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The Nucleophilic Substitution Reactions of 2-Aminotropone Derivatives

Takashi Toda, Shôji Ryu[1] and Tetsuo Nozoe

Department of Chemistry, Faculty of Science, Tohoku University, Katahira-cho, Sendai

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The nucleophilic substitution reactions of 2-aminotropone (I), 2-methylaminotropone (II), 2-dimethylaminotropone (III), and 2-troponyl trimethylammonium iodide (IV), and their alkyl derivatives were investigated. It was found that the properties of I and II are similar to those of tropolones. On the other hand, those of III are analogous to those of tropolone methyl ethers, while those of IV are, rather, comparable to those of 2-halotropones or tropolone tosylates.

2-Aminotropone (I) and its derivatives have been obtained early in the history of troponoid chemistry.[2-4] However, only a few examples of the electrophilic and nucleophilic substitution reactions of these compounds have been investigated[3,4] other than the syntheses of many 1-azaazulan-2-one derivatives from 2-aminotropones by the action of active methylene compounds.[3b,4,5] Recently, the present authors investigated the electrophilic substitution reactions[6] of I and its *N*-alkyl derivatives —2-methylaminotropone (II)[3a] and 2-dimethylaminotropone (III)[3i]— and found that the reaction of III caused the hydrolysis of the dimethylamino group, thus giving tropolone derivatives.[6] The reaction mechanism of the hydrolysis was later clarified.[7] In this paper, the authors wish to report their

1) Present address: Zenyaku Kogyo K. K., Oizumi-machi, Nerima-ku, Tokyo.

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findings on the nucleophilic substitution reactions of I, II, III, and 2-troponyl trimethylammonium iodide (IV)[3i] and their alkyl derivatives; especially, the properties of these compounds in relation to nucleophiles will be compared with those of tropolones, tropolone methyl ethers, tropolone tosylates, and 2-halotropones.

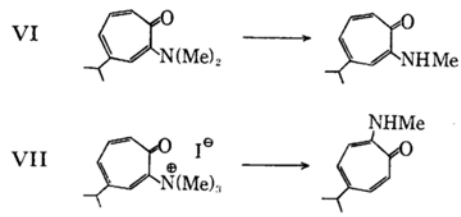
I: R=NH_2 IV: R=$N(Me)_3^{\oplus}\cdot I^{\ominus}$
II: R=NHMe V: R=OH
III: R=$N(Me)_2$

It has been shown that I gives tropolone (V) by the action of aqueous alkali.[3i] II and III afforded V under the same reaction conditions; however, IV gave a rearrangement product, benzoic acid. Although the treatment of III and IV with hydrochloric acid in alcohol gave V in a good yield, the same treatment of I and II resulted in the recovery of the starting substances. The action of hydrogen chloride on I, II, and III in absolute dioxane gave the corresponding hydrochlorides; on the other hand, IV afforded 2-chlorotropone.[3a,8] When III was treated with sodium methoxide in methanol, V and its methyl ether were obtained in 74% and 25% yields respectively. The treatment of IV resulted in 59% methyl benzoate and 26% benzoic acid, but I and II were recovered unchanged under the same reaction conditions. I, II, and III are stable entities on heating. IV is recovered when heated in acetone, methanol, and ethanol for a short period; however, when it is heated in water or directly under reduced pressure, IV gives III, and methyl iodide is liberated. III was a detectable product only by the treatment of IV with silver oxide with heating; however, when IV was treated with silver oxide in ethanol, benzoic acid was obtained in a good yield.

I and II were recovered unchanged when treated with amines at room temperature or even when heated with aniline under reflux. On the other hand, III gave I, II, and 2-hydrazinotropone[3a] in good yields by treatment with ammonia, methylamine, and hydrazine respectively. IV also afforded I and II under the same conditions. The treatment of III with *p*-thiocresol, potassium cyanide, cupric cyanide, or potassium thiocyanate resulted in the recovery of the starting substance, while IV gave 2-(*p*-tolylthio)-tropone[8,9] with *p*-thiocresol and III with inorganic cyano compounds.

Generally, the reaction of tropolone methyl ethers with nucleophilic reagents gives normal substitution products.[4,10] On the other hand, the reaction of 2-halotropones and tropolone tosylates with nucleophiles affords abnormal substitution products.[4,10]

The reaction of 2-dimethylamino-4-isopropyltropone (VI)[11] and its methyl iodide (VII) with methylamine gave a normal substitution product, 2-methylamino-4-isopropyltropone, from the former, and an abnormal substitution product, 2-methylamino-5-isopropyltropone,[11] from the latter. Therefore, the reaction mode of 2-dimethylaminotropones is analogous to that of tropolone methyl ethers, and the reactions of their quaternary bases to nucleophilic reagents take place in abnormal ways, much as with 2-halotropones and tropolone tosylates.[12]



The Grignard reaction of tropolone methyl ethers gave 2-substituted tropone derivatives[13-15]; the reaction mechanism has been proved to proceed by way of 1,8-addition.[16]

The reactions of III with methylmagnesium bromide, phenylmagnesium bromide, and butyllithium afforded 2-methyltropone,[17] 2-phenyltropone,[13a,14] and 2-butyltropone[14] respectively in good yields. In order to clarify the mechanism of the above reaction, the reaction of VI with phenylmagnesium bromide was investigated and found to give 5-isopropyl-2-phenyltropone.[13,17] Therefore, the Grignard reaction of 2-dimethylaminotropone proceeds in the fashion of 1,8-addition, similar to that of tropolone methyl ethers.

8) a) B. A. Abadir, J. W. Cook, L D. Loudon and D. K. V. Steel, *J. Chem. Soc.*, **1952**, 2350. b) W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **74**, 5683 (1952).

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10) Y. Kitahara, *Sci. Repts. Tohoku Univ., I*, **39**, 250 (1956).

11) T. Sato, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **80**, 1056 (1959).

12) The reactions of deuterio derivatives of III and IV with several different kinds of nucleophiles were investigated by T. Kanno and S. Ito. The results obtained agreed with ours. The Master's thesis of T. Kanno, submitted to Tohoku University.

13) a) T. Nozoe, T. Mukai and J. Minegishi, *Proc. Japan Acad.*, **27**, 419 (1951). b) T. Nozoe, S. Seto, T. Ikemi, T. Sato and K. Watanabe, *ibid.*, **28**, 413 (1952).

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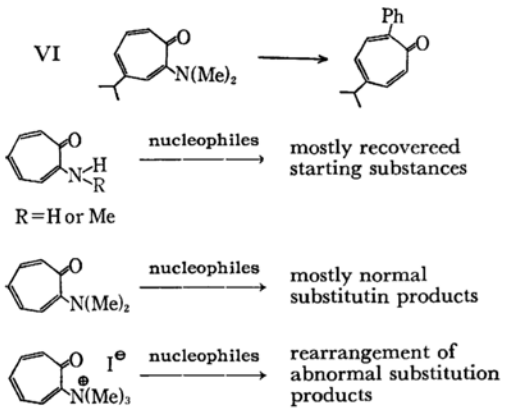
15) P. Akroyd, R. D. Haworth and P. R. Jefferies, *J. Chem. Soc.*, **1954**, 286.

16) R. D. Haworth and P. B. Tinker, *ibid.*, **1955**, 911.

17) T. Mukai, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **79**, 1547 (1958).



As has been shown above, 2-aminotropones and 2-methylaminotropones behave similar to tropolones[4] in both electrophilic[6] and nucleophilic substitution reactions. On the other hand, 2-dimethylaminotropones show different properties toward electrophiles compared with those of tropolone methyl ethers,[6] but they possess properties analogous with those of tropolone methyl ethers toward nucleophilic reagents. The properties of the quaternary bases of 2-dimethylaminotropones are similar to those of 2-halotropones and troplone tosylates.[4] The reason why alkaline hydrolyses are the only exchange reactions of the amino and methylamino groups of I and II with nucleophiles to take place is as follows: a hydrogen atom on the nitrogen in these compounds can be ionized, especially under the basic conditions, and the attack of nucleophiles on the formed aminotroponates is not easy, while the attacks of electrophiles on such entities occur readily.[6] A weak nucleophile such as the chloride anion can not be exchanged with amino groups of I, II, and III, even under acidic conditions. Only IV gives 2-chlorotropone, as has been mentioned above.

Experimental[18]

Base Hydrolyses. a) III (450 mg) was heated under reflux for 4 hr with 5 m*l* of 1.6N ethanolic potassium hydroxide. On the removal of the ethanol, a yellow crystalline mass was obtained; water was then added, and the solution was made slightly acidic (pH 6—6.5) with dilute hydrochloric acid and extracted with chloroform. On the evaporation of the solvent under reduced pressure, the residual oil crystallized in needles; it was recrystallized from petroleum ether - cyclohexane to give light yellow needles, mp 46—47°C (400 mg); undepressed when mixed with an authentic sample of tropolone.

b) From 450 mg of II, 400 mg of V were obtained by the same procedure.

c) VI was hydrolyzed as above to give light yellow plates, mp 49—50°C, which was identical with that of an authentic sample of hinokitiol. Yield, 150 mg from 200 mg of VI.

d) IV (600 mg) was refluxed for 3 hr on a water bath with 5 m*l* of 1.6N ethanolic potassium hydroxide. After the solution had been cooled, water was added; then the solution made weakly acidic with dilute hydrochloric acid and extracted several times with ether. An oily product solidified on the removal of the solvent, and recrystallization from benzene yielded white needles, mp 117—118°C (230 mg), which was undepressed on admixture with benzoic acid.

Acid Hydrolyses. a) I (243 mg) was heated under reflux with a mixture of 10% hydrochloric acid (5 m*l*), water (3 m*l*), and ethanol (5 m*l*) on a water bath for 6 hr. After the reaction mixture had cooled, it was made neutral and extracted with chloroform. The removal of the solvent and the recrystallization of the residue from cyclohexane yielded 220 mg of pale yellow needles, mp 105—106°C, identified as the recovered starting material from its IR and UV and by a mixed-melting-point determination with an authentic sample of I.

b) When the procedure described above was run using 270 mg of II, 250 mg of II, mp 76—77°C, were recovered.

c) When 300 mg of III were treated as above, 200 mg of V were obtained, mp 47—47.5°C. Its mixed melting point with an authentic sample of tropolone was undepressed.

The mother layer, after the separation of the tropolone, was made neutral with sodium bicarbonate, and extracted with chloroform, and the extract was dried over sodium sulfate. On the removal of the solvent, a brownish-yellow oily residue was obtained. Its IR and UV spectra were identical with those of III, and the oil gave a picrate, mp 144—146°C; yield, 75 mg.

d) When IV was treated as above, it gave tropolone; yield, 200 mg from 500 mg of IV.

Reactions with Anhydrous Hydrogen Chloride in Dioxane. a) I (365 mg) was dissolved in 5 m*l* of anhydrous dioxane in an ampoule through which dry hydrogen chloride was passed. The hydrogen chloride-saturated reaction mixture was then heated on a boiling-water bath for 3 hr. After the ampoule had been cooled, it was opened and the contents transferred to a small, round-bottomed flask. The removal of the solvent left white needles, mp 198—200°C; yield, 450 mg. IR: ν_{KBr} 3000—2400 cm^{-1} (broad, $\nu_{NH_2^+}$). This was dissolved in water, neutralized with aqueous sodium bicarbonate, extracted with benzene, and dried over sodium sulfate; the subsequent removal of the solvent gave a pale yellow solid. The recrystallization of the solid from cyclohexane-benzene afforded 320 mg of needles, mp 105—107°C, which had IR and UV spectra identical with those of an authentic specimen of 2-aminotropone.

b) When II (405 mg) was treated at above, a nearly quantitative yield of the hydrochloride (mp 250°C) was obtained as white needles. On the neutralization of the hydrochlorides, 350 mg of the starting substance (mp 74—76°C) were recovered.

c) From 450 mg of III, 530 mg of the hydrochloride (mp *ca.* 250°C) were obtained by the above procedure. On neuntralization with dilute sodium carbonate, followed by the usual working-up and alumina chromatography, 320 mg of III were regenerated.

18) All melting points are uncorrected.

d) IV (500 mg) was heated with 5 m*l* of hydrogen chloride-saturated dioxane in a sealed tube at 40—50°C for 4 hr. By the usual working-up and by purifying the reaction product through alumina chromatography, 200 mg of white needles were obtained, mp 59—60°C. This was found by a mixed-melting-point determination to be identical with and authentic sample of 2-chlorotropone.

Reactions with Sodium Methoxide. a) III (450 mg) was refluxed for 3 hr with a solution of sodium methoxide prepared by dissolving 90 mg of sodium in 5 m*l* of freshly-distilled absolute methanol, while moisture was carefully excluded. When the methanol was evaporated under reduced pressure, the reaction mixture partly solidified; it was washed three times with 2N potassium hydroxide and then extracted with benzene. The benzene layer was dried over sodium sulfate, and evaporated; the residue, on vacuum distillation, afforded a light yellow oil, 300 mg, whose IR spectrum was identical with that of 2-methoxytropone. From the product, a picrate, mp 115—117°C, was prepared in the usual way; its melting point was undepressed on admixture with an authentic sample of 2-methoxytropone picrate.

The water layer obtained in the alkaline washings described above was acidified, extracted with chloroform, dried, and evaporated to dryness. The residue crystallized from cyclohexane-light petroleum gave light yellow needles, mp 48—49°C, identified as tropolone by a mixed-melting-point determination.

b) I and II were treated by the procedure described above. The starting substances were recovered unchanged in nearly quantitative yields in both cases.

c) Metallic sodium (110 mg) was dissolved in 5 m*l* of absolute methanol, and to the resulting solution IV (600 mg) was added. The reaction mixture was allowed to stand at room temperature for 2 hr, and then refluxed on a water bath for one hour. The methanol was removed under reduced pressure, and to the residue water was added; the solution was washed three times with 2N potassium hydroxide to remove free benzoic acid, and it was extracted with benzene. The benzene layer was dried, and evaporated, and the residual oil was purified by vacuum distillation to afford a colorless oil (160 mg) which was found by a comparison of their IR spectra to be identical with an authentic sample of methyl benzoate.

From the water layer, benzoic acid was obtained (65 mg) following the same procedure after acidification with dilute hydrochloric acid and subsequent extraction with ether. The identification was made by a mixed-melting-point determination with an authentic sample.

Reactions with Amines and Hydrazine Hydrate. *2-Aminotropone.* a) III (450 mg) was allowed to react with an excess of liquid ammonia in a sealed tube at room temperature for 6 days. The removal of the excess ammonia and the liberated dimethylamine left a solid residue which was then recrystallized from cyclohexane-benzene to give 350 mg of pale yellow needles, mp 105—106°C; this substance was identified as I by a study of its IR spectrum and by a mixed-melting-point test with an authentic sample.

b) IV was treated as above to give 300 mg of I from 600 mg of IV.

c) II was treated in the same manner, but the starting substance was recovered quantitatively.

2-Methylaminotropone. a) III was allowed to react with a large excess of liquid methylamine in a sealed tube at room temperature for 6 days. The recryltallization of the solid residue obtained after the removal of the amine afforded yellow needles, mp 78—79°C, identified as 2-methylaminotropone; yield, 290 mg from 450 mg of III.

b) The treatment of IV (600 mg) with an excess of liquid methylamine yielded 350 mg of II.

c) I was recovered quantitatively when treated as above,

4-Isopropyl-2-methylaminotropone VI (200 mg) was allowed to react with liquid methylamine in a sealed tube for 4 days at room temperature. On the removal of the excess amine, the reaction mixture solidified; it was recrystallized from petroleum ether to give yellow crystals, mp 83—84°C (180 mg), undepressed on admixture with an authentic sample of 4-isopropyl-2-methylaminotropone.[19]

5-Isopropyl-2-methylaminotropone. VII (350 mg) was treated as above with liquid methylamine. After the excess amine had been removed, the product was dissolved in benzene and chromatographed on alumina. The benzene effluent gave a picrate in the usual way; the mp 208—210°C from ethanol did not show any depression on admixture with the authentic picrate of 5-isopropyl-2-methylaminotropone.

2-Hydrazinotropone. a) III (450 mg) was dissolved in 10 m*l* of ethanol, and to the resulting solution there were added 250 mg of 80% hydrazine hydrate. The reaction mixture was then refluxed on a water bath for 40 min, The evaporation of the solvent left a crystalline residue which was recrystallized from cyclohexane to give 400 mg of 2-hydrazinotropone, mp 94—95°C. The identification was made by study of its IR spectrum and by a mixed-melting-point determination with an authentic sample of 2-hydrazinotropone.

b) IV (600 mg) was treated with 170 mg of 80% of hydrazine hydrate in 10 m*l* of ethanol as above to gave 135 mg of 2-hydrazinotropone.

c) When I and II were treated under the same reaction conditions as above, the starting sudstances were recovered quantitatively.

Attempted Reaction of I and II with Aniline. a) A mixture of 365 mg of I and 5 m*l* of aniline was heated to reflux on an oil bath at 200°C for 3 days. The aniline was then expelled under reduced pressure, and the the black resinous residue was subjected to vacuum (0,1 mmHg) sublimation to give brownish-yellow prisms, mp 103—105°C. The crude crystals were further recrystallized from cyclohexane-benzene to afford 330 mg of recovered I, which was confirmed by a mixed-melting-point determination with an authentic sample of I.

d) The attempted reaction of II with aniline under the conditions described above gave rise to only the recovery of the starting materials unchanged.

Reaction with *p*-Thiocresol. a) IV (600 mg) and *p*-thiocresol (300 mg) were added to an ethanolic solution of sodium ethoxide prepared by dissolving metallic sodium (46 mg) in 10 m*l* of absolute ethanol. The reaction mixture was then refluxed, while all

19) Unpublished, prepared in the authors' laboratory.

moisture was excluded, on a water bath for 2 hr. After the solvent had been removed, the residual solid mass was recrystallized from cyclohexane to afford yellow crystals, mp 144—145°C (450 mg), identified as 2-(*p*-tolylthio)-tropone by a study of the IR spectrum and by a mixed-melting-point determination with an authentic sample.

b) When II was treated with a 1-equivalent mole of *p*-thiocresol and with 2-equivalent moles of sodium ethoxide under the same conditions, the starting substances were recovered in *ca.* a 90% yield.

Reaction with Silver Oxide. Silver nitrate (500 mg) was dissolved in 5 m*l* of water. To the resulting solution there was added a 1N sodium hydroxide solution until no more precipitation occurred. The grayish-brown precipitate was washed thoroughly until neutral to pH test paper and then used directly in the subsequent step.

To a stirred solution of IV (290 mg) in 50% aqueous ethanol, the moist silver oxide prepared above was added, portion by portion, at room temperature. Immediately after the addition of the reagent, a conspicuous evolution of trimethylamine was observed; it was detected from its odor, the alkaline reaction to pH test paper, and a picrate formation; mp 214—216°C.

The reaction mixture exhibited an alkalinity at pH *ca.* 8.5 (pH test paper) because of the dissolved trimethylamine. The reaction mixture, after having been stirred for 15 min at room temperature, was made acidic (pH *ca.* 4) and extracted with ether (20 m*l* ×4). The removal of the solvent and recrystallization from benzene afforded 110 mg of needles, mp 120—121.5°C, undepressed in a mixed-melting-point test with authentic benzoic acid.

b) When IV was reacted with dry silver oxide in xylene at 150°C for 5 hr and then worked-up as usual, *ca.* 90% of III was obtained.

Reaction with Organometallic Compounds. a) To a stirred solution of phenylmagnesium bromide prepared from bromobenzene (3.4 g) and magnesium ribbons (525 mg) in 50 m*l* of anhydrous ether under a nitrogen stream, there was added, drop by drop, a solution of III (1.0 g) in 30 m*l* of anhydrous ether; the reaction mixture was then heated under reflux for one hour. Upon the addition of the reactant, a solid yellowish mass attached to the wall of the vessel gradually turned grey white. After refluxing, 50 m*l* of a 40% ammonium chloride solution was added. The ether layer was separated, and the water layer was extracted several times with ether; then the combined organic layer was washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The residue which solidified on cooling was purified through vacuum sublimation and then recrystallized from cyclohexane to give 1.05 g of needles (mp 84°C, which did not show any depression on admixture with authentic 2-phenyltropone).

b) An ethereal solution of III (1.0 g) was added to a stirred solution of methylmagnesium iodide, and then reacted as above. The residual oil, on vacuum distillation, gave 860 mg of a light yellow oil which was identified as 2-methyl tropone by a comparison of its IR spectrum with that of an authentic specimen.

c) III (500 mg) was dissoved in 100 m*l* of dry ether, and into the resulting solution there was vigorously stirred, drop by drop and in a nitrogen atmoshpere, an ethereal solution containing 7 m*l* of 1.8 mol *n*-butyllithium (supplied by Japan Chem. Industry K. K.). The reaction mixture was subjected to gentle reflux for 1.5 hr and then decomposed with dilute hydrochloric acid; the product was taken up in ether and dried. After the removal of the solvent, the residual oil was purified through vacuum distillation to give 500 mg of oil identified as 2-*n*-butyltropone by a comparison of its IR spectrum with that of an authentic specimen prepared by the reaction of 2-methoxytropone with *n*-butyllithium.[14]

d) VI (500 mg) was allowed to react with phenylmagnesium bromide prepared from magnesium ribbons (250 mg) and bromobenzene (1.57 g) in an ethereal solution with stirring for 2 hr under a nitrogen stream. After the usual working-up, the oily product thus obtained was chromatographed on alumina, and from the cyclohexane effluent, on the removal of the solvent, there were obtained pale yellow plates (mp 86—88°C, undepressed on admixture with an authentic sample of 5-isopropyl-2-phenyltropone).

Reaction with Potassium Thiocyanate. IV was dissolved in dimethylformamide, and to the resulting solution 2 equimoles of potassium thiocyanate were added. The reaction mixture was then refluxed for 3 hr and the excess solvent was removed under reduced pressure. After the usual working up, the residual oil was distilled under reduced pressure to give 89% of III, identified by a comparison of its IR spectrum with that of an authentic sample.

When potassium cyanide or cupric cyanide were used instead of potassium thiocyanate, almost the same results were obtained.

The treatment of III with these cyanides under the same conditions resulted in the recovery of the starting substances.