*Preparation of 4-Aminotropolones by Amination of 3-Iodotropolones with Alkali Amides in Liquid Ammonia**

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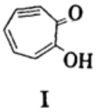
Elimination-addition mechanisms involving intermediates of benzyne or dehydrobenzene (C_6H_4) type have been established in the rearrangement reactions occurring in the amination of non-activated aryl halides[1], high-temperature alkaline hydrolysis of aryl halides[2], and the coupling of aryl halides and phenyllithium[3]. Further, such mechanism has been extended to the rearrangement reaction in the amination of 3-bromopyridine[4] and the coupling of 1-chlorocyclohexene and phenyllithium[5].

The possibility of the extension of the elimination-addition mechanism involving dehydrotropolone (I), an intermediate corresponding to benzyne, in the field of tropolones has been suggested in the formation of 4-hydroxytropolone[6,7] (VII) and 4-hydroxy-6-isopropyltropolone[8] (XVII) on respective high-temperature alkaline hydrolysis of 3-bromotropolone (II) and 3-bromo-6-isopropyltropolone (V), and the formation of 4-cyanotropolone[6,9] (VIII) on high-temperature treatment of 3-bromotropolone (II) with potassium cyanide. Johnson and his co-workers[10] stated, with no experimental evidence, that dehydrotropolone (I) would be liable to form more easily than benzyne because of a decrease of the steric strain.



I

For the purpose of synthesizing 4-aminotropolones, examinations were made on the amination of 3-iodotropolones with alkali amides in liquid ammonia, the results of which will be described below in this paper.

Reaction of 3-iodotropolone (III) with three moles of potassium amide in liquid ammonia resulted in 4-aminotropolone (IX) in low yield. In order to confirm its structure, the same aminotropolone was synthesized through the Curtius reaction from 4-carboxytropolone (X), the structure of which had been established. The tropolone X was converted to 4-ethoxycarbonyltropolone (XI) in a good yield on being heated with ethanolic hydrogen chloride. The melting point (91°C) and the ultraviolet spectrum of XI were in agreement with those of the authentic sample[11] which had been obtained from the ring-enlargement of veratrole with ethyl diazoacetate. When treated with hydrazine hydrate under the ordinary condition, XI yielded the hydrazide XII which was converted with nitrous acid to the corresponding azide less soluble in water. Hydrolysis of the azide in an acidic medium afforded 4-aminotropolone (IX) in a poor yield.

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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); ibid., **78**, 601 (1956).

[2] A. T. Bottini and J. D. Roberts, ibid., **79**, 1458 (1957).

[3] G. Wittig and L. Pohmer, *Angew. Chem.*, **67**, 348 (1955).

[4] R. Levine and W. W. Leake, *Science*, **121**, 780 (1955).

[5] F. Scardiglia and J. D. Roberts, *Tetrahedron*, **1**, 343 (1957).

[6] T. Nozoe and Y. Kitahara, *Proc. Japan Acad.*, **30**, 204 (1954).

[7] Y. Kitahara, *Science Repts. Tohoku Univ., Ser. I*, **39**, 258 (1956).

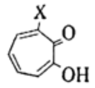
[8] T. Toda, private communication.

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

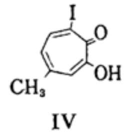
[10] R. B. Johns, A. W. Johnson and M. Tisler, *J. Chem. Soc.*, **1954**, 4605.

[11] J. R. Bartels-Keith, A. W. Johnson and W. I. Taylor, ibid., **1951**, 2352.

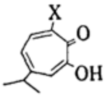
Amination of 3-iodo-6-methyltropolone[12] (IV) and 3-iodo-6-isopropyltropolone (VI) with potassium amide under the same condition as that described above resulted in the formation of 4-amino-6-methyltropolone (XIII) and 4-amino-6-isopropyltropolone (XVIII), respectively. The structure of the former XIII was confirmed by the synthesis of XIII from 4-carboxy-6-methyltropolone[13] (XIV) according to an authentic method[14]. The structure of XVIII was deduced from the close resemblance of its ultraviolet absorption to those of IX and XIII.



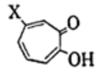
II : X=Br
III : X=I



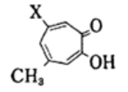
IV



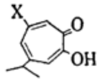
V : X=Br
VI : X=I



VII : X=OH
VIII : X=CN
IX : X=NH_2
X : X=COOH
XI : X=COOEt
XII : X=$CONHNH_2$



XIII : X=NH_2
XIV : X=COOH
XV : X=COOEt
XVI : X=$CONHNH_2$



XVII : X=OH
XVIII : X=NH_2

It has been known to date that the halogen atom in 3-halotoropolone is reactive and undergoes various anionoid substitutions such as the following: nitrile formation with cuprous cyanide[6], methoxylation with sodium methoxide[6], phenoxylation with sodium phenoxide[6], arylsulfonamidation with potassium arylsulfonamide[6], hydroxylation with concentrated caustic alkali[7], with aqueous sodium naphthalene-β-sulfonate[15] and with hydrochloric acid[10], and alkylation with some active methylene compounds[16]. In this reaction with potassium amide in liquid ammonia, however, the normal substitution products, 3-aminotropolones, were not isolated. This means probably that the elimination of iodide ion precedes the substitution in this reaction and the subsequent addition results in formation of 4-aminotropolones. The use of sodium amide instead of potassium amide and the use of 3-bromotropolones in place of the iodo compounds caused a marked decrease in the yield of the aminotropolones. Secondary and tertiary amines are expected to be produced as by-products[17], but no such products were separated in pure states.

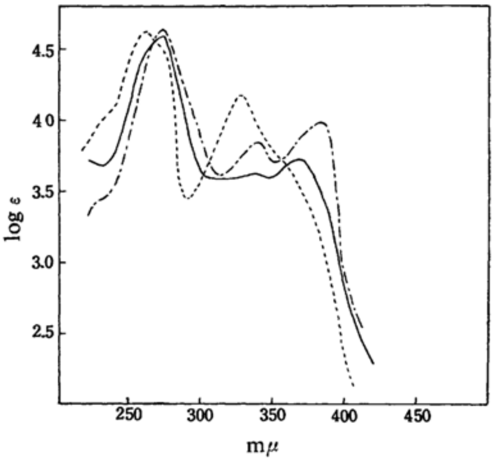


Fig. 1. The ultraviolet absorption spectra of 4-aminotropolone (IX) ; curve ——, in methanol, curve ----, in 0.1 N HCl, curve —·—·, in 0.1 N NaOH.

Fig. 1 indicates the ultraviolet absorption spectra of 4-aminotropolone (IX). In acid solution, the band near 350 mμ in the neutral solution shows a blue shift to give a tropone-type spectrum, whereas in alkaline solution it shows a red shift to give a tropolone-type spectrum. The ultraviolet spectra of the other two aminotropolones (XIII and XVIII) are also essentially similar to those of IX. These facts suggest that the aminotropolones possess an amphoteric character.

In Table I are listed some principal absorption bands in the infrared spectra of the aminotropolones.

TABLE I. MAIN ABSORPTIONS OF 4-AMINOTROPOLONES IN THE INFRARED SPECTRA (cm^{-1})

	ν_{NH_2}		ν_{OH}	I	II	δ_{C-N}
IX	3410	3325	3185	1640	1596	1335
XIII	3400	3340	3190	1648	1592	1325
XVIII	3400	3330	3195	1640	1588	1338

According to the result of Kinumaki, Ikegami and Aida[18], the carbonyl frequencies, measured in the solid state, of aminotropolones (3- and

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[12] T. Nozoe, K. Doi, K. Kitahara and K. Omura, This Bulletin, to be published.

[13] W. D. Crow and R. D. Haworth, *J. Chem. Soc.*, **1951**, 1325.

[14] W. D. Crow, R. D. Haworth and P. R. Jefferies ibid., **1952**, 3705.

[15] T. Nozoe, K. Doi and T. Hashimoto, This Bulletin, **33**, 1071 (1960).

[16] K. Takase, to be published.

[17] J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **23**, 904 (1958).

[18] S. Kinumaki, Y. Ikegami and K. Aida, *Bull. Chem. Research Inst. Tohoku Univ.*, **6**, 49 (1956).

5-aminotropolones, and 3, 5- and 3, 7-diaminotropolones) appear in the region of 1660~1609 cm^{-1}, whereas 4-aminotropolones have two bands (I and II bands in Table I) in the same region, and the II band of these two is stronger in its intensity and, therefore, it may be taken as the band due to the carbonyl stretching vibration in the respective aminotropolones. This assumption appears to be reasonably supported from the following observation on the relationship between frequencies of the II band and substituent constants.

It has been elucidated by many investigators[19] that the carbonyl frequencies of acetophenones, benzophenones, benzaldehydes and benzoic acids, and the substituent constants are in good linear relationship. It has also been found[20] in the tropolone field that Hammett's rule is satisfied between the dissociation constants and the substituent constants in a way similar to the case of benzene derivatives. It follows, naturally, that there would also be the same relationship between carbonyl frequencies of 4- and 5-substituted tropolones and substituent constants.

In Table II are shown the values of carbonyl frequency of several of the 4- and 5-substituted tropolones and substituent constants, σ, concerned.

TABLE II. RELATIONSHIP BETWEEN CARBONYL FREQUENCIES AND SUBSTITUENT CONSTANTS IN SEVERAL SUBSTITUTED TROPOLONES

Substituent	4-NH_2	4-Me	4-iso-C_3H_7	H
$\nu_{C=O}$*, cm^{-1}	1056	1610[21]	1605[22]	1613[23]
σ*2	-0.161	-0.069	-0.120*3	0.000

Substituent	4-Cl	4-Br	4-$COCH_3$	5-Me
$\nu_{C=O}$, cm^{-1}	1615[24]	1613[24]	1620[24]	1603[21]
σ	0.373	0.391	0.306	-0.17

* All were measured in solid state.

*2 L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill Book Co., New York, N. Y. (1940).

*3 σ_m for *tert*-C_4H_9 was used.

Graphically, a fairly good linear relationship is observed between ν and σ. Therefore, the II band in Table I is considered to correspond to the carbonyl stretching frequencies of the 4-aminotropolones. The use of the values measured in solution makes it probable to expect the existence of a better linear relationship between them.

Experimental

The ultraviolet absorptions were determined with a Beckman model DU spectrophotometer. The infrared spectra were measured on potassium bromide disks with a Perkin-Elmer model 21 infrared spectrometer, using a rock salt prism.

Amination of 3-Iodotropolones with Potassium Amide.

4-Aminotropolone (IX).—To a solution of liquid ammonia (100 ml.) and potassium amide obtained from potassium (2.6 g.), 3-iodotropolone[25] (III, 5.5 g.) was added during about 10 min., and the reaction mixture was allowed to reflux at the boiling point of ammonia. For the reaction was used a 300 ml. three-necked, round-bottomed flask equipped with a dry ice reflux condenser, an efficient mechanical stirrer and an Erlenmeyer flask fitted to one of the tubulatures of the reaction vessel by a section of rubber tubing for adding the iodotropolone. After 2 hr., ammonium chloride (2.4 g.) was added to the mixture and the ammonia was allowed to evaporate. The residual solid was dissolved in water (200 ml.), acidified to Congo red with concentrated hydrochloric acid, and extracted with chloroform (300 ml.). The extract was shaken with three 50 ml. portions of 6 N hydrochloric acid. This acid solution was combined with the foregoing aqueous solution, neutralized with sodium carbonate, and extracted continuously with ether for 5 hr. The ether extract, after evaporation of the solvent, sublimation in vacuo, and subsequent crystallization from methanol, yielded 4-aminotropolone (IX, 0.7 g.) as colorless needles, m. p. 187~188°C.

Found: C, 61.25; H, 5.08; N, 10.19. Calcd. for $C_7H_7O_2N$: C, 61.31; H, 5.15; N, 10.21%.

λ_{max} mμ (log ε): 274 (4.60), 338 (3.62), 367 (3.72), in methanol; 260 (4.61), 328 (4.16) in 0.1 N HCl; 273 (4.64), 338 (3.86), 385 (4.00) in 0.1 N NaOH.

Picrate: A mixture of the aminotropolone (IX, 35 mg.), picric acid (120 mg.), and methanol (5 ml.) was heated under reflux for 5 min., cooled, and the residual precipitate was collected. Yellow prisms, m. p. 202~203°C.

Found: N, 15.08. Calcd. for $C_7H_7O_2N \cdot C_6H_3O_7N_3$: N, 15.06%.

4-Amino-6-methyltropolone (XIII).—To a stirred mixture of liquid ammonia (300 ml.) and potassium amide prepared from potassium (4.7 g.) was added 3-iodo-6-methyltropolone[12] (IV, 10 g.) at -50°C for 5 min. and the reaction mixture was allowed to reflux for 2 hr. When the following procedure was carried out essentially as described in the preceding experiment, the aminotropolone (XIII, 1.7 g.) was obtained as colorless needles (from methanol) of m. p. 199~200°C (reported[13] m. p. 199~200°C).

Found: C, 63.59; H, 5.85; N, 8.85. Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27%.

λ_{max} mμ (log ε): 274 (4.64), 340 (3.67), 360 (3.68) in methanol; 260 (4.54), 328 (4.06) in 0.1 N HCl; 273 (4.62), 340 (3.84), 380 (3.95) in 0.1 N NaOH.

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19) N. Fuson et al., *J. Am. Chem. Soc.*, **76**, 2526 (1954); R. N. Johns et al., *Can. J. Chem.*, **35**, 504 (1957); H. W. Thompson et al., *Spectrochim. Acta*, **9**, 208 (1957); M. St. Flett, *Trans. Faraday Soc.*, **44**, 767 (1948).

20) N. Yui, *Science Repts. Tohoku Univ., Ser. I*, **40**, 114 (1956).

21) T. Nozoe, T. Mukai et al., ibid., **35**, 242 (1951).

22) K. Kuratani et al., This Bulletin, **25**, 250 (1952).

23) S. Kinumaki, K. Aida and Y. Ikegami, *Science Repts. Research Inst. Tohoku Univ.*, **A8**, 263 (1956).

24) K. Doi, This Bulletin, to be published.

25) Y. Kitahara and T. Arai, *Proc. Japan Acad.*, **27**, 423 (1951).

Picrate: Yellow needles (from methanol), m. p. 178~180°C.

Found: N, 14.64. Calcd. for $C_8H_9O_2N \cdot C_6H_3O_7N_3$: N, 14.94%.

4-Amino-6-isopropyltropolone (XVIII). — To a stirred mixture of liquid ammonia (400 ml.) and potassium amide obtained from potassium (8 g.) was added 3-iodo-6-isopropyltropolone[26] (VI, 19 g.) during 10 min. When the procedure which followed was carried out as the above, the aminotropolone (XVIII, 3.7 g.) was isolated from benzene as colorless needles of m. p. 145~146°C.

Found: C, 67.32; H, 7.18; N, 8.00. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82%.

λ_{max} mμ (log ε): 275 (4.63), 340 (3.68), 360 (3.66) in methanol; 263 (4.55), 328 (4.08) in 0.1 N HCl; 273 (4.74), 338 (3.96), 385 (4.10) in 0.1 N NaOH.

Picrate: Yellow needles (from benzene-methanol), m. p. 96~97°C.

Found: N, 13.49. Calcd. for $C_{10}H_{13}O_2N \cdot C_6H_3O_7N_3$: N, 13.72%.

Preparation by the Curtius Reaction.

4-Aminotropolone (IX). — After dry hydrogen chloride was saturated in a mixture of 4-carboxytropolone (X, 1.1 g.) and ethanol (20 ml.), the mixture was heated under reflux for one hour. The solution was evaporated to dryness under reduced pressure, the residue was sublimed in vacuo, and the sublimate was recrystallized from cyclohexane to give 4-ethoxycarbonyltropolone (XI, 0.95 g.) as yellow needles, m. p. 91°C (reported[11] m. p. 90~91°C).

Found: C, 61.74; H, 5.23. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19%.

λ_{max}^{MeOH} mμ (log ε): 250 (4.43), 313 (3.69), 325 (3.73), 375 (3.72), 388 (3.68).

A solution of XI (1.5 g.), 80% hydrazine hydrate (1 ml.) and ethanol (10 ml.) was heated under reflux for 3 hr.; the solution was concentrated to a small volume under reduced pressure, and the residue so obtained was recrystallized from ethanol to form tropolone-4-carbohydrazide (XII, 0.7 g.) as yellow needles, m. p. 258°C (decomp.).

Found: N, 15.63. Calcd. for $C_8H_8O_3N_2$: N, 15.55%.

λ_{max}^{MeOH} mμ (log ε): 230 (4.16), 245 (4.18), 297 (4.41), 386 (4.29), 440 (4.01).

To a cold stirred solution of XII (0.54 g.), concentrated hydrochloric acid (1 ml.) and water (3 ml), was added dropwise a solution of sodium nitrite (0.21 g.) in water (1 ml.), and the deposited colorless azide was collected. The crude azide was then added to a solution of acetic acid (5 ml.), concentrated hydrochloric acid (1 ml.) and water (0.5 ml.), and the mixture was heated under reflux for 2 hr. This was evaporated under reduced pressure to a small volume, diluted with water (40 ml.), neutralized with sodium carbonate, and extracted with ether continuously for 5 hr. The ether extract, after evaporation of the solvent and crystallization from methanol, afforded the aminotropolone (IX, 0.25 g.), m. p. and mixed m. p. 187~188°C.

4-Amino-6-tropolone (XIII).—A cold mixture of 4-carboxy-6-methyltropolone (XIV, 1.8 g.) and ethanol (10 ml.), was saturated with dry hydrogen chloride, and the mixture was heated under reflux for 2 hr. By the procedure as described in the preceding experiment 4-ethoxycarbonyl-6-methyltropolone (XV, 1.92 g.) was obtained as pale yellow needles (from cyclohexane), m. p. 103~104°C.

Found: C, 63.62; H, 5.63. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81%.

λ_{max}^{MeOH} mμ (log ε): 251 (4.46), 312 (3.66), 330 (3.72), 378 (3.72), 388 (3.72).

A mixture of XV (0.21 g.) and 80% hydrazine hydrate (0.19 g.) was heated on a boiling water bath for 20 min., acidified with dilute acetic acid, and an insoluble solid was collected. Recrystallization of it from ethanol gave 6-methyltropolone-4-carbohydrazide (XVI, 0.13 g.) as yellow leaflets, m. p. 177~178°C (decomp.) (reported[13] m. p. 171~172°C (decomp.)).

Found: N, 14.76. Calcd. for $C_9H_{10}O_3N_2$: N, 14.43%.

λ_{max}^{MeOH} mμ (log ε): 247 (4.19), 300 (4.43), 389 (4.28), 444 (3.99).

XVI was derived, by the reported experimental procedures[13], to the aminotropolone (XIII), m. p. and mixed m. p. 199~200°C.

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[26] T. Nozoe et al., *Science Repts. Tohoku Univ., Ser. I*, 36, 299 (1952).