg.) and 75% sulfuric acid (2 ml.) was heated for 1 hr. at 120~125°C and then poured into ice-water and extracted with chloroform. The solvent was removed, and the residue was recrystallized from benzene to give XI (200 mg.) as cream-colored needles, m. p. 149°C (decomp.).

Found: C, 63.78; H, 4.19. Calcd. for $C_8H_6O_3$: C, 64.00; H, 4.03%.

The Bromination of XI.—To a solution of XI (50 mg.) in glacial acetic acid (2 ml.) bromine (160 mg.) was added; the mixture was then stirred for 1 hr. The addition of water and extraction with chloroform gave an oily substance. This oil was heated in glacial acetic acid for 1 hr., and then the mixture was diluted with water, affording crystals. Recrystallization from benzene afforded 2, 7-dibromotoropone as pale orange plates (m. p. 169~170°C), identified by admixture with an authentic specimen.[10]

Methoxycarbonyltropne (XIII).—To a solution of XI (100 mg.) in methanol (1 ml.), an ethereal solution of diazomethane was added under cooling. The removal of the solvent gave an oily XIII. λ_{max}^{MeOH} mμ (log ε); 228 (4.18), 305 (3.77).

A mixture of XIII *p*-toluidine and methanol was heated for 1 hr. The removal of the solvent and recrystallization from benzene gave a *p*-toluidide derivative (XIV) as colorless plates, m. p. 152~153°C.

Found: N, 5.70. Calcd. for $C_{15}H_{13}O_2N$; N, 5.85%.

The Reaction of XI with Thionyl Chloride.—A mixture of XI (100 mg.) and thionyl chloride (100 mg.) in dry benzene (2 ml.) was refluxed for 3 hr.; the removal of the solvent then gave acid chloride, m. p. 155~156°. To a solution of this acid chloride in benzene (2 ml.), a solution of benzoylhydrazide (200 mg.) in benzene (5 ml.) was added, and the new mixture was refluxed for 30 min. The crystals thereby obtained were recrystallized from methanol to give a benzoylhydrazide derivative (XV) (200 mg.) as yellow prisms, m. p. 191~192°C.

Found: N, 10.78. Calcd. for $C_{15}H_{12}O_3N_2$: N, 10.44%. λ_{max}^{MeOH} mμ (log ε); 235 (4.44), 305 (3.86).

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