Partial Debromination of Polybromotropolones with Cuprous Cyanide and Some Reactions of 4-Bromotropolone

By Kozo Doi

(Received September 30, 1960)

In the previous papers the author reported that amination of 3-iodotropolones with potassium amide in liquid ammonia, whose process is an example of extensive application of the elimination-addition mechanism$^{1)}$ involving benzyne-type intermediate to the tropolone field, resulted in the formation of 4-aminotropolone (I) and its derivatives$^{2)}$. Further, he reported that an application of the Schmidt reaction to the acetyl, formyl, and isopropenyl derivatives of tropolone resulted also in the formation of the aminotropolones in satisfactory yields$^{3)}$.

The present study was undertaken in order to derive 3, 6-dibromotropolone (II), which is obtainable comparatively$^{4)}$, to 4-bromotropolone

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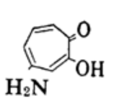
1) J. D. Roberts, H. E. Simmons, L. A. Carlsmith and C. W. Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953); **78**, 601 (1956).

2) K. Doi, This Bulletin, **34**, 488 (1961).

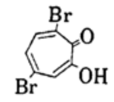
3) K. Doi, ibid., **34**, 501 (1961).

4) T. Nozoe, Y. Kitahara et al., *Science Repts. Tohoku Univ. Ser. I*, **36**, 166 (1952); S. Iseda, This Bulletin, **28**, 617 (1955); T. Nozoe, K. Doi and S. Endo, ibid.. **33**, 1285 (1960).

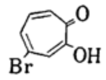
(III) and to convert it to the aminotropolone (I) by a suitable method.



I



II



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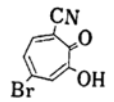
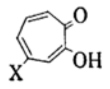


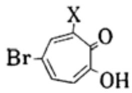
IV

It has been found that treatment of alkali salt of 3-bromotropolones with cuprous cyanide in pyridine produces 3-cyanotropolone[5,6] in general. The author's attention, therefore, was directed towards obtaining 6-bromo-3-cyanotropolone (IV), which is expected to be derived to 4-bromotropolone (III) on its hydrolysis and subsequent decarboxylation, by application of this synthetic process to 3,6-dibromotropolone (II).

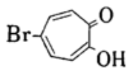
It was found in practice, however, that, when the copper salt, in place of alkali salt, of the dibromotropolone (II) was heated with cuprous cyanide in pyridine, the anticipated 6-bromo-3-cyanotropolone (IV) did not form but 4-bromotropolone (III) and 4-cyanotropolone (V) resulted in formation as the reaction products. The structure of III was proved by the mixed melting point determination and comparison of the ultraviolet spectrum with that of an authentic specimen[7]. The direct formation of the cyanotropolone (V) from the dibromotropolone (II) in the above reaction is probably due to a secondary reaction of the bromotropolone (III) with cuprous cyanide, since the reaction of III and cuprous cyanide in the same condition was proved to give the cyanotropolone (V) really.



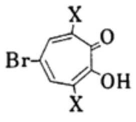
V : X=CN
XIV : $X=NHSO_2Ts$



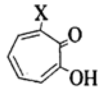
VI : X=Br
VIII : X=CN



VII



IX : X=Br
X : X=CN



XI : X=Br
XII : $X=NHSO_2Ts$
XIII : $X=NH_2$

With the reaction of 3,5-dibromotropolone (VI) in the same condition, both a partially debrominated product, 5-bromotropolone (VII), and a substitution product, 5-bromo-3-cyanotropolone (VIII), were obtained as the reaction products. The structure of the latter (VIII) is proved from the formation of VII on hydrolyzing it with sulfuric acid followed by decarboxylation and from the resemblance of its ultraviolet spectrum (Fig. 1) to that of 3-cyanotropolone[6].

A similar result was also recognized in the reaction of 3,5,7-tribromotropolone (IX). Thus the reaction products were a partially debrominated product, 3,5-dibromotropolone (VI), and a substitution product, 5-bromo-3,7-dicyanotropolone (X), which derived to 5-bromotropolone (VII) on hydrolysis with sulfuric acid followed by decarboxylation.

The ultraviolet absorption spectra of the above two cyanotropolones are shown in Fig. 1.

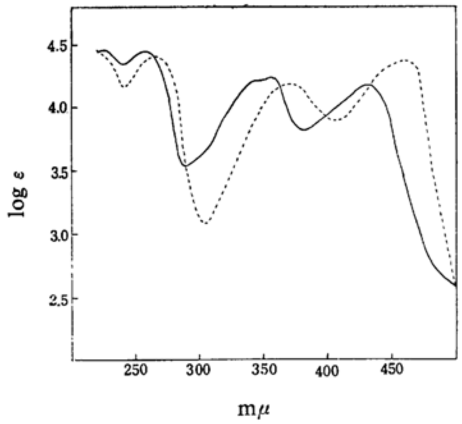


Fig. 1. The ultraviolet absorption spectra.
(——) : 5-Bromo-3-cyanotropolone (VIII)
(------) : 5-Bromo-3,7-dicyanotropolone(X)

It has now been clarified, as shown in the above description, that the reaction of copper salt of some polybromotropolones with cuprous cyanide in pyridine results in the formation of a partially debrominated product in general. On the other hand, it is noteworthy that such a fact has not been observed in the case of the reaction with alkali salt, not copper, of bromotropolones. For instance, the alkali salt of 3-bromotropolone (XI) was reported to give only a corresponding nitrile in a fairly good yield in a reaction with cuprous cyanide in pyridine[5,6]. However, it has now been ascertained that the copper salt of the bromotropolone (XI) gives not only a substitution product, 3-cyanotropolone, but also a debrominated product, tropolone itself, although in an extremely poor yield, in the reaction with cuprous cyanide.

There have already been reported a few

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5) a) B. J. Abadir, J. W. Cook, J. D. Loudon and D. K. V. Steel, *J. Chem. Soc.*, **1952**, 2350. b) T. Nozoe, Y. Kitahara and S. Masamune, *Proc. Japan Acad.*, **29**, 17 (1953). c) T. Nozoe and Y. Kitahara, ibid., **30**, 204 (1954).

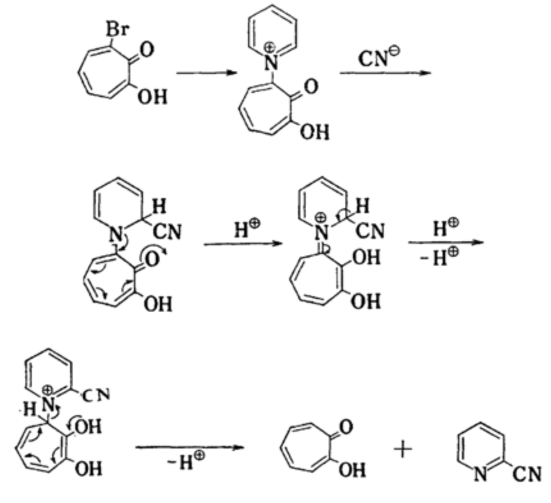
6) Y. Kitahara, *Science Repts. Tohoku Univ. Ser. I*, **40**, 74 (1956).

7) T. Sato, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1171 (1959).

examples of obtaining a dehalogenated product in place of a corresponding nitrile in a reaction of halogenated compound and cuprous salt-pyridine complex. Edwards and Stewart[8] found that the treatment of 5-bromoacenaphthene, α-bromonaphthalene, bromobenzene or chlorobenzene with cuprous acetate in pyridine led not to the objective acetoxyl compound but to the corresponding dehalogenated product, all in yields of about 60 per cent of the theory. In the same reaction, Campbell, McKail and Muir[9] used cuprous cyanide instead of cuprous acetate and obtained a similar result, attributing this mechanism to nitrile formation, hydrolysis, and subsequent decarboxylation to a dehalogenated product.

However, the application of such a mechanism to the case of the debromination of polybromotropolones previously described seems not to be reasonable from the following points of view: (1) dehydrated pyridine was used in this series of experiments, whereas in the reported conditions[8] pyridine containing a small amount of water was used; (2) only a bromine atom, which is activated by the adjacent carbonyl group, in the 3 (or 7)-position is removed, whereas bromine in the 5-position is not; (3) 3-cyanotropolone was inert at least to cuprous cyanide in pyridine under the condition employed; (4) copper salt of bromotropolones is very soluble in pyridine, while alkali salt is scarcely soluble.

The author supposes that the debromination of bromotropolones can probably be explained by a mechanism similar to the formation of benzaldehyde by hydrolytic decomposition of Reisert compounds[10], although this is not founded on any concrete basis.



It was reported that the reaction of copper salt of 3-bromotropolone (XI) and its derivatives with potassium salt of arylsulfonamide in pyridine produced 3-arylsulfonylaminotropolones (XII), which hydrolyzed to 3-aminotropolones (XIII)[5c,11]. Application of this process to 4-bromotropolone (III) for the purpose of preparing 4-aminotropolone (I), however, resulted in no formation of any reaction product.

On the other hand, the bromine atom of III was replaced by the amino group to form the aminotropolone (I), though in a poor yield, on being treated with concentrated ammonia in the presence of cupric sulfate, the process of which had been used to prepare an aminophenol from a bromophenol[12]. The amino compound I gave easily, under a condition of the Schotten-Baumann method, 4-*p*-toluenesulfonylaminotropolone (XIV), which returned back to I on action of concentrated sulfuric acid, likewise in the case of the 3-analogue.

An attempt to synthesize 4,4′-bitropolonyl by treatment of copper salt of 4-bromotropolone (III) with copper powder in pyridine did not succeed unfortunately, whereas in the same condition 3,3′-bitropolonyls have been synthesized satisfactorily from 3-iodotropolones[13].

That the bromine atom of 4-bromotropolone (III) was replaced by the amino or cyano group to form a corresponding substituted product is clarified from the above description, but its reactivity against anionoid reagents seems to be smaller than that of isomeric 3-bromotropolone (XI). This is probably due to the fact that the mesomeric effect of the bromine of 4-bromotropolone (III) predominates its inductive effect to result in the decrease of activation of the bromine, whereas the inductive effect of the bromine of 3-bromotropolone (XI) becomes stronger through a hydrogen bond with the hydroxyl group of the molecule and in consequence the electron density at the 3- (or 7-)position is much decreased to result in promotion of anionoid substitutions.

Some electrophilic substitutions were also attempted on the bromotropolone (III). Nitration of III afforded in a poor yield 6-bromo-3-nitrotropolone (XV), whose structure was proved by its derivation to 3,6-dibromotropolone (II) on treatment with hydrobromic

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[8] W. G. H. Edwards and R. G. Stewart, *Chem. & Ind.*, **1952**, 472.

[9] N. Campbell, J. E. McKail and J. Muir, ibid., **1952**, 739.

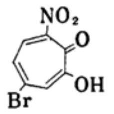
[10] W. E. McEven and R. N. Hazlett, *J. Am. Chem. Soc.*, **71**, 1949 (1949).

[11] Y. Kitahara, *Science Repts. Tohoku Univ. Ser. I*, **40**, 83 (1956); T. Nozoe, Y. Kitahara and K. Doi, ibid., **40**, 121 (1957).

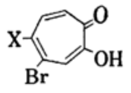
[12] H. E. Podall and W. E. Foster, *J. Org. Chem.*, **23**, 280 (1958).

[13] T. Nozoe, K. Doi and K. Kitahara, *Proc. Japan Acad.*, **32**, 480 (1956).

acid in acetic acid[14], and by the resemblance of its ultraviolet absorption (Fig. 2) to that of 3-nitrotropolone[14].



XV



XVI : X=-N=N-Ph
XVII : X=NH_2

Similarly to many tropolones, III underwent azo-coupling to give 4-bromo-5-phenylazotropolone (XVI), which was hydrogenolyzed to 5-aminotropolone via 5-amino-4-bromotropolone (XVII). The ultraviolet absorptions of XVI and XVII resemble closely those of the respective debrominated compound (Fig. 2).

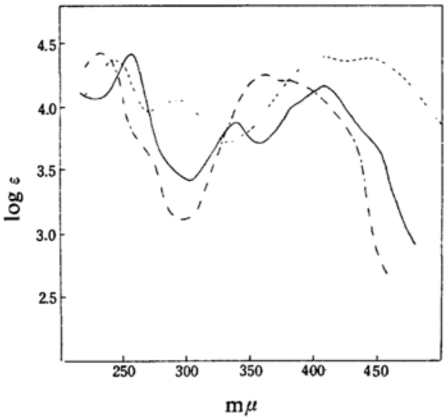


Fig. 2. The ultraviolet absorption spectra.
(——) : 6-Bromo-3-nitrotropolone (XV)
(----) : 4-Bromo-5-phenylazotropolone (XVI)
(-·-·-) : 5-Amino-4-bromotropolone (XVII)

Experimental

All of the ultraviolet absorption spectra were measured in methanol solution with a Beckman model DU quartz spectrophotometer.

Reactions of Bromotropolones with Cuprous Cyanide.—*Reaction of 3, 6-Dibromotropolone (II).*—A mixture of the copper salt (7g.) of II, cuprous cyanide (2.2g.) and pyridine (26 ml.), distilled over solid potassium hydroxide, was heated under reflux for 2 hr., acidified to Congo red with dilute hydrochloric acid; then chloroform (100 ml.) was added to this mixture. After hydrogen sulfide was introduced into it, copper sulfide was removed by filtration and the chloroform layer was evaporated in vacuo to dryness. The residual solid, after sublimation in vacuo and subsequent recrystallization, yielded 4-bromotropolone (III, 1.2 g), from the soluble part in cyclohexane, as pale yellow needles, m. p. 86∼87°C, undepressed on admixture with an authentic specimen which was kindly supplied by Dr. Teruko Sato[7]. The less soluble part in cyclohexane was recrystallized from ethanol to give 4-cyanotropolone (V, 0.17 g.) as yellow needles, m. p. and mixed m. p.[6] 194∼195°C.

Reaction of 3, 5-Dibromotropolone (VI).—A mixture of the copper salt (1.5 g.) of VI[4], cuprous cyanide (0.47 g.) and pyridine (10 ml.) was heated under reflux for 2 hr. The following procedure was essentially as described in the previous experiment and the evaporated solid of the chloroform extract was recrystallized from ethanol to separate into more soluble 5-bromotropolone (VII, 0.2 g.), undepressed on admixture with an authentic sample[14], and less soluble 5-bromo-3-cyanotropolone (VIII, 0.05 g.) as yellow prisms, m. p. 168∼170°C.

Found: N, 5.82. Calcd. for $C_8H_4O_2NBr$: N, 6.19%. λ_{max} mμ (log ε): 225 (4.45), 257 (4.45), 355 (4.25), 435 (4.18).

A mixture of VIII (40 mg.) and 75% sulfuric acid (0.2 ml.) was heated on an oil bath at 150°C for 30 min., diluted with water (1 ml.), and the residual crystals were collected by filtration. This product, which corresponds to 5-bromo-3-carboxytropolone melted at 166∼170°C, 25 mg., without any further purification, was heated at reflux for 30 min. in pyridine (0.5 ml.), acidified to Congo red with dilute hydrochloric acid, and the residual solid was crystallized from cyclohexane to afford 5-bromotropolone (VII, 5 mg.), m. p. and mixed m. p.[14] 189∼190°C.

Reaction of 3, 5, 7-Tribromotropolone (IX).—A mixture of the copper salt (3.5 g.) of IX, cuprous cyanide (0.9 g.) and pyridine (5 ml.) was heated at reflux for 2 hr. The chloroform extract obtained by the usual procedure was evaporated in vacuo and the residue was recrystallized fractionally from ethanol. The more soluble portion yielded 3, 5-dibromotropolone (VI, 0.12 g.) as pale yellow needles, m. p. and mixed m. p. 154∼155°C. The less soluble portion afforded 5-bromo-3, 7-dicyanotropolone (X, 60 mg.) as yellow needles, m. p. 231∼232°C.

Found: N, 11.07. Calcd. for $C_9H_3O_2N_2Br$: N, 11.15%. λ_{max} mμ (log ε): 265 (4.41), 370 (4.19), 460 (4.39).

A mixture of X (50 mg.) and 75% sulfuric acid (0.5 ml.) was heated at 150°C for 1 hr., acidified with dilute mineral acid, and the residual solid, which corresponded to 5-bromo-3, 7-dicarboxytropolone, m. p. 233∼235°C (decomp.), 40 mg., without any further purification, was heated in pyridine (1 ml.), giving 5-bromotropolone (VII, 5 mg.), undepressed on admixture with an authentic specimen.

Reaction of 3-Bromotropolone (XI).—A mixture of the copper salt (11.6 g.) of XI, cuprous cyanide (6.5 g.) and pyridine (50 ml.) was heated under reflux for 3 hr., acidified to Congo red with dilute hydrochloric acid, and the solid deposited was collected by filtration. Hydrogen sulfide was bubbled through the suspension of this solid in chloroform (200 ml.), copper sulfide was removed by filtration, the chloroform solution was evaporated in vacuo to dryness, and the residue, after washing with cyclohexane, was crystallized from methanol

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[14] T. Nozoe, Y. Kitahara, K. Doi and T. Arai, *Bull. Chem. Research Inst. Non-Aqueous Solns. Tohoku Univ.*, **7**, 13 (1957).

to give 3-cyanotropolone (5.4 g.) as yellow needles, m. p. and mixed m. p.[5] 174~174.5°C. From the part soluble in cyclohexane, tropolone (0.1 g.) was obtained, after evaporation of the extract and sublimation in vacuo followed by crystallization from petroleum ether.

Reaction of 4-Bromotropolone (III).—*4-Cyanotropolone (V).*—A mixture of the copper salt (0.47 g.) of III, cuprous cyanide (0.21 g.) and pyridine (3 ml.) was heated under reflux for 2 hr. and the following procedure was carried out essentially as described in the preceding experiments. The chloroform extract was evaporated in vacuo and the residue therefrom was recrystallized from methanol to afford 4-cyanotropolone (V, 0.05 g), undepressed on admixture with an authentic specimen. From the mother-liquor of recrystallization unreacted bromotropolone (III, 0.07 g.) was recovered.

4-Aminotropolone (I).—A mixture of III (0.4 g.), cupric sulfate pentahydrate (10 mg.) and concentrated ammonia (4 ml.) was heated at 130~140°C for 1 hr. in an autoclave. The reaction mixture was diluted with water (10 ml.), acidified with mineral acid to pH 6, and then extracted continuously with ether. The ether extract, after evaporation of the solvent, yielded 4-aminotropolone (I, 0.12 g.) as colorless needles, m. p. 187~189°C, undepressed on admixture with an authentic specimen[2].

4-p-Toluenesulfonylaminotropolone (XIV).—To a stirred solution of the aminotropolone (I, 70 mg.), pyridine (1 ml.) and water (2 ml.) was added *p*-toluenesulfonyl chloride (100 mg.), and then the reaction mixture was stirred for 1 hr. This was neutralized with dilute hydrochloric acid, the deposited solid was collected and recrystallized from a mixed solvent of methanol and acetic acid to yield XIV (80 mg.) as pale yellow prism, m. p. 195~196°C.

Found: C, 57.27; H. 4.63; N, 4.97. Calcd. for $C_{14}H_{13}O_4NS$: C, 57.73; H, 4.50; N, 4.82%.

A mixture of XIV (60 mg.) and concentrated sulfuric acid (0.2 ml.) was heated at 50°C for 30 min., diluted with water (1 ml.), and neutralized with sodium carbonate, by which 4-aminotropolone (I), m. p. and mixed m. p. 187~188°C, was deposited.

6-Bromo-3-nitrotropolone (XV).—A solution of nitric acid (0.3 g., $d=1.42$) and acetic acid (1 ml.) was added dropwise at room temperature to a stirred solution of III (0.79 g.) and acetic acid (4 ml.). The resulting solution was then diluted with water (10 ml.) and extracted with ether (20 ml. × 2). The extract, after evaporation of the solvent, sublimation in vacuo followed by recrystallization from ethanol, gave XV as yellow prisms, m. p. 159~160°C, in 13% yield.

Found: N, 6.09. Calcd. for $C_7H_4O_4NBr$: N, 5.69%. λ_{max} mμ (log ε): 256 (4.42), 338 (3.88), 407 (4.16).

A solution of XV (50 mg.), concentrated hydrobromic acid (1 ml.) and acetic acid (1 ml.) was heated in a sealed tube at 120°C for 1 hr., the resulting solution was evaporated to dryness, and the residue, after sublimation in vacuo followed by recrystallization from ethanol, afforded 3, 6-dibromotropolone (II, 10 mg.), m. p. and mixed m. p.[4] 120~121°C.

4-Bromo-5-phenylazotropolone (XVI).—To a stirred solution of the bromotropolone (III, 0.2 g.) and pyridine (1.5 ml.) was added dropwise when cold a solution of benzenediazonium chloride obtained from aniline (95 mg.). The reaction mixture was acidified to Congo red with dilute hydrochloric acid and the precipitated solid was recrystallized from ethyl acetate to yield XVI (0.3 g.) as red needles, m. p. 194~195°C.

Found: N, 9.64. Calcd. for $C_{13}H_9O_2N_2Br$: N, 9.18%. λ_{max} mμ (log ε): 245 (4.37), 295 (4.40), 410 (4.38), 444 (4.37).

5-Amino-4-bromotropolone (XVII).—A solution of XVI (0.9 g.), 5% palladium-on-carbon (0.5 g.) and ethanol (100 ml.) was shaken in hydrogen atmosphere until the uptake of hydrogen had reached one mole equivalent. The reaction mixture, from which the catalyst was removed, was evaporated in vacuo and the residue was crystallized from benzene to give XVII (0.12 g.) as yellow needles, m. p. 116~117°C.

Found: N, 6.39. Calcd. for $C_7H_6O_2NBr$: N, 6.48%. λ_{max} mμ (log ε): 235 (4.42), 360 (4.25).

When a mixture of XVII (100 mg.), 5% palladium-on-carbon (100 mg.), and sodium acetate trihydrate (70 mg.), and methanol (15 ml.) was shaken in hydrogen atmosphere until no further hydrogen was absorbed, 5-aminotropolone, undepressed on admixture with an authentic specimen[15], was obtained from the reaction mixture.

The author expresses his sincere gratitude to Professor Y. Kitahara for his unfailing guidance throughout the course of this work, to Mr. S. Endo and Mr. T. Terasawa for their helpful assistance with experiments, and to Messrs. K. Kato, S. Ohyama, A. Iwanaga and S. Azumi for microanalyses.

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[15] T. Nozoe, S. Seto, S. Ebine and S. Ito, *J. Am. Chem. Soc.*, 73, 1895 (1951).