Syntheses and Reactions of 2-Bromomethyltropones

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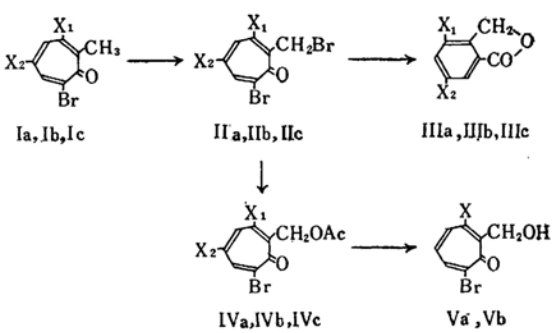
Recently it was reported that tropone, 2-phenyltropone and several kinds of their bromine substituted compounds were comparatively easily brominated on their tropone nucleus through addition of bromine to their double bonds and subsequent dehydrobromination (and debromination in some instances), showing the unsaturated properties of the tropone nucleus[1,2].

In the present paper the bromination of 7-bromo-2-methyltropone (Ia), 3, 7-dibromo-2-methyltropone (Ib) and 2-methyl-3, 5, 7-tribromotropone (Ic)[3] was undertaken. The aim of the experiment of this paper is twofold; (1) 2-methyltropone is considered to be a vinylog of methylketone and accordingly it would be important to examine whether bromination occurs on a tropone nucleus or on a methyl group; and (2) 2-bromomethyltropones, if they were obtained, would be easily converted to 2-hydroxymethyltropones, the key intermediates for the preparation of 2-formyltropones.

Application of one molecular equivalent of bromine or *N*-bromosuccinimide on Ia afforded pale yellow needles (IIa) in a good yield. Although attempted conversion of IIa to phthalide (IIIa) directly by treating with alkali failed, the structure of IIa was proved to be 7-bromo-2-bromomethyltropone as described later. Similarly, both Ib and Ic, when treated with bromine, afforded 2-bromomethyl-3, 7-dibromotropone (IIb) and 2-bromomethyl-3, 5, 7-tribromotropone (IIc), respectively. Treatment of IIb with dilute alkali gave 4-bromophthalide (IIIb)[4], which on reduction over palladium charcoal aforded IIIa. Similar treatment of IIc with alkali afforded 4, 6-dibromophthalide (IIIc), whose debromination gave IIIa.



Bromination of IIa gave pale yellow needles (IId), the structure of which is not clear yet. On the other hand, further bromination of IIb was found to be difficult even under prolonged heating on a water bath. This fact is rather interesting from the fact that 3, 7-dibromo-2-phenyltropone was easily brominated to give 2-phenyl-3, 5, 7-tribromotropone[1]. Ultraviolet absorption spectra of IIa, IIb and IIc were shown in Fig. 1.

Although the preparations and reactions of

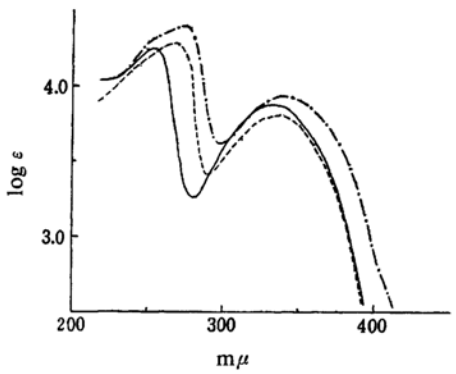


Fig. 1. Ultraviolet absorption spectra of IIa(——), IIb (----) and IIc(-·-·-) in methanol.

1) T. Mukai, *Sci. Repts. Tohoku Univ., Ser.* I, **38**, 280 (1954).
2) T. Nozoe, T. Mukai and K. Takase, ibid., **39**, 164 (1956).
3) K. Kikuchi, This Bulletin, **33**, 628 (1960).
4) J. Tirouflet, *Bull. soc. sci. Bretagne, Spec. No.*, **26**, 7 (1951); *Chem. Abstr.*, **47**, 8693 (1953).

hydroxymethyltropolone[5-7] and formyltropolone[7,8] derivatives have been examined in some detail, 2-hydroxymethyltropone and 2-formyltropone derivatives have remained unknown. Therefore, the synthesis of these materials were next attempted.

Application of silver acetate on IIa in acetic acid gave 2-acetoxymethyl-7-bromotropone (IVa) which, when heated with a mixture of dilute hydrochloric acid and ethanol, easily underwent hydrolysis to give 7-bromo-2-hydroxymethyltropone (Va). Va showed no coloration with ferric chloride characteristic of tropolone. The ultraviolet absorption spectrum of Va reveals that it retains tropone nucleus as shown in Fig. 2. Treatment of Va with dilute alkali gave IIIa though in a poor yield. These facts indicate that Va has the expected structure and that bromination of Ia has undoubtedly occurred on a side chain methyl group as described before.

Similar treatment of IIb with silver acetate or sodium acetate afforded 2-acetoxymthyl-3, 7-dibromotropone (IVb), which was hydrolyzed to 3, 7 - dibromo - 2 - hydroxymethyltropone (Vb). Similarly, treatment of IIc with silver acetate gave 2-acetoxymethyl-3, 5, 7-tribromotropone (IVc). Acid hydrolysis of IVc, however, resulted in the formation of IIIc. This result is curious compared with the fact that 2-halotropones usually do not rearrange to aromatic acids in acidic media.

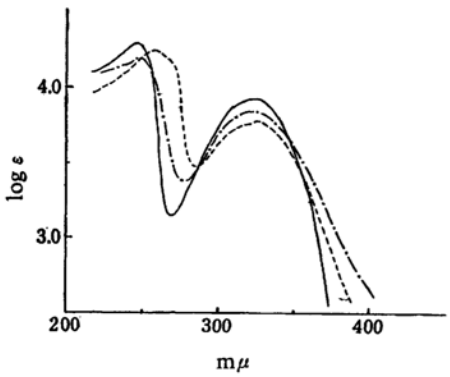
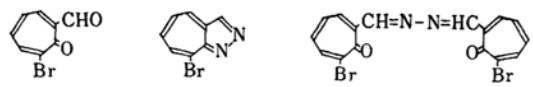


Fig. 2. Ultraviolet absorption spectra of Va(——), Vb(----) and VI(-·-·-) in methanol.

Mild oxidation of Va with activated manganese dioxide in benzene[8] or with chromium trioxide in a mixture of acetic acid and acetic anhydride afforded 7-bromo-2-formyltropone (VI). VI reduces ammoniacal silver nitrate solution and Fehling's solution and gives phenylhydrazone.

An attempted synthesis of 8-bromo-1, 2-diazaazulene (VII) by treating VI with hydrazine has not succeeded, and the only product was yellow crystals which was assumed to be symmetrical azine (VIII) of VI from its analytical value.



VI VII VIII

Experimental

7-Bromo-2-bromomethyltropone (IIa).—a) To a solution of 200 mg. of 7-bromo-2-methyltropone (Ia) in 1.5 cc. of acetic acid was added 170 mg. of bromine and the mixture was heated on a water bath for 30 min. and cooled. The crystals that separated were collected by filtration. Yield, 80 mg. Mother liquor was diluted with water, extracted with benzene and the benzene layer was washed successively with water, 2 N sodium carbonate and water. Removal of the solvent afforded second crop of 60 mg. of crystals. These crystals were combined and recrystallized from ethanol to give colorless needles (IIa), m. p. 103~104°C.

Found: C, 34.50; H, 2.07. Calcd. for $C_8H_6OBr_2$: C, 34.57; H, 2.18%.

b) A mixture of 520 mg. of Ia, 520 mg. of *N*-bromosuccinimide and 6 cc. of carbon tetrachloride was heated to reflux for four and one-half hours under irradiation. The crystals were filtered, washed well with benzene and the combined solution was washed with water. Removal of the solvent provided 500 mg. of crystals, m. p. 97~101°C. These crystals showed no depression of the melting point on admixture with IIa obtained by the method of a).

2-Bromomethyl-3, 7-dibromotropone (IIb).—A mixture of 100 mg. of 3, 7-dibromo-2-methyltropone (Ib), 0.8 cc. of acetic acid and 60 mg. of bromine was heated on a water bath for about 30 min. From the reaction mixture 110 mg. of IIb was obtained as pale yellow needles of m. p. 141~143°C. Recrystallization from ethanol raised the melting point to 142~143°C.

Found: C, 27.26; H, 1.88. Calcd. for $C_8H_5OBr_3$: C, 26.92; H, 1.41%.

2-Bromomethyl-3, 5, 7-tribromotropone (IIc).—To a solution of 200 mg. of 2-methyl-3, 5, 7-tribromotropone (Ic) dissolved in 1 cc. of acetic acid was added 100 mg. of bromine, and the mixture was heated on a water bath for about 30 min. On cooling, 220 mg. of IIc was obtained as pale yellow plates of m. p. 104~106°C. Recrystallization from ethanol raised the melting point to 107~108°C.

Found: C, 22.13; H, 1.14. Calcd. for $C_8H_4OBr_4$: C, 22.05; H, 0.93%.

Bromination of 7-Bromo-2-bromomethyltropone (IIa).—A mixture of 50 mg. of IIa and 35 mg. of bromine in 0.3 cc. of acetic acid was heated on a water bath for about 30 min. and cooled. The crystals that separated were collected by filtration and recrystallized from ethanol to give pale yellow needles

5) T. Nozoe, T. Mukai and K. Matsui, *Proc. Japan Acad.*, 27, 561 (1951).
6) T. Nozoe, T. Mukai and K. Takase, *Sci. Repts. Tohoku Univ., Ser.* I, 36, 40 (1952).
7) S. Seto and K. Ogura, This Bulletin, 32, 493 (1959).
8) E. Sebe and S. Matsumoto, *Sci. Repts. Tohoku Univ., Ser.* I, 38, 308 (1954).

(IId), m. p. 131～133°C. Yield, 45 mg. Further recrystallization from ethanol raised the melting point to 133～134°C.

Found: C, 27.56; H, 1.76. Calcd. for $C_8H_5OBr_3$: C, 26.92; H, 1.41%.

Action of dilute aqueous sodium hydroxide on IId gave only unidentified black resinous matter. Attempted debromination of side chain bromine with zinc and acetic acid also failed.

Attempted Bromination of 2-Bromomethyl-3, 7-dibromotropone (IIb).—A mixture of 50 mg. of IIb and 30 mg. of bromine in 0.4 cc. of acetic acid was heated for two hours on a water bath in a closed vessel. On cooling, 20 mg. of pale yellow crystals, m. p. 136～140°C was obtained and identified as starting material by the mixture melting point method. Mother liquor, on being diluted with water, gave pale yellow crystals of m. p. 113～125°C, purification of which was difficult.

Reaction of 2-Bromomethyl-3, 7-dibromotropone (IIb) and Alkali.—A mixture of 100 mg. of IIb and 1 cc. of 1 N sodium hydroxide solution was heated on a water bath for one hour, treated with active carbon and filtered. Acidification of the filtrate with dilute hydrochloric acid gave 35 mg. of 4-bromophthalide (IIIb) as colorless plates of m. p. 94～97°C. Recrystallization from cyclohexane raised the melting point to 98～99°C. Reported melting point of IIIb is 103～104°C.

Found: C, 45.39; H, 2.43. Calcd. for $C_8H_5O_2Br$: C, 45.10; H, 2.37%.

Catalytic debromination of IIIb afforded phthalide (IIIa), m. p. 70～71°C, undepressed of melting point on admixture with authentic sample.

Reaction of 2-Bromomethyl-3, 5, 7-tribromotropone (IIc) and Alkali.—A mixture of 100 mg. of IIc, 0.6 cc. of 1 N aqueous sodium hydroxide and 0.1 cc. of ethanol was treated as in the case of IIb, and 4, 6-dibromophthalide (IIIc) thereby obtained, was recrystallized from dilute ethanol to give colorless needles, m. p. 112～113°C.

Found: C, 33.15; H, 1.51. Calcd. for $C_8H_4O_2Br_2$: C, 32.91; H, 1.38%.

Debromination of IIIc afforded IIIa, m.p. 71～72°C.

2-Acetoxymethyl-7-bromotropone (IVa).—To a solution of 150 mg. of 7-bromo-2-bromomethyltropone (IIa) dissolved in 1.2 cc. of acetic acid 150 mg. of silver acetate was added, and the mixture was heated on a water bath for 15 min. with occasional stirring and filtered. Acetic acid was removed from the filtrate by evaporation, and the residue was extracted with benzene. The benzene solution was washed with water and the solvent evaporated. The crystals thereby obtained were recrystallized from a mixture of benzene and petroleum ether to give colorless needles (IVa), m. p. 108～110°C. Yield, 130 mg. Further recrystallization raised the melting point to 110～111°C.

Found: C, 46.30; H, 3.16. Calcd. for $C_{10}H_9O_3Br$: C, 46.72; H, 3.53%.

2-Acetoxymethyl-3,7-dibromotropone (IVb). — a) To a solution of 200 mg. of 2-bromomethyl-3, 7-dibromotropone (IIb) dissolved in 2 cc. of acetic acid was added 160 mg. of sodium acetate, the mixture was heated on a water bath for one and one-half hours and filtered. The filtrate was diluted with water, extracted with benzene, and the benzene extract was washed with water and concentrated. The crystals thereby obtained were recrystallized from ethanol to give colorless crystals (IVb), m. p. 84～87°C. Yield, 160 mg. Further recrystallization from ethanol raised the melting point to 88～89°C.

Found: C, 35.90; H, 2.30. Calcd. for $C_{10}H_8O_3Br_2$: C, 35.74; H, 2.40%.

b) Similar treatment of 200 mg. of IIb with 150 mg. of silver acetate as in the case of IIa afforded 150 mg. of colorless crystals of m. p. 85～88°C, undepressed of the melting point on admixture with IVb obtained in a).

2-Acetoxymethyl-3, 5, 7-tribromotropone (IVc).—Similar treatment of 300 mg. of 2-bromomethyl-3, 5, 7-tribromotropone (IIc) with 180 mg. of silver acetate as in the case of IIa afforded 240 mg. of IVc, m. p. 87～90°C. Recrystallization from ethanol gave colorless needles, m. p. 88～90°C.

Found: C, 28.59; H, 1.95 Calcd. for $C_{10}H_7O_3Br_3$; C, 28.95; H, 1.70%.

7-Bromo-2-hydroxymethyltropone (Va).—A solution of 330 mg. of 2-acetoxymethyl-7-bromotropone (IVa) dissolved in a mixture of 3 cc. of ethanol and 1.5 cc. of 2 N hydrochloric acid was heated to reflux for 50 min. Evaporation of most of ethanol afforded 260 mg. of pale brown crystals (Va), m. p. 116～118°C (decomp.). Recrystallization from dilute ethanol gave colorless needles, m. p. 120～121°C (decomp.).

Found: C, 44.92; H, 3.74. Calcd. for $C_5H_7O_2Br$: C, 44.68; H, 3.28%.

Reaction of 7-Bromo-2-hydroxymethyltropone (Va) and Alkali.—A mixture of 40 mg. of Va and 0.5 cc. of 1 N sodium hydroxide solution was heated on a water bath for 30 min. The resulting clear solution was acidified with hydrochloric acid, treated with charcoal, filtered while hot and cooled. Colorless plates, m. p. 69～71°C, thereby obtained, showed no depression of melting point on admixture with phthalide.

3, 7-Dibromo-2-hydroxymethyltropone (Vb). — A solution of 100 mg. of 2-acetoxymethyl-3, 7-dibromotropone (IVb) dissolved in a mixture of 1 cc. of ethanol and 0.5 cc. of 2 N hydrochloric acid was heated on a water bath for one hour. Similar treatment of the reaction mixture as in the case of Va afforded 70 mg. of Vb, m. p. 100～103°C (decomp.). Recrystallization from ethanol gave colorless crystals, m. p. 109～110°C (decomp.).

Found: C, 33.08; H, 2.20. Calcd. for $C_8H_6O_2Br_2$: C, 32.68; H, 2.06%.

Acid Hydrolysis of 2-Acetoxymethyl-3,5,7-tribromotropone (IVc).—A solution of 300 mg. of IVc dissolved in a mixture of 2 cc. of ethanol and 1 cc. of 2 N hydrochloric acid was heated on a water bath for two hours and cooled. The crystals thereby obtained were recrystallized from ethanol to give colorless needles, m. p. 112～113°C, which showed no depression of melting point on admixture with IIIc obtained by the action of alkali on IIc.

7-Bromo-2-formyltropone (VI).—a) To a solution of 200 mg. of 7-bromo-2-hydroxymethyltropone (Va) dissolved in 10 cc. of benzene was added 800 mg. of active manganese dioxide, and the mixture was stirred for two hours at room temperature and filtered.

Evaporation of the solvent afforded 100 mg. of VI, m. p. 147~149°C (decomp.). Recrystallization from ethanol gave yellow needles, m. p. 148~150°C (decomp.).

Found: C, 45.05; H, 2.74. Calcd. for $C_8H_5O_2Br$: C, 45.10; H, 2.37%.

b) To a suspension of 100 mg. of Va in a mixture of 0.3 cc. each of acetic acid and acetic anhydride was added 0.3 cc. of chromium trioxide solution (prepared by dissolving 1 g. chromium trioxide in a mixture of 5 cc. each of acetic acid and acetic anhydride) at room temperature. The solution was warmed at 35~45°C for 50 min., cooled and the crystals that separated out were collected by filtraton. Yield, 40 mg. Recrystallization from ethanol gave yellow needles, m. p. 146°C (decomp.).

Phenylhydrazone of 7-Bromo-2-formyltropone (VI).—To a solution of 50 mg. of VI dissolved in 2 cc. of ethanol was added a solution of 40 mg. of phenylhydrazine hydrochloride in 0.3 cc. of water at room temperature. Phenylhydrazone of VI was obtained as purple needles, m. p. 142°C (decomp.). It was difficult to recrystallize from usual organic solvents.

Found: C, 55.51; H, 3.53; N, 9.15. Calcd. for $C_{14}H_{11}ON_2Br$: C, 55.46; H, 3.66; N, 9.24%.

Azine (VIII) of 7-Bromo-2-formyltropone (VI).—To a solution of 50 mg. of VI dissolved in 2.5 cc. of ethanol was added a solution of 20 mg. of hydrazine hydrochloride in 0.3 cc. of water at room temperature. Azine (VIII) was obtained as yellow crystals, m. p. 147~148°C (decomp.), which were difficult to recrystallize from usual organic solvents.

Found: C,45.72; H, 2.47; N, 6.49. Calcd. for $C_{16}H_{10}O_2N_2Br_2$: C, 45.55; H, 2.39; N, 6.64%.

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