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The Reaction of Tropones with Alkali and Amines in the Presence of the Copper Ammine Complex and Potassium Ferricyanide

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The reaction of tropone and potassium hydroxide in the presence of potassium ferricyanide gave tropolone, salicylaldehyde, and *p*-hydroxybenzaldehyde, while in the presence of the copper ammine complex it afforded 2-aminotropone and salicylonitrile. Similarly, when tropone was reacted with aqueous ammonia, methylamine, or dimethylamine, 2-aminotropone and its *N*-methyl derivatives were formed. The reaction of 2-phenyltropone with ammonia and methylamine, and the reaction of 2-α-naphthyltropone and 4-bromo-2-phenyltropone with methylamine in the presence of copper salt, also afforded 2-aminotropone derivatives and/or salicylaldehyde derivatives.

It is known that tropone is susceptible to bases and that, when treated with aqueous ammonia or alkali, it gives only resinous materials.[1] However, 2-phenyltropone is fairly stable, and when treated with alcoholic sodium hydroxide it gives biphenyl-2-carboxylic acid.[2] In the latter case, the acid is thought to be formed through air oxidation or the disproportionation of a dihydrobenzoic acid derivative formed intermediately. The formation of such dihydrobenzene derivatives was actually observed in the rearrangement of tropone-carboxylic acids and 2-phenyltropone with alkali.[3] In connection with these reactions in which tropone or 2-phenyltropone is involved, it was supposed that if the reaction is carried out in the presence of an oxidizing reagent, benzoic acid derivatives will be formed in good yields. The reaction of tropones with alkali and amines in the presence of metal complexes, such as potassium ferricyanide or copper ammine complexes was, therefore, undertaken. The reaction proceeded, unexpectedly, through the attack of bases on a carbon other than carbonyl carbon of the tropone nucleus, with or without rearrangement, to give 2-aminotropone derivatives or hydroxybenzaldehyde derivatives.

When tropone was heated at 70°C with a dilute potassium hydroxide solution in the presence of potassium ferricyanide for about 30 hr, tropolone (I), salicylaldehyde (II), and *p*-hydroxybenzaldehyde (III) were obtained in about 14, 3 and 8% yields respectively, with the recovery of about 6% of tropone. At first, the formation of benzoic acid was expected, as has been mentioned above, but it could not be isolated. I must be formed by the attack of the hydroxide ion on the C_2 of the tropone nucleus, followed by the hydride (C_2–H) abstraction by ferricyanide (path A); II seems to be produced through the same intermediate, but by the hydride (C_3–H) elimination and rearrangement (path B) as depicted below.

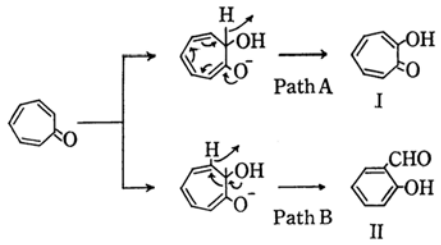

Fig. 1

The rearrangement of 2-halotropone derivatives to hydroxybenzaldehyde derivatives has already been observed in the case where the attack of bases on the carbonyl carbon of the tropone nucleus is hindered sterically. For example, the reaction of 2-bromo-7-chlorotropone and alkali gives 3-chlorosalicylaldehyde,[4] while the reaction of 2-chloro-7-phenyltropone and aniline affords Schiff's base of 3-phenylsalicylaldehyde.[5] Recently Nozoe *et al.* reported that 2-chloro-7-nitrotropone underwent rearrangement to give 4-chloro-3-hydroxy-2-nitrobenzaldehyde without the elimination of the chlorine atom.[6] A similar rearrangement was also reported by Forbes and Warrell.[7] However,

1) T. Nozoe, T. Mukai and K. Takase, *Sci. Repts. Tohoku Univ., Ser. I,* **39**, 164 (1956).
2) T. Nozoe, T. Mukai, J. Minegishi and T. Fujisawa, *ibid.,* **37**, 388 (1953).
3) K. Kikuchi, This Bulletin, **40**, 355 (1967).
4) S. Seto, *Sci. Repts. Tohoku Univ., Ser. I,* **37**, 378 (1954).
5) T. Mukai, This Bulletin, **32**, 272 (1959).
6) T. Nozoe, T. Mukai and K. Sakai, *Tetrahedron Letters,* **1965**, 1041.
7) E. J. Forbes and D. C. Warrell, *Chem. & Ind.,* **1964**, 2056.

so far as the present author is aware, this is the first example in which simple tropone is rearranged to hydroxybenzaldehydes.

It was expected that the copper ammine complex might behave similarly as potassium ferricyanide, and so the reaction of tropone with this salt was next examined. Tropone was warmed with a dilute sodium hydroxide solution in the presence of tetrammine copper sulfate; 2-aminotropone (IV) and salicylonitrile (V) were then isolated in yields of 18 and 38% respectively. IV seems to be formed by the attack of ammonia on tropone, because ammonia is liberated by the action of sodium hydroxide on the copper ammine complex; V must be formed by the dehydrogenation of the salicylidene imine intermediately formed. The formation of nitriles by the reaction of aldehydes and ammonia in the presence of copper salt has already been reported.[8] From the above result, it was suspected that if aqueous ammonia was used instead of sodium hydroxide, the yield of IV and/or V might be increased; in part, this was actually the case, for the yield of IV was raised to about 60%, but V could not be isolated. Similarly, the reaction of aqueous methylamine in the presence of copper ammine salt gave 2-methylaminotropone (VI) in a 62% yield. In the reactions described above, the color of the solution gradually changed from deep blue to pale brown, but on exposure to air it again turned blue, indicating that the reactions actually contained an oxidation step. The reaction of tropone and dimethylamine gave 2-dimethylaminotropone (VII) in about a 20% yield[9] (as its picrate). The reactivity sequence is dimethylamine$\simeq$methylamine$>$ammonia. In these reactions the expected rearranged products, *i. e.*, amide, methylamide or dimethylamide of benzoic acid, could not be obtained.

Similar reactions were carried out with 2-phenyltropone. When it was stirred with copper sulfate in concentrated aqueous ammonia for 30 hr, 2-amino-7-phenyltropone (VIII)[2,10] and colorless crystals (IX) ($C_{13}H_9ON$; mp 184°C) were obtained in 21 and 6% yields respectively. The compound (IX) was proved to be 3-phenylsalicylonitrile by comparing it with a sample obtained from 3-phenylsalicylaldehyde (X)[5] by the usual method. Similarly, when a benzene solution of 2-phenyltropone was stirred with a solution of copper sulfate in methylamine, 2-methylamino-7-phenyltropone (XI)[5] (3%) and yellowish orange crystals (XII) ($C_{14}H_{13}ON$; mp 97°C) (45%) were obtained. The slight warming of XII with dilute sulfuric acid afforded 3-phenylsalicylaldehyde (X). From this result and from the analytical value, XII was thought to be 3-phenylsalicylidene methylimine. The reaction of 2-phenyltropone and dimethylamine gave no crystalline products.

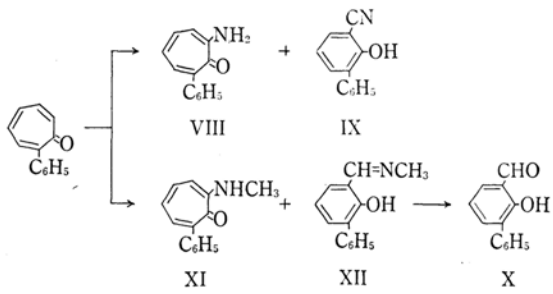

Fig. 2

A similar reaction of 2-α-naphthyltropone and methylamine in the presence of copper salt gave 3-α-naphthylsalicylidene methylimine (XIII) in a 36% yield. XIII was easily converted by dilute sulfuric acid into 3-α-naphthylsalicylaldehyde (XIV), which, with ferric chloride, exhibited a dark violet colorlation like that of salicylaldehyde. Similarly, when 4-bromo-2-phenyltropone[11] was treated with methylamine, orange crystals (XV), mp 137°C, and methylamide of biphenyl-2-carboxylic acid (XVI)[5] were obtained in yields of 26 and 6% respectively. The structure of XV was proved to be 5-bromo-2-methylamino-7-phenyltropone from the fact that it was converted by alkali into 5-bromo-3-phenyltropolone (XVII).[11] XVI must have been formed by a mechanism similar to that illustrated in the reaction of 4-bromo-2-phenyltropone and alkali to form biphenyl-2-carboxylic acid.[12]

It is not easy at present to determine the exact role of copper ammine salt or potassium ferricyanide. However, as has been noted before, the reaction of 2-phenyltropone and alkali gave biphenyl-2-carboxylic acid[2] or its dihydro derivative.[3] Similarly, when 2-phenyltropone was treated with methylamine or ethylamine in the absence of copper salt, methylamide or ethylamide of 2-phenylcyclohexadiene-1-carboxylic acid was formed in a reasonable yield through the attack of amines on carbonyl carbon.[13] Therefore, it seems certain that these complexes act not only as oxidizing reagents, but that they also change the atmosphere around the carbonyl group of tropones

8) W. Brackman and P. J. Smit, *Rec. Trav. Chim.*, **82**, 757 (1963).

9) Copper sulfate is not soluble in aqueous dimethylamine, and the reaction of tropone in this mixture is essentially heterogeneous; this is thought to be the reason why the yield of VII is poor.

10) In a private communication Professor Toshio Mukai noticed that the reaction of 2-phenyltropone and liquid ammonia in the presence of potassium ferricyanide afforded VIII in about a 70% yield.

11) T. Nozoe, S. Ito and K. Sonobe, *Sci. Repts Tohoku Univ., Ser. I*, **38**, 141 (1954); T. Muroi, This Bulletin, **33**, 1166 (1960).

12) Y. Kitahara, I. Murata and T. Muroi, This Bulletin, **34**, 1359 (1961).

13) K. Kikuchi, unpublished result.

in such a way as to make the attack of bases on carbonyl carbon difficult.

Experimental

The Reaction of Tropone and Alkali in the Presence of Potassium Ferricyanide. To a solution of 5.94 g of potassium ferricyanide in 32 m*l* of 1 N potassium hydroxide, 950 mg of tropone was added; the solution was then warmed at 70°C for about 30 hr, during which time the solution turned dark red. The resinous material (130 mg) was removed, the filtrate was extracted with chloroform, and the chloroform solution was washed with water. The evaporation of the solvent gave 210 mg of a dark red oil, which was then dissolved in benzene and passed through an alumina column. The fraction eluted with benzene gave 160 mg of a pale brown oil. When this was treated with picric acid, 190 mg of tropone picrate was obtained.

The aqueous solution was acidified with dilute hydrochloric acid and extracted with ether. The ether solution was shaken with a 20% copper sulfate solution; tropolone (I) was thus separated as a green copper complex. By the treatment of this salt with dilute sulfuric acid, I was liberated as brown crystals, mp 45—48°C; yield, 150 mg.

The evaporation of the solvent from the filtrate left 193 mg of a dark red oil. Distillation under reduced pressure afforded; a) the first fraction, 32 mg (bath temp. 90°C/55 mmHg), b) the second fraction, several mg (bath temp., 90—100°C/55 mmHg), and c) the third fraction, 84 mg (bath temp., 100—120°C/2 mmHg). The first fraction showed the same infrared spectrum as salicylaldehyde (II) and gave 2, 4-dinitrophenylhydrazone identical with that of II. The third fraction solidified to colorless crystals with a melting point of 107—112°C. Recrystallization raised the melting point to 116—118°C; it was undepressed on admixture with an authentic sample of *p*-hydroxybenzaldehyde (III).

The Reaction of Tropone and Alkali in the Presence of Copper Ammine Salt. To a solution of 2.00 g of tetrammine copper sulfate monohydrate in 10 m*l* of water, 430 mg of tropone and 3 m*l* of 2 N sodium hydroxide were added; the whole was then warmed at 70°C for 20 hr. The dark brown precipitate (A) was collected, suspended in chloroform, and hydrogen sulfide was passed through. The copper sulfide was removed, the solvent was evaporated, and the residue was dissolved in a mixture of benzene and chloroform (1 : 1) and passed through an alumina column. The evaporation of the solvent from the eluate gave 77 mg of 2-aminotropone (IV), mp 103—106°C. The filtrate from the precipitate (A) was extracted with chloroform, the solution was washed with water, and the solvent was evaporated. When the residue was passed through an alumina column, 20 mg of tropone and 15 mg of IV were obtained.

The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. The ether solution was washed with water, and the solvent was evaporated to give 186 mg of pale brown crystals, mp 85—92°C (sintered at about 75°C). Recrystallization from water gave colorless prisms, mp 91—93°C, identical with that of salicylonitrile (V).

The Reaction of Tropone with Ammonia, Methylamine, and Dimethylamine in the Presence of Copper Ammine Salt. *a) Reaction with Ammonia.* To a solution of 4.00 g of copper sulfate dissolved in 20 m*l* of concentrated aqueous ammonia, 850 mg of tropone was added; the solution was then warmed at 50°C for 24 hr, during which time the solution gradually turned greenish brown and a dark brown solid was separated. This precipitate (A) was filtered, and the filtrate was extracted with chloroform. The chloroform solution and A were combined, hydrogen sulfide was passed through, and the copper sulfide was removed. The evaporation of the solvent left a dark reddish-brown crystalline residue which was then recrystallized from benzene to give 655 mg of brown crystals, mp 92 — 102°C. Purification by chromatography on an alumina column, followed by recrystallization from benzene, gave 605 mg of 2-aminotropone (IV), mp 102—105°C. No other crystalline product was obtained.

b) Reaction with Methylamine. To a solution of 2.00 g of copper sulfate in 20 m*l* of 40% methylamine, 425 mg of tropone was added; the mixture was then stirred at room temperature for 1 hr. The solution turned pale greenish brown, and within a few minutes a yellowish-green copper complex began to separate. The mixture was diluted with water, and the complex was collected. When the complex was treated as in the case of a), 375 mg of 2-methylaminotropone (VI), mp 79—81°C, were obtained as orange prisms.

c) Reaction with Dimethylamine. To 4.0 m*l* of 40% dimethylamine, 1.00 g of copper sulfate (not dissolved) and 235 mg of tropone were added; the mixture was then stirred at room temperature for 2 hr, during which time the mixture turned greenish yellow. Chloroform was added to the reaction mixture, hydrogen sulfide was passed through, and the copper sulfide was removed. The chloroform solution was washed with water, and the solvent was removed to give 250 mg of a dark red oil. This oil was dissolved in a mixture of benzene and cyclohexane (1 : 1) and passed through an alumina column. The yellow band was eluted with benzene to give 117 mg of crude 2-dimethylaminotropone (VII) as a yellowish-orange oil. The treatment of this oil with picric acid gave 180 mg of the picrate of VII as yellow crystals, mp 140—150°C. Recrystallization from alcohol raised the melting point to 150—154°C.

The Reaction of 2-Phenyltropone with Ammonia and Methylamine in the Presence of Copper Ammine Salt. *a) Reaction with Ammonia.* To a solution of 750 mg of copper sulfate in 4.0 m*l* of concentrated ammonia, 185 mg of powdered 2-phenyltropone was added, and the mixture was heated at 50—55°C for about 32 hr. The precipitate was collected and dissolved in chloroform, and the solution was washed with a 2 N sodium hydroxide solution. Hydrogen sulfide was passed through the chloroform solution, and the copper sulfide was removed. The evaporation of the solvent gave about 150 mg of an oily residue which partially solidified when left standing. Washing with benzene gave yellow crystals, mp 200—208°C; yield, 32 mg. The filtrate was passed through an alumina column to give 10 mg of second crops, mp 200—208°C. Recrystallization from a mixture of dioxane and water gave 2-amino-7-phenyltropone (VIII) as yellow prisms,

mp 207—209°C; the reported melting point is 211°C.[2]

The alkaline solution was acidified with dilute sulfuric acid to give 27 mg of brown crystals, mp 160—175°C. Purification through recrystallization from ethanol, followed by sublimation under reduced pressure, gave 10 mg of pale yellow plates, mp 180—184°C; this substance was identified as 3-phenylsalicylonitrile (IX) by a mixed-melting-point determination with the sample obtained below.

b) Reaction with Methylamine. To a solution of 1.00 g of copper sulfate in 4.0 m*l* of 40% methylamine there was added a solution of 360 mg of 2-phenyltropone in 1.0 m*l* of benzene; the mixture was then stirred vigorously at 35°C in a closed vessel for 7 hr, during which time it turned faint yellow and greenish-brown crystals were separated out. After the mixture had stood overnight, the crystals were collected and washed with water and ethanol. A chloroform solution of the crystals was treated with hydrogen sulfide, the solvent was evaporated, and the residue was dissolved in a mixture of benzene and cyclohexane (1 : 1) and passed through an alumina column. The first fraction, eluted with the same solvent mixture, afforded 140 mg of 3-phenylsalicylidene methylimine (XII) as yellow prisms with a melting point of 93—96°C. The second fraction, eluted with benzene, afforded 13 mg of 2-methylamino-7-phenyltropone (XI) as yellow plates with a melting point of 154—157°C (identical with that of an authentic specimen[5]). The filtrate from the copper complex was extracted with chloroform, and the solution was treated in a similar manner to give another crop of XII (43 mg; mp 92—96°C).

The recrystallization of XII from cyclohexane containing a small amount of benzene gave yellow prisms, mp 95.5—97°C.

Found: C, 79.64; H, 6.08; N, 6.33%. Calcd for $C_{14}H_{13}ON$: C, 79.59; H, 6.20; N, 6.63%.

3-Phenylsalicylaldehyde (X) from XII. The slight heating of 25 mg of XII with 0.5 m*l* of dilute sulfuric acid afforded 21 mg of colorless crystals, mp 43—45°C. Recrystallization from dilute ethanol gave colorless plates (X), mp 43—45°C; identical with that of 3-phenylsalicylaldehyde.[5]

3-Phenylsalicylonitrile (IX) A 150 mg sample of X was heated with 75 mg of hydroxylamine hydrochloride in a mixture of 0.5 m*l* portions of pyridine and ethanol in the usual manner to give 140 mg of oxime, mp 152—154°C. The oxime was heated with 0.5 m*l* of acetic anhydride for 30 min at 120°C. The crystalline product was treated with alkali, and 28 mg of IX was obtained as colorless plates, mp 177—183°C. Several recrystallization from dilute ethanol afforded colorless plates, mp 180—184°C.

Found: C, 79.64; H, 4.61; N, 7.11%. Calcd for $C_{13}H_9ON$: C, 79.98; H, 4.65; N, 7.17%.

The Reaction of 2-α-Naphthyltropone and Methylamine. A similar treatment of 2-α-naphthyltropone (270 mg) and 40% methylamine (4 m*l*) in the presence of copper sulfate (600 mg) afforded 90 mg of 3-α-naphthylsalicylidene methylimine (XIII) as yellow prisms, mp 146—148°C (after recrystallization from a mixture of benzene and cyclohexane).

Found: C, 82.26; H, 5.89; N, 5.24%. Calcd for $C_{18}H_{15}ON$: C, 82.73; H, 5.79; N, 5.36%.

3-α-Naphthylsalicylaldehyde (XIV). This was obtained from XIII by a manner similar to that used in the case of X. Recrystallization from a mixture of benzene and cyclohexane gave colorless needles, mp 117—118°C. An alcoholic solution of XIV turns reddish purple with ferric chloride.

Found: C, 82.35; H, 4.89%. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87%.

The Reaction of 4-Bromo-2-phenyltropone and Methylamine. A similar treatment of 520 mg of 4-bromo-2-phenyltropone with 4.0 m*l* of 40% aqueous methylamine in the presence of 1.00 g of copper sulfate gave 138 mg of 5-bromo-2-methylamino-7-phenyltropone (XV) as yellow prisms, mp 134—136°C, and 30 mg of the methylamide of biphenyl-2-carboxylic acid (XVI),[5] mp 161—164°C.

The recrystallization of XV from ethanol raised the melting point to 136—137°C.

Found: C, 58.42; H, 4.26; N, 5.31%. Calcd for $C_{14}H_{12}ONBr$: C, 57.95; H, 4.17; N, 4.83%.

5-Bromo-3-phenyltropolone (XVII) from XV. The heating of XV with dilute alcoholic sodium hydroxide gave XVII as pale yellow crystals, mp 130—133°C; undepressed on admixture with an authentic sample.[11]

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