On 2-Arylaminotropones. I. The Syntheses of Several 2-Arylamino-4,7-dibromotropones and Their Dehalogenation Products[1]

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(Received March 3, 1955)

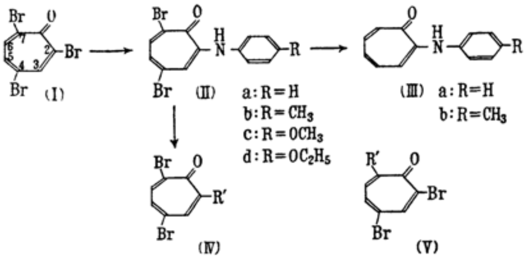
Nozoe and his co-workers reported[2] some time ago on the action of amines on 2, 4, 7-tribromotropone (I)[3]. In the case of aniline and *p*-toluidine, debromination of the reaction products without isolating the intermediates afforded liquid 2-anilinotropone (picrate, m.p. 142°C) and 2-(*p*-toluidino)-tropone, m.p. 108.5–109.5°C. The present writer followed these reactions and this paper describes the structure of the brominated products, their dehalogenation products, and similar reactions in several of the related compounds.

The reaction of 2, 4, 7-tribromotropone and aniline or *p*-toluidine proceeded well in benzene, in the presence of anhydrous sodium acetate, as has been described before[2]. The reaction products were obtained in a good yield and in pure state after several recrystallizations. The anilino derivative (II a) melted at 196–197°C and the *p*-toluidino derivative (II b) melted at 196°C, both crystallizing in fine yellow needles. None of their possible isomers was isolated.

The use of *o*-toluidine, *p*-bromoaniline, or *p*-nitroaniline as the anionoid reagent resulted in the recovery of the starting material possibly due to the steric hindrance in the case of *o*-toluidine and to lower basicity in the two latter reagents. When the *para*-position was occupied by an electron-releasing group other than the methyl, as in *p*-anisidine and *p*-phenetidine, crystalline products were obtained, though in an inferior yield, under the same conditions, affording (II c), m.p. 182°C, and (II d), m.p. 172°C.

Both (II a) and (II b) easily underwent hydrolysis by hot diluted ethanolic potassium hydroxide and afforded the same 3, 6-dibromotropolone (IV, R′=OH), indicating that (II a) and (II b) are 2-anilino- and 2-(*p*-toluidino)-4, 7-dibromotropone, respectively. As anticipated, the rate of hydrolysis of (II a) was greater than that of (II b).

It has been shown[2] that the hydrolysis of 2, 4, 7-tribromotropone in the presence of sodium acetate or the application of hydrazine hydrate yields a mixture (IV) and (V) of two kinds of dibromo compounds formed by the substitution of the bromine in C_2 or C_7. In the present series of experiments, however, only the C_2-substituted product was obtained. This was assumed to be due to the fact that the electron density at C_2 is lower than that at C_7 by the inductive effect of the bromine at C_4 and by the resonance effect, as well as to the steric condition between 2, 4, 7-tribromotropone and arylamines at the time of the reaction. In this connection, it would be interesting to study the reaction between 2, 4, 7-tribromotropone and alkylamines.



Catalytic debromination of (II a) and (II b) respectively yielded 2-anilinotropone (III a), m.p. 42–43°C, and 2-(*p*-toluidino)-tropone (III b), m.p. 109–110°C[2]. The respective picrates melting at 141–142°C and 117–118°C. (III a) dissolved in concentrated hydrochloric acid and perchloric acid but their salts could not be obtained in crystalline state. (III b) gives a crystalline hydrochloride of m.p. 175–180°C (decomp.) which was unstable in water and the original base was recovered on attempting its recrystallization from water. The perchlorate of the *p*-toluidino derivative was obtained in two different colors, red and yellow crystals, both melting at 176–177°C.

The ultraviolet absorption spectra (Fig 1)[4] show that the two pairs, (II a and II b) and (III a and III b) have a similar structure. The infrared spectra of these com-

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[1] This is part of a report presented at the Kyushu Local Meeting of the Chemical Society of Japan, Kumamoto, December 4, 1954.

[2] T. Nozoe, Y. Kitahara, S. Masamune and K. Yamaguchi, *Proc. Japan Acad.*, 28, 85 (1952); T. Nozoe, Y. Kitahara, T. Ando, S. Masamune and H. Abe, *Sci. Repts. Tohoku Univ.*, Ser. I, 36, 166 (1952).

[3] T. Nozoe, Y. Kitahara, T. Ando and S. Masamune, *Proc. Japan Acad.*, 27, 415 (1951).

[4] Ultraviolet absorption spectra were determined by a Beckman spectrophotometer by members (especially by Miss Ayako Iwanaga) of the Chemical Institute, Faculty of Science, Tohoku University, Sendai.

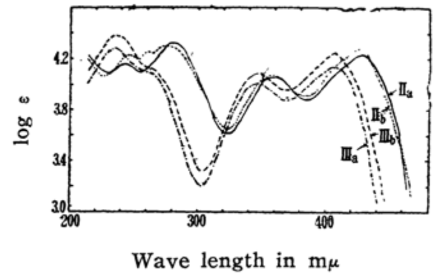

Fig. 1. Ultraviolet absorption spectra of 2-anilino-4, 7-dibromotropone (————), 2-anilinotropone (—·—·—), 2-(*p*-toluidino)-4, 7-dibromotropone (············), and 2-(*p*-toluidino)-tropone (— — —). Solvent: methanol.

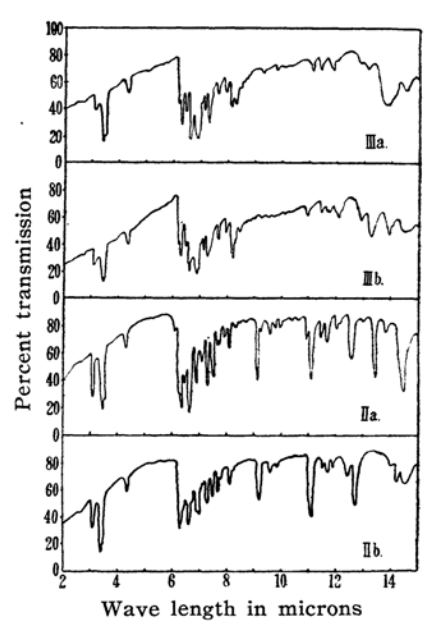

Fig. 2. Infrared absorption spectra of 2-anilino-4, 7-dibromotropone (II a), 2-(*p*-toluidino)-4, 7-dibromotropone (II b), 2-anilinotropone (III a) and 2-(*p*-toluidino)-tropone (III b).

pounds[5] (Fig. 2) all show absorption in 3.08–3.11 μ, attritutable to the N-H bond (probably hydrogen bonded) but no absorption corresponding to the tropone carbonyl group (about 6.16 μ).

Experimental

2,4,7-Tribromotropone (I)[6].—Prepared according to the method of Nozoe, et al[2]. The crude product, m.p. 180–182°C, was dissolved in benzene and passed through a chromatographic column of alumina. Nearly colorless needles were obtained from the eluate and recrystallized from benzene, m.p. 182°C. It evolved a camphor-like odor when heated to 90°C or higher.

2-Anilino-4,7-dibromotropone (II a).—To a mixture of 1.0 g. of 2, 4, 7-tribromotropone, 0.3 g. of anhydrous sodium acetate, and 20 g. of benzene, 0.4 g. of aniline was added under stirring at room temperature. The mixture was refluxed for two hours. After cooling, about 200 cc. of benzene was added to dissolve the separated crystals completely and the benzene solution was washed successively with water, diluted aqueous sodium hydroxide, diluted hydrochloric acid, and water. The filtered benzene solution was evaporated to dryness and the brownish residue was washed with a small amount of acetone. The yellow crystals thereby obtained, 0.85 g. (78%), were recrystallized three times from hot ethyl acetate to yellow needles, m.p. 196–197°C. Yield, 0.55 g. They were slightly soluble in cold ether, acetone, ethanol, and methanol. A solution of 0.50 g. of the crude crystals dissolved in 15 cc. of benzene was chromatographed on an alumina column. The initial fraction of colorless eluate afforded 10 mg. of 2, 4, 7-tribromotropone, m.p. and mixed m.p. with the authentic sample 182°C. Elution with benzene (total, 750 cc.) yielded 0.47 g. of yellow needles, m.p. 196–197°C, showing no depression on admixture with the sample of m.p. 196–197°C, obtained by the above method. Found: C, 44.22; H, 2.58; N, 4.16%. Calcd. for $C_{13}H_9ONBr_2$: C, 43.96; H, 2.56; N, 3.95%[7].

2-Anilino-4, 7-dibromotropone failed to form any salts with hydrogen chloride in ether, saturated ethanolic solution of picric, flavianic, or picrolonic acid, or concentrated hydrochloric acid. On refluxing with one molar equivalent of aniline in benzene, the starting material was recovered.

Hydrolysis of 2-anilino-4,7-dibromotropone. Isolation of 3,6-dibromotropolone.—A mixture of 200 mg. of (II a) and 11 cc. of N ethanolic potassium hydroxide solution was refluxed for twenty minutes after the crystals completely dissolved to give a clear reddish brown solution. After adjusting the reaction mixture to pH 3.5 with 2 N hydrochloric acid, majority of ethanol was distilled off under a reduced pressure, cooled, 10 cc. of water was added to the residue, and the mixture was extracted several times with benzene. The combined benzene extract was evaporated under a reduced pressure and the residue was sublimed in vacuo (bath temperature, 110–120°C). The sublimate was crystallized from dilute ethanol or water to light yellow needles, m.p. 121–122°C. Yield, 70 mg. Admixture with an authentic sample of 3, 6-dibromotropolone[2] did not show any depression of m.p.

The mother liquor was extracted with chloroform and a second crop of crystals was obtained. Total yield, 85 mg. (74%).

2-Anilinotropone (III a).—A mixture of 5 g. of (II a) and 200 cc. of methanol was hydrogenated in the presence of 3 g. of anhydrous sodium ace-

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[5] Infrared spectra were determined by the Perkin-Elmer Model 21 double-beam instrument with NaCl prism, Nujol mull method, by Messrs. H. Kozuma and K. Kawasaki, Technical Department, Minamata Factory, Shin Nippon Chisso Hiryo K.K., Minamata, Kumamoto.

[6] Suberone and a part of 2, 4, 7-tribromotropone were provided by the Chemical Institute, Faculty of Science, Tohoku University.

[7] The microanalyses were carried out at the Institute of Polytechnics, Osaka City University, and at the Pharmaceutical Department, Kumamoto University. Some of the nitrogen analyses were carried out by Miss K. Kato of Tohoku University.

tate and 1 g. of 5% palladium-carbon. On a every hour, the vessel was immersed in a hot water bath for ten to fifteen minutes with occasional shaking to dissolve the remaining crystals. After absorption of 2.2 mol. of hydrogen, the reaction was stopped, the catalyst was removed by filtration, and the solvent was evaporated. The residue was extracted with benzene, the benzene layer was washed successively with water, diluted sodium hydroxide, and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent under ordinary pressure left a viscous brown oil (yield, 1.86 g. or 67%) which was extracted several times with cold petroleum ether (b.p. 60–80°C). The extract was concentrated under reduced pressure and allowed to stand in an ice box for several days. Light yellow prisms, m.p. 42–43°C, were obtained. Yield 1.1 g. Slightly unstable to heat. Very easily soluble in all organic solvents, except petroleum ether. Presence of even a trace of solvent prevents crystallization. Found: N, 7.05%. Calcd. for $C_{13}H_{11}ON$: N, 7.10%.

The compound dissolved easily in hydrochloric acid and perchloric acid (70%), but their crystalline salts could not be obtained.

Picrate.—An ethanolic solution of picric acid was added to the base dissolved in a minimum amount of ethanol and the precipitate thereby formed was recrystallized from ethanol containing a few drops of picric acid to yellowish brown, short prisms, m.p. 141–142°C, which showed no depression on admixture with an authentic sample[2]. The picrate was resolved into components by chromatography through alumina and the base thereby recovered melted at 42°C.

2-(*p*-Toluidino)-4,7-dibromotropone (II b).—A mixture of 10 g. of 2,4,7-tribromotropone, 3.0 g. of anhydrous sodium acetate, 150 cc. of benzene, and 3.75 g. of *p*-toluidine was treated as in the case of aniline. The crude product (11.2 g.) was recrystallized twice from ethyl acetate to yellow needles, m.p. 196°C. Yield, 8.2 g. (76.2%). Admixture with the anilino compound (II a) melted at 175–185°C. Further purification by chromatography through alumina failed to any other product. Found: C, 45.79; H, 3.06; N. 4.12%. Calcd. for $C_{14}H_{11}ONBr_2$: C, 45.54; H, 3.01; N, 3.79%.

A residue (0.5 g.) obtained from the initial recrystallization mother liquor of ethyl acetate was dissolved in 150 cc. of benzene, chromatographed through 20 g. of alumina, and the eluate from 400 cc. of benzene was fractionated into 20 cc. each. Fractions 1–4 (colorless) yielded 10 mg. of 2,4,7-tribromotropone. Fractions 8–18 (yellow) yielded 150 mg. of crystals melting at 195°C, alone and in admixture with (II b). Residual fractions and elution with other solvents failed to give any other products.

Hydrolysis of 2-(*p*-toluidino)-4,7-dibromotropone.—A mixture of 100 mg. of (II b), 5 cc. of ethanol, and 2 cc. of 2 N ethanolic solution of potassium hydroxide was refluxed for 40 minutes on a water bath. The crystals that separated out on cooling melted at 192–194°C and were identified as the starting material (II b). After refluxing for two hours more, when the color of the solution turned wine-red, the solvent was evaporated under a reduced pressure, water was added to the residue, and the solution was extracted with ether. The ether-soluble portion had an odor resembling that of *p*-toluidine. The aqueous alkaline layer was acidified with hydrochloric acid, extracted with chloroform, and the solvent was evaporated from the chloroform extract. The residual, semicrystalline mass was sublimed in vacuo and the sublimate was recrystallized from water to slightly yellow needles, m.p. 120°C, alone and inadmixture with 3,6-dibromotropolone. Yield, 15 mg.

2-(*p*-Toluidino)-tropone (III b).—This compound was obtained by the catalytic debromination of (II b) (3.50 g.) with 5% palladium-carbon and hydrogen, as in the case of the anilino analog, and the reaction was completed in four hours. Evaporation of the benzene washing yielded some brownish yellow prisms which were recrystallized from benzene and showed m.p. and mixed m.p. with an authentic sample[2] of 109–110°C. Yield, 1.48 g. (73.7%). Found: N, 6.69%. Calcd. for $C_{14}H_{13}ON$: N, 6.63%.

Hydrochloride.—The base was dissolved in hot 5 N hydrochloric acid, allowed to stand over-night in an ice box, and the crystals that precipitated out were recrystallized from 5 N hydrochloric acid to reddish brown prisms, which softened at 120°C, solidified again, and decomposed at 175–180°C. The decomposed product solidified in the capillary tube when allowed to cool and melted at 108–109°C. On attempting to recrystallize this compound from water or when water was added to the hydrochloric acid solution, yellow crystals precipitated out and were identified as (III b), m.p. 109°C.

Perchlorate.—The base was added to cold 70% perchloric acid, warmed gradually, and filtered while warm. On cooling the filtrate, red prisms separated. These were recrystallized from absolute ethanol and melted at 177–178°C. The crystals were labile in water and recrystallization from water yielded yellow needles which softed at 160°C and melted at 177–178°C. Admixture with the foregoing red crystals showed no depression of the m.p. When the yellow crystals were treated with 70% perchloric acid, the red crystals regenerated. (III b) was recovered from both crystals by ammonia and identified as its picrate.

Found: (red), C, 63.92; H, 4.90% (yellow), C, 63.47, H. 4.77%. Calcd. for $C_{14}H_{13}ON\ 1/2\ HClO_4$: C, 64.30; H, 5.20%.

Picrate.—Prepared as in the case of the anilino compound. Yellow needles (from ethanol), m.p. 117–118°C; fairly soluble in ethanol. Found: C, 54.15; H, 3.65; N, 12.53%. Calcd. for $C_{20}H_{16}O_8N_4$: C, 54.55; H, 3.66; N, 12.72%.

Other reactions.—No crystalline products were obtained by reaction with acetic anhydride, either alone or in the presence of sodium acetate (refluxed for thirty minutes), or with one to three mol. equivalents of hydrazine hydrate in ethanol, heated for one hour in a water bath.

2-(*p*-Methoxyphenylamino)-4,7-dibromotropone (II c).—A mixture of 2.06 g. of 2,4,7-tribromotropone and 0.74 g. of *p*-anisidine was treated as in the case of (II a) and 1.25 g. (52.1%) of thick yellow rods were obtained. Recrystallized from acetone and then from ethyl acetate, m.p. 182°C. Found: C, 43.66; H, 3.14%. Calcd. for $C_{14}H_{11}O_2NBr_2$: C, 43.64; H, 2.86%.

2-(*p*-Ethoxyphenylamino)-4,7-dibromotropone (II d).—A mixture of 2.06 g. of tribromtropone and an equivalent amount (0.85 g.) of *p*-phenetidine was refluxed for four hours. The crude product obtained was dissolved in benzene, passed through an alumina column, and the column was eluted with benzene. The combined eluates were evaporated and the residue was recrystallized first from acetone and then from ethanol, to yellowish brown needles, m.p. 172°C. Yield, 1.01 g. (43.5%). Found: C, 44.91; H, 2.93%. Calcd. for $C_{15}H_{13}O_2NBr_2$: C, 45.12; H, 3.26%.

The majority of the experiments reported herein were carried out at the Chemical Institute, Faculty of Science, Tohoku University, Sendai, and the writer takes this opportunity to express his sincere gratitude to Professor Tetsuo Nozoe for his kind guidance and encouragement throughout the course of this work. The writer is also indebted to the members of the Institute for their friendly cooperation and kind criticisms, and to those who supplied analytical data.

The present series of studies constitute a part of the general research on troponoid compounds (Representative: Prof. T. Nozoe). Part of the expenses for the present work was defrayed by a Grant in Aid for Scientific Research provided by the Ministry of Education, which is gratefully acknowledged.

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