On 2-Arylaminotropones. II[1]*. Bromination of 2-Anilino- and 2-(p-Toluidino)tropones*[2]

By Syun ISEDA

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The present paper describes the bromination of 2-anilino- and 2-(*p*-toluidino)-tropone, reported in Part I of this series[1], together with discussions on related matter.

Bromination in glacial acetic acid, in the presence of anhydrous sodium acetate, of 2-anilinotropone affords, irrespective of the amount of bromine added, a tribromo derivative (I) of m.p. 262.8°C*, and the same of 2-(*p*-toluidino)-tropone affords a dibromo derivative (II), m.p. 180–181°C or a tribromo derivative (III), m.p. 190°C, with a given amount of bromine. In the absence of sodium acetate, I is obtained from 2-anilinotropone and III from 2-(*p*-toluidino)tropone.

In order to establish the structure of these compounds, their hydrolysis was attempted by heating with 4N ethanolic potassium hydroxide. I afforded *p*-bromoaniline(N-acetyl derivative, m.p. 163.5°C) as a basic component and 3,5-dibromotropolone, m.p. 154°C(*p*-toluidine salt, m.p. 122.5°C)[3] as an acidic component. II formed *p*-toluidine (N-acetyl derivative, m.p. 153°C) and 3,5-dibromotropolone. III remained inert on refluxing with 2N ethanolic potassium hydroxide for 30 minutes, almost all the starting material being recovered. Its ultraviolet absorption spectrum (Fig. 1)[4] indicated the presence of a tropone ring and that aromatization had not taken place.

When III was refluxed with 6N ethanolic potassium hydroxide for 6—8 hours or with sodium methoxide in methanol for 3 hours, it was separated into a basic component IV (N-acetyl derivative, m.p. 118–119°C) and an acidic component. Vacuum sublimation of this acidic component yielded a small amount of 3,5-dibromotropolone, indicating that no additional bromine substitution of the tropone ring had taken place and that the substitution occurred in the benzenoid portion. It is therefore assumed that IV is a bromo-*p*-toluidine and that the bromine had entered into the position *meta* to the methyl group in *p*-toluidine, in accordance with the results of bromination of *p*-acetotoluidide[5] and 3-nitrosalicylic acid *p*-toluidide[6]. Comparison with an authentic specimen proved IV to be 4-amino-3-bromotoluene.

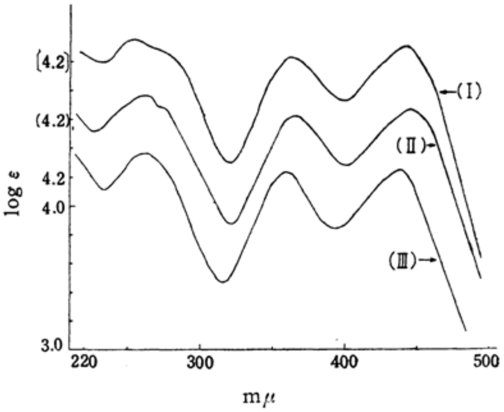

Fig. 1. Ultraviolet absorption spectra of (III), (II) (log ε+0.4), and (I) (log ε +0.8) (in methanol).

It can be concluded from the foregoing results that I is 2-(4′-bromoanilino)-5,7-dibromotropone, and II and III are respectively 2-(*p*-toluidino)- and 2-(2′-bromo-*p*-toluidino)-5,7-dibromotropone. The ultraviolet absorption spectra of I, II, and III are shown in Fig. 1.

Their infrared spectra[7] all indicated the absorption of 1,4-disubstituted benzene

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[1] Part I: S. Iseda, *Bull. Chem. Soc. Japan*, **28**, 617 (1955).

[2] Presented at the Kyushu Local Meeting of the Chemical Society of Japan, Kumamoto, December 4, 1954.

* All melting points corrected.

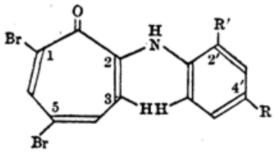
[3] T. Nozoe, Y. Kitahara, K. Yamane and A. Yoshikoshi, *Proc. Japan Acad.*, **27**, 18 (1951).

[4] Ultraviolet absorption spectra were determined by a Beckman spectrophotometer by members of the Chemistry Department, Faculty of Science, Tohoku University, Sendai.

[5] "Organic Syntheses", Coll. Vol. I (Japanese translation), p. 113 (1935).

[6] G. V. Jadhav and P. G. Nerlekar, *J. Indian Chem. Soc.*, **29**, 765 (1952); *J. Univ. Bombay*, **20**, part 3, 47 (1951).

[7] Infrared spectra were determined by Messrs. H. Kozuma and K. Kawasaki, Technical Department, Shin Nippon Chisso Hiryo K. K., Minamata.



	R	R′
(I)	Br	H
(II)	CH_3	H
(III)	CH_3	Br

TABLE I

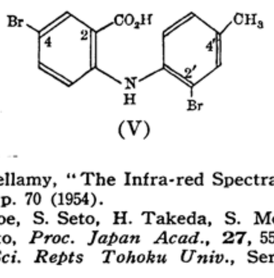
WAVE LENGTH OF ABSORPTIONS OF 1,4-DISUBSTITUTED BENZENE AT 8–10 μ region.
(Unit in microns).

I	8.28	9.15	9.59
II	8.29	9.16	9.62
III	8.25	9.15	9.62

(Table I), while that of III indicated the additional absorption at 8.74 μ characteristic of 1,2,4-trisubstituted benzene[8].

The substitution of bromine in the tropone ring of 2-aminotropone itself occurs in the order of C_7, C_5 and C_3[9]. In the present series of experiments, no significant difference was observed between C_7 and C_5 but the third bromine atom entered the benzene ring, instead of the tropone ring. This indicates that the C_3 position of the tropone ring in 2-arylaminotropone suffers the steric hindrance of the arylamino group while such a hindrance does not exist in the 2-aminotropone [see constitution of I].

Application of sodium methoxide to III yielded a small amount of 4-amino-3-bromotoluene and 3,5-dibromotropolone, and most part (73% of the starting material) of the product turned to yellow prisms (V), m.p. 247°C, $C_{14}H_{11}O_2NBr_2$. V is negative to the ferric chloride test and forms a sodium salt of pale yellow needles, sparingly soluble in water. Application of diazomethane to V easily affords its methyl derivative VI, m.p. 93–94°C, $C_{15}H_{13}O_2NBr_2$. The infrared spectra of V and VI (Fig. 2) indicate the presence of a carboxyl (5.93μ) in V and an ester (5.85μ) in VI, and their ultraviolet spectra (Fig. 3) are notable in that the absorption in the wave length region longer than 420 mμ has disappeared. The probable constitution of V, 2-carboxy-2′,4-dibromo-4′methyldiphenylamine, is now under study by synthesis.



(V)

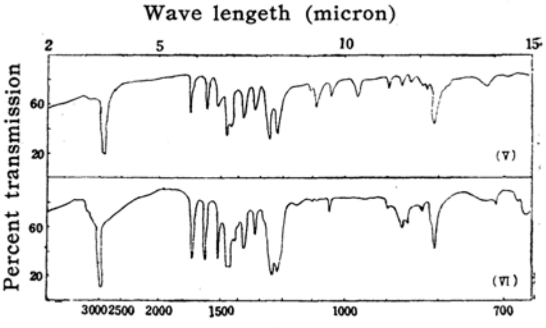


Fig. 2. Infrared absorption spectra of (V) and (VI) (in Nujol).

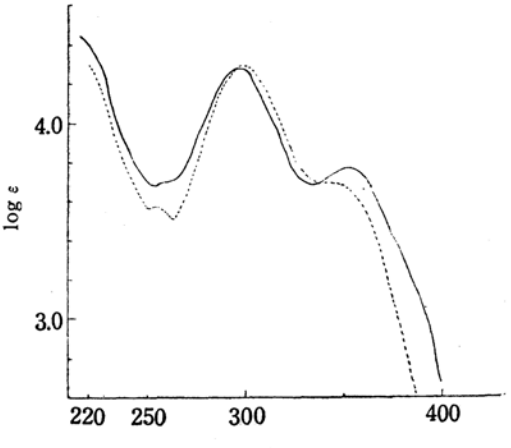


Fig. 3A. Ultraviolet absorption spectra of (V) in neutral (——), and in alkaline medium (……).

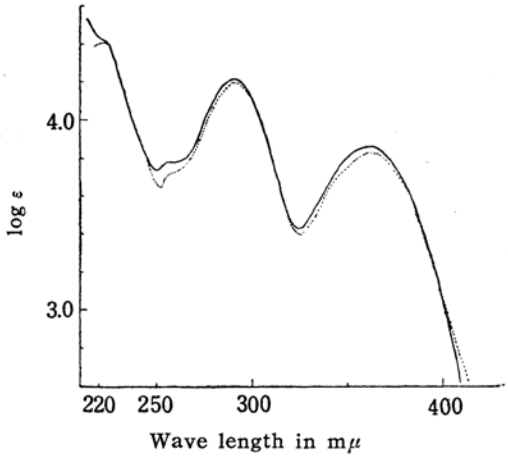


Fig. 3B. Ultraviolet absorption spectra of (VI) in neutral (——), and in alkaline medium (……).

(Note. Neutral: in methanol. Alkaline: in 0.1 N NaOH in methanol).

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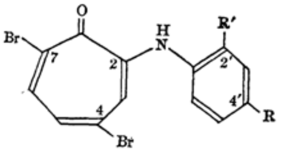
[8] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", p. 70 (1954).

[9] T. Nozoe, S. Seto, H. Takeda, S. Morosawa and K. Matsumoto, *Proc. Japan Acad.*, **27**, 556 (1951); **28**, 192 (1952); *Sci. Repts Tohoku Univ.*, Ser., I, **36**, 126 (1952).

Bromination of 2-anilino- and 2-(*p*-toluidino)-4,7-dibromotropone2) in glacial acetic acid, with or without the addition of sodium acetate, resulted in an introduction of one atom of bromine in both cases and respectively afforded orange yellow prismatic needles, (VII), m.p. 294.5°C, $C_{13}H_8ONBr_3$, and VIII, m.p. 264°C, $C_{14}H_{10}ONBr_3$. Since the newly introduced bromine atom is not in the form of a salt, the following structure in which the substitution has occurred in the benzene ring, can be assumed. This structure is supported by the fact that its ultraviolet spectra are similar to those of I and III. (See Fig. 4.)



	R	R'
(VII)	Br	H
(VIII)	CH_3	Br

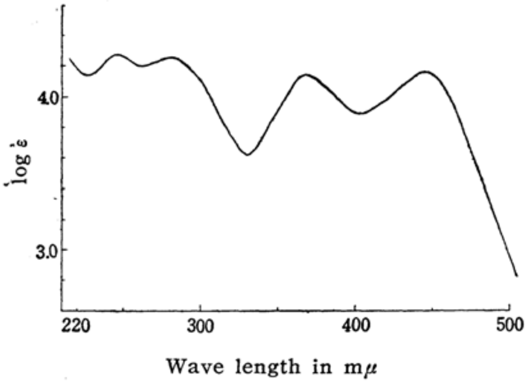


Fig. 4. Ultraviolet absorption spectra of (VII) (in methanol).

Experimental

2-(4'-Bromoanilino)-5,7-dibromotropone (I)—Bromination of 2-anilinotropone gave the same results whether sodium acetate was added or not, but when it was added, some complications arose in making the product completely free of ash. A solution of 600 mg. (0.003 mole) of 2-anilinotropone dissolved in 5.0 cc. of glacial acetic acid was treated with 1020 mg. (0.0063 mole) of bromine10) under stirring and the yellow precipitate that began to form a few minutes later was collected by filtration after 3 hours. Yield, 510 mg.

The mother liquor failed to yield any more crystals on further standing for 2 days, but precipitated crystals immediately on the addition of further 510 mg. of bromine. Total yield, 1260 mg. (almost 100% of the calculated amount). The two lots of precipitate were each dried over sodium hydroxide in vacuo, weighed and recrystallized successively from ethyl acetate and benzene. Both formed the same yellow prisms, m.p. 262–262.8°C (sealed tube), and their admixture indicated them to be an identical substance.

Anal. Found: C, 36.15; H, 1.94%. Calcd. for $C_{13}H_8ONBr_3$: C, 35.96; H, 1.86%.

The same product was obtained whether 3.5 molar equivalents of bromine were added at once or 4–5 molar equivalents. In the case of the latter, some red prisms were found to be mixed in the yellow crystals but these turned yellow during suctional filtration. The crystals of m.p. 262–262.8°C remained unchanged on heating in 5% aqueous ammonia or on shaking of its benzene solution with 2% sodium hydroxide. Its infrared spectrum also failed to exhibit the absorption of $>C=N^+<$ at around 5.9 μ.

Bromination of 2-(*p*-Toluidino)tropone.— a) *With the addition of sodium acetate*: To a solution of 210 mg. (0.001 mole) of 2-(*p*-toluidino)-tropone dissolved in 4.0 cc. of glacial acetic acid and containing 0.5 g. of anhydrous sodium acetate, 180 mg. (0.0011 mole) of bromine was added while stirring under chilling in ice water, by which crystals began to precipitate out after a few minutes. After allowing the mixture to stand overnight with occasional agitation, the precipitate was collected by filtration, dried over sodium hydroxide in vacuo, and 210 mg. of the product was dissolved in 50 cc. of benzene. The benzene solution was washed consecutively with water, diluted hydrochloric acid, dilute sodium hydroxide solution, and water, dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was recrystallized three times from ethyl acetate and afforded 2-(*p*-toluidino)-5,7-dibromotropone (II) as lemon-yellow needles, m.p. 180–181°C.

Anal. Found: C, 45.57; H, 3.25; N, 3.87%. Calcd. for $C_{14}H_{11}ONBr_2$: C, 45.54; H, 3.01; N, 3.79 %.

Crystals did not appear on standing of the mother liquor of II for one week and addition of 320 mg. (0.002 mole) of bromine gradually precipitated crystals. The mixture was allowed to stand at 30°C for 40 hours and the precipitate was purified as for II, affording 180 mg. of 2-(2'-brome-*p*-toluidino)-5,7-dibromotropone (III). Recrystallization from ethyl acetate gave lemon-yellow needles, m.p. 190°C, which melted at 150–153°C on admixture with II.

Anal. Found: C, 37.94; H, 2.44; N, 3.23 %. Calcd. for $C_{14}H_{10}ONBr_3$: C, 37.52; H, 2.25; N, 3.13 %.

Addition of water to the glacial acetic acid mother liquor of III only formed a minute amount of reddish brown resinous matter.

b) *Without the addition of sodium acetate*: To a stirred solution of 210 mg. of 2-(*p*-toluidino)-tropone dissolved in 4.0 cc. of gracial acetic acid, 500 mg. (0.0031 mole) of bromine was added under cooling and crystals began to precipitate out gradually after about one hour. After this

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10) All the bromine used in this experiment was a glacial acetic acid solution containing 100 mg. of bromine in 1.0 cc. of the solution.

11) The microanalyses were carried out at the Institute of Polytechnics, Osaka City University, and at the Pharmaceutical Department, Kumamoto University.

mixture being set aside for 5 hours with occasional agitation, the yellow crystals mixed with yellowish brown to reddish brown crystals were collected by suctional filtration by which all the crystals turned yellow. Yield, 400 mg. (88 %). After drying, the crystals were recrystallized twice from ethyl acetate to yellow needles, m.p. 190°C, identical with III.

When 180 mg. (0.0011 mole) of bromine was added under the same conditions, the crystals failed to precipitate out even after a few days. When a further amount of bromine (220 mg.) was added, or 400 mg. (0.0025 mole) of bromine was added at first, 330 mg. of III, m.p. 190°C, was obtained.

Decomposition of 2-(4′-Bromoanilino)-5,7-dibromotropone (I).—A mixture of I (500 mg.) and 40 cc. of 4 N ethanolic solution of sodium hydroxide was refluxed for 4 hours, the solvent was distilled off under a slight suction, and the distillate was collected in a receiver containing a small amount of hydrochloric acid. The residue in the distillation flask was mixed with water, and the mixture (A) was extracted with ether. The combined distillate and the ether extract was adjusted to pH 3.0 with hydrochloric acid and evaporated to dryness. A few drops of acetic anhydride was added to the residue, allowed to stand over night, mixed with water and again evaporated to dryness. The residue was recrystallized from aqueous ethanol and 25 mg. of *p*-bromoacetanilide was obtained as colorless needles, m.p. and mixed m.p. 161°C.

The alkaline aqueous solution (A) left after shaking with ether was acidified with hydrochloric acid, extracted with ether, and the ether was evaporated. Vacuum sublimation of the residue resulted in the sublimation of ca. 1/4 of the substance and 55 mg. of pale yellow crystals, giving positive ferric chloride reaction, was obtained. Recrystallization from dilute ethanol with charcoal afforded crystals of m.p. 152°C, which formed a *p*-toluidine salt, m.p. 122°C, by the usual method. No depression of the melting point occurred on admixture with 3,5-dibromotropolone.

Decomposition of 2-(*p*-Toluidino)-5,7-dibromotropone (II).—The sample (400 mg.) was refluxed for 6 hours as with I to effect hydrolysis and 20 mg. of *p*-acetotoluidide, m.p. 151°C and 30 mg. of 3,5-dibromotropolone were obtained.

Reaction of 2-(2′-Bromo-*p*-toluidino)-5,7-dibromotropone (III) and 2N Sodium Hydroxide.—A mixture of 300 mg. of (III) and 30 cc. of 2N ethanolic sodium hydroxide solution was refluxed for 30 minutes; cooling of the clear reaction mixture precipitated crystals. Recrystallization from ethyl acetate afforded crystals m.p. 186–188°C, undepressed on admixture with III. Rate of recovery, ca. 160 mg.

Reaction of (III) and Sodium Methoxide.—A mixture of 300 mg. of III and sodium methoxide solution (2g. of metallic sodium dissolved in 50cc. of absolute methanol) was refluxed for 3 hours. the most part of the solvent was distilled off under a reduced pressure, and the residue was treated as for I, affording 10 mg. of a basic component. Its acetylation and recrystallization of the product from dilute ethanol gave the N-acetate as fine needles, m.p. 119–120°C, undepressed on admixture with the synthesized 4-acetamino-3-bromotoluene, m.p. 119–120°C. This substance melted at 90–93°C when admixed with 4-acetamino-2-bromotoluene, m.p. 112–113°C12). 4-Acetamino-2-bromotoluene was obtained through the diazotation of 2-amino-4-nitrotoluene to 2-bromo-4-nitrotoluene, followed by reduction with tin and hydrochloric acid, and application of acetic anhydride to the amine so obtained, at room temperature.

The acidic component obtained from this hydrolysis was warmed with 4 cc. of ethyl acetate and the solution was allowed to stand for a few days, depositing 220 mg. of crystals. The ethyl acetate mother liquor was evaporated to dryness and the residue (30 mg.) was submitted to vacuum sublimation, from which ca. 8 mg. of 3,5-dibromotropolone, m.p. 152°C, was obtained. The sublimation residue was an acidic, amorphous brown mass. Crude crystals (220 mg.) were recrystallized several times from 80 % ethanol, using charcoal a few times, to lustrous yellow needles, m.p. 247°C (V).

Anal. Found: C, 44.00; H, 2.91 %. Calcd. for $C_{14}H_{11}O_2NBr_2$: C, 43.66; H, 2.88 %.

This substance gives negative ferric chloride reaction in ethanol and forms a sodium salt of almost colorless needles, somewhat sparingly soluble in water, with sodium bicarbonate solution. This sodium salt melts once at 95°C, solidified again, and does not melt up to 275°C. The sodium salt regenerates the original substance, m.p. 246–247°C, by the action of hydrochloric acid.

An excess of diazomethane in ether was added to 150 mg. of the substance of m.p. 247°C suspended in 30 cc. of ether, by which the crystals gradually disappeared. After 3 hours, the remaining diazomethane was decomposed with acetic acid and recrystallization of the product from 85 % ethanol afforded the methyl ester (VI) as pale yellow needles, m.p. 93–94°C. Maximum absorption in Nujol: 5.85 μ (ester carbonyl). The analytical values corresponded to those of the monomethyl derivative.

Anal. Found: C, 45.35; H, 3.39 %. Calcd. for $C_{15}H_{13}O_2NBr_2$: C, 45.15; H, 3.28 %.

2-(4′-Bromoanilino)-4,7-dibromotropone (VII).—A mixture of 0.7 g. of 2-anilino-4,7-dibromotropone and 60 cc. of glacial acetic acid, containing 2 g. of anhydrous sodium acetate, was heated, cooled, and 500 mg. of bromine was added to the crystalline brei. After a little time, yellow crystals began to precipitate out. The mixture was allowed to stand over night and the crystals were recrystallized from benzene or ethyl acetate, affording 0.50 g. of (VII) as reddish yellow prisms, m.p. 294–295°C.

Anal. Found: C, 35.90; H, 1.90 %. Calcd. for $C_{13}H_8ONBr_3$: C, 35.96; H, 1.86 %.

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12) J. J. Blanksma, *Chem. Weekbl.*, **6**, 899 (1909); *Chem. Zentr.*, **1910**, I, 260.

2-(2′-Bromo-*p*-toluidino)-4,7-dibromotropone (VIII).—This was prepared from 1.2 g. of 2-(*p*-toluidino)-4,7-dibromotropone by the method used for that of the aniline analog and recrystallization from benzene afforded 1.2 g. of (VIII) as yellow prisms with a slight reddish tint, m.p. 264°C.

Anal. Found: C, 37.47; H, 2.30%. Calcd. for $C_{14}H_{10}ONBr_3$: C, 37.52; H, 2.25%.

Concentration of the benzene mother liquor yielded 0.14 g. of yellow fine prisms, m.p. 213-215°C.

A part of the experiment reported herein was carried out at the Chemistry Department 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 those who supplied analytical data.

The present series of studies constitute a part of the general research on azulenoid compounds (Representative: Professor 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.

Department of Chemistry, Kumamoto
Women's University
Kumamoto