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3,4-Benzotropolone and Related Compounds. VI.[1] Brominated 6-Hydroxy-2,3-benzotropone (or Brominated 3-Hyroxy-4,5-benzotropone). Formation and Reaction

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6-Hydroxy-2,3-benzotropone (or 3-hydroxy-4,5-benzotropone) (I) was brominated under various conditions, and the bromination products were subjected to debromination, substitution, and some other reactions. I reacted with a molar equivalent of bromine at 25°C to give 7-bromo-6-hydroxy-2,3-benzotropone (II), and with two molar equivalents of bromine at 25°C to give an adduct of II with bromine (V), which, on heating, was dehydrobrominated to 5,7-dibromo-6-hydroxy-2,3-benzotropone (IV). On the other hand, I reacted with bromine at 100°C to give 5-bromo-6-hydroxy-2,3-benzotropone (III), IV, and 2,2,7-tribromo-4,5-benzocyclohepta-4,6-diene-1,3-dione (VI), depending on the amount of bromine employed. All these bromination products could be debrominated with ease with hydrogen in the presence of catalyst to yield I. When II was heated with hydrobromic acid, the 7-bromo substituent was in part eliminated to give I and migrated in part to give III. When IV and 4,7-dibromo-6-hydroxy-2,3-benzotropone (X) were heated with hydrobromic acid, the 7-bromo substituents were eliminated and the 4- or 5-bromo substituent remained unreacted, producing III and 4-bromo-6-hydroxy-2,3-benzotropone (IX) respectively. When II and IV were heated with hydrochloric acid, the 7-bromo substituents were not eliminated but, rather, substituted with chlorine atoms to give 7-chloro-6-hydroxy-2,3-benzotropone (VII) and 5-bromo-7-chloro-6-hydroxy-2,3-benzotropone (VIII) respectively. These facts suggest that I and its bromo derivative sometimes behave as unsaturated β-diketones (I').

In a previous paper[1] the present authors reported the formation of 6-hydroxy-2,3-benzotropone (I). Attention has now been directed toward the chemical properties of I and toward comparing those properties with those of three well-known isomers, 3,4-benzotropolone,[2,3] 4,5-benzotropolone,[4] and 4-hydroxy-2,3-benzotropone.[5] The present paper will deal with the formation and reaction of bromo derivatives of I. I is tautomeric with 4,5-benzocyclohepta-4,6-diene-1,3-dione (I') and with 3-hydroxy-4,5-benzotropone (I''). In this paper the (I) formula is tentatively employed as representative of these tautomers because it is at present unknown which of these is predominant.

An acetic acid solution of I was brominated under various conditions. The reaction of I with a molar equivalent of bromine at 25°C gave 7-bromo-6-hydroxy-2,3-benzotropone (II), the position of the bromo substitutent of which was established by its oxidation with alkaline hydrogen peroxide to *o*-carboxycinnamic acid, and by a study of its NMR absorption spectrum which contained AB-type double doublets at 7.55 and 6.98 ppm, doublets ascribable to two hydrogen atoms at the 4 and 5 positions. The same reaction of I with bromine, but at 100°C instead of 25°C, gave 5-bromo-6-hydroxy-2,3-benzotropone (III), which was identified by a mixed-melting-point determination and by a comparison of its infrared spectrum with that of a sample obtained previously[1] by another method. On being heated at 100°C with a molar equivalent of bromine, both II and III produced dibromo-2,3-benzotropone (IV). This fact indicates that the dibromo substituents of IV are situated at the 5- and 7-positions. IV was oxidized to phthalic acid under the same conditions as in the oxidation of II to *o*-carboxycinnamic acid. II, III, and IV were debrominated with ease to I when treated with hydrogen in the presence of a palladium-charcoal catalyst. These bromo derivatives exhibit two peaks in the 265—285 mμ and 355—365 mμ ranges in the ultraviolet absorption spectra (Fig. 1) and a carbonyl band below 1650 cm^{-1} in the infrared spectra (see

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[1] Part V: S. Ebine, M. Hoshino and K. Takahashi; This Bulletin, **41**, 2942 (1968).

[2] J. W. Cook and A. R. Sommerville, *Nature*, **163**, 410 (1949); J. W. Cook, A. R. Gibb, R. A. Raphael and A. R. Sommerville, *J. Chem. Soc.*, **1952**, 603.

[3] S. Ebine, This Bulletin, **35**, 114, 117, 122 (1962); **38**, 2029 (1965).

[4] H. Fernholz, E. Hartwig and J. G. Salfeld, *Ann.*, **576**, 137 (1952).

[5] G. L. Buchanan, *J. Chem. Soc.*, **1954**, 1060; G. L. Buchanan and J. K. Sutherland, *ibid.*, **1956**, 2620.

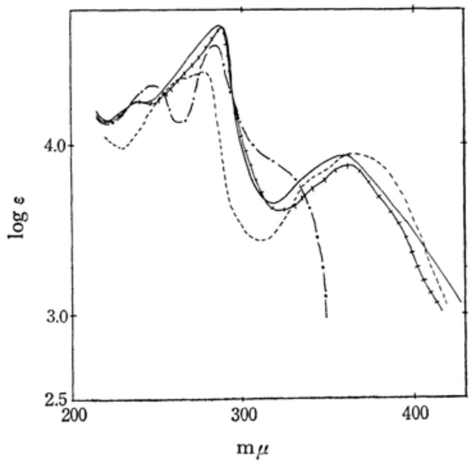

Fig. 1. Ultraviolet absorption spectra of 7-bromo-6-hydroxy-2,3-benzotropone (II, ----), 5,7-dibromo-6-hydroxy-2,3-benzotropone (IV, —+), 7-chloro-6-hydroxy-2,3-benzotropone (VII, —·) and 5-bromo-7-chloro-6-hydroxy-2,3-benzotropone (VIII, ——).

Experimental section), in agreement with the spectral features of troponoids.6) It has been reported that the methylation of 3-bromotropolone gives two isomeric methyl ethers, 3-bromo-2-methoxy- and 7-bromo-2-methoxy-tropones.7) However, II, III, and IV gave a single methyl ether and acetate, suggesting that one form predominates in their tautomerism. IV was further brominated at 100°C to 2,2,7-tribromo-4,5-benzocyclohepta-4,6-diene-1,3-dione (VI), which had carbonyl bands at 1710 and 1692 cm^{-1} in the infrared absorption spectrum. VI was also produced directly from I, II, and III when they were heated at 100°C with excess bromine. VI was debrominated to IV when its methanolic solution was left to stand with alkali and to I when treated with hydrogen in the presence of a palladium-charcoal catalyst. II reacted with bromine at 20°C to give an adduct (V), which was debrominated with ease to IV when its ethanolic or acetic acid solution was heated. I, with two molar equivalents of bromine at 20°C, gave the same adduct. Under the same conditions, III did not add bromine, but gave IV. V and VI showed ultraviolet absorption spectra entirely different from those of troponoids, as is shown in Fig. 2. From the above results, it is evident that the bromination of I proceeds in the sequence of II and V at 20°C, and in that of III, IV, and VI at 100°C.

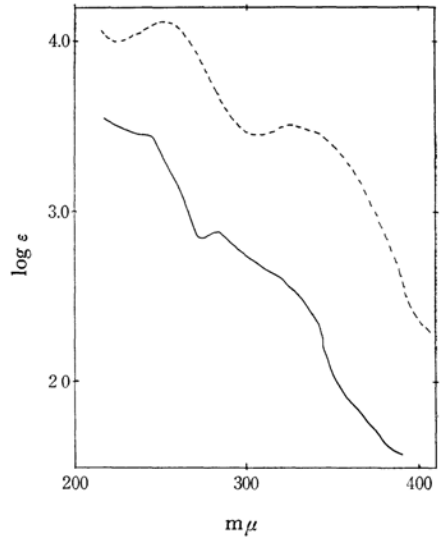

Fig. 2. Ultraviolet absorption spectra of adduct of II with Bromine (V, ----), and 2,2,7-tribromo-4,5-benzocyclohepta-4,6-diene-1,3-dione (VI, ——).

When II was heated at 100°C with hydrobromic acid in an acetic acid solution, its 7-bromo substituent migrated in part to the 5-position, giving III, and was in part eliminated, giving I. II reacted with hydrochloric acid in a similar way to give 7-chloro-6-hydroxy-2,3-benzotropone (VII) and I. However, III remained unreacted when heated with hydrobromic or hydrochloric acid. IV as well as VI reacted with hydrobromic acid to give III, and with hydrochloric acid to give 5-bromo-7-chloro-6-hydroxy-2,3-benzotropone (VIII). To make sure of the positions of the substituents, VII and VIII were oxidized with alkaline hydrogen peroxide to give *o*-carboxycinnamic acid and phthalic acid respectively, and VIII was treated with one molar equivalent of hydrogen in the presence of a palladium-charcoal catalyst to give III and VII. Both VII and VIII were dehalogenated to I with the calculated amount of hydrogen in the presence of the catalyst. The formation of free bromine was verified during the reaction of II, IV, and VI with hydrobromic acid. These debromination reactions, therefore, may be illustrated as in the scheme. The bromo migration may consist of two reactions: the debromination of II with hydrobromic acid to I, with the liberation of bromine, and the subsequent bromination of I to give III. It has been described above that the bromination of I at 100°C takes place at the 5-position to give III. In a similar manner, 4-bromo-6-hydroxy-2,3-benzotropone (IX), reported on in the preceding paper,1) was brominated to 4,7-dibromo-6-hydroxy-2,3-benzotropone (X), while the latter was debrominated to the former when heated with hydrobromic acid.

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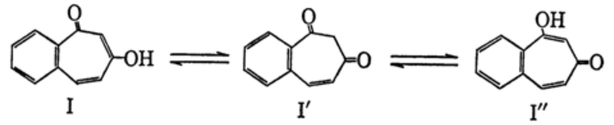
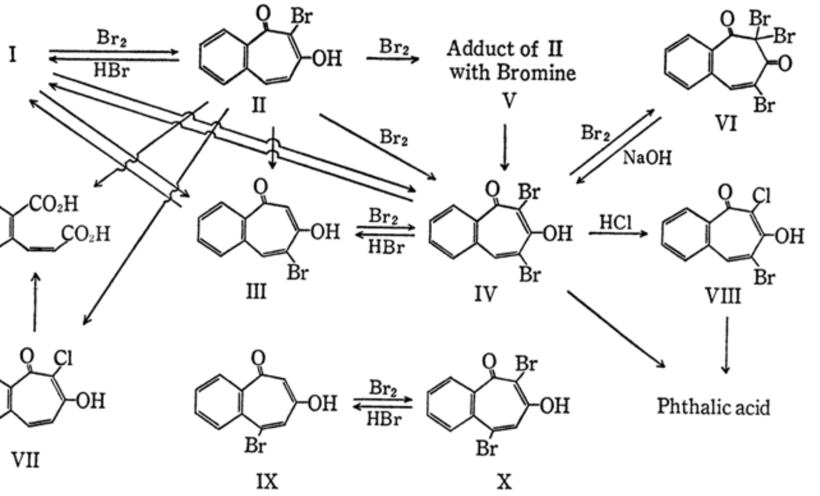
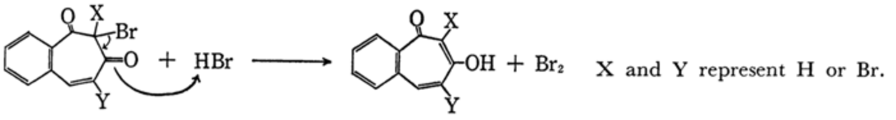
6) M. Tsuboi, This Bulletin, **25**, 369 (1952); S. Kinumaki, K. Aida and Y. Ikegami, *Sci. Rept. Res. Inst. Tohoku Univ.*, **A-8**, 263 (1956); E. Kloster-Jensen, N. Tarkoy, A. Eschenmoser and E. Heilbronner, *Helv. Chim. Acta*, **39**, 780 (1956).

7) T. Nozoe, Y. Kitahara and S. Masamune, *Proc. Japan Acad.*, **27**, 649 (1951); T. Sato, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **80**, 1340 (1959).







X and Y represent H or Br.

From the above results it has become evident that, although I and its bromo derivatives exhibit ultraviolet and infrared spectra characteristic of troponoids, they sometimes behave like unsaturated β-diketones represented by the (I′) formula; for example, the bromination of I, III, and IX takes place at the 7-position (or the 2-position as a β-diketone) to give II, IV, and X respectively, IV is further brominated to VI, and II adds bromine to give V. Furthermore, it has proved that the 7-bromo substituents of brominated 6-hydroxy-2,3-benzotropones is especially reactive; for example, upon heating with hydrobromic acid, the 7-bromo substituents of II, IV, and X were eliminated to give I, III, and IX respectively, while simultaneously the substituent of II migrated in part to give III. No such type of reaction has ever been described in connection with the bromo derivatives of isomeric 3,4-benzotropolone, 4,5-benzotropolone, and 4-hydroxy-2,3-benzotropone. It is of peculiar interest to compare the enhanced reactivity of the 7-bromo substituent described above with the reported[8] inertness of 7-chloro-2,3-benzotropone.

Experimental

7-Bromo-6-hydroxy-2,3-benzotropone (II). To a solution of 300 mg (1.74 mmol) of I in 30 m*l* of acetic acid, there was dropped, at 15°C, a solution of 280 mg (1.75 mmol) of bromine in 1 m*l* of acetic acid. After the mixture had stood for an hour at room temperature (17°C), the acetic acid was removed below 25°C under reduced pressure and the crystalline residue was fractionally recrystallized from ethanol to give 215 mg (55%) of II (pale yellow granular crystals melting at 173—173.5°C (dec.); also, 30 mg of unreacted I were recovered. The same bromination in the presence of 215 mg of anhydrous sodium acetate gave 421 mg (96%) of II. Ultraviolet spectrum (methanol): mμ (log ε), 269 (4.40), 365 (3.93), infrared spectrum (KBr) in the region above 1500 cm^{-1}: 3026, 1645, 1569, 1511 cm^{-1}.

Found: C, 52.92; H, 2.87%. Calcd for $C_{11}H_7O_2Br$: C, 52.61; H, 2.81%.

The NMR spectrum in deuterated dimethyl sulfoxide (d_6-DMSO): 8.47—7.85 ppm (4H, multiplet, aromatic hydrogens), 7.55 and 6.98 ppm (2H, AB-type doublets, J=12.8 cps, two hydrogens at the 4 and 5 positions).

5-Bromo-6-hydroxy-2,3-benzotropone (III). Bromine (110 mg, 0.69 mmol), diluted with 1 m*l* of acetic acid, was dropped into a warm solution of 100 mg (0.58 mmol) of I in 5 m*l* of acetic acid, and the resulting solution was heated at 100°C for 3 hr. When the mixture stood overnight at room temperature, a crystalline product separated out; this product was collected by filtration. The filtrate was concentrated to give a further crop of the product. The combined products (90 mg, 62%) were recrystallized from ethanol to give pale yellow needles of III melting at 234°C (dec.),

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[8] W. E. Parham, D. A. Bolon and E. E. Schweizer, *J. Am. Chem. Soc.*, **83**, 603 (1961).

ultraviolet spectrum (methanol): 275 mμ, (log ε 4.64), infrared spectrum (KBr) in the region above 1500 cm^{-1}: 3050, 2970, 2730, 2580, 1615, 1584, 1552, 1512 cm^{-1}.

Found: C, 52.38; H, 2.88%. Calcd for $C_{11}H_7O_2Br$: C, 52.61; H, 2.81%.

Adduct of II with Bromine (V). *a) From I.* To a solution of 300 mg (1.74 mmol) of I in 45 m*l* of acetic acid, there was added, drop by drop at 20°C, a solution of 560 mg (3.5 mmol) of bromine in 5 m*l* of acetic acid. After it has stood at this same temperature for 2.5 hr, the reaction mixture was concentrated below 25°C under diminished pressure; the product which separated was collected and recrystallized from benzene or dilute ethanol to give 460 mg (64%) of V in the form of colorless, granular crystals with a double melting point of 135—136°C and 179—180°C (dec.).

b) From II. A solution of 100 mg (0.63 mmol) of bromine in 1 m*l* of acetic acid was added to a solution of 150 mg (0.60 mmol) of II in 14 m*l* of acetic acid, and the resulting solution was worked up as above to give 105 mg (43%) of III.

The above two samples showed the same ultraviolet and infrared spectra. Ultraviolet spectrum (methanol): 330—336 mμ (log ε 3.82), infrared spectrum (KBr): 3340, 1635, 1617, 1595, 1552, 1540, 1525 cm^{-1}.

Found: C, 32.50; H, 1.77%. Calcd for $C_{11}H_7O_2 \cdot Br_3$: C, 32.15; H, 1.72%.

5,7-Dibromo-6-hydroxy-2,3-benzotropone (IV). *a) From I.* A solution of 100 mg (0.58 mmol) of I and 200 mg (1.25 mmol) of bromine in 6 m*l* of acetic acid was heated at 100°C for 3 hr and then worked up in the same way as has been described for the bromination of I to III; this gave 180 mg (94%) of pale yellow needles of IV melting at 181—182°C (dec.).

b) From II. A similar work-up of a solution of 150 mg (0.60 mmol) of II and 100 mg (0.63 mmol) of bromine in 14 m*l* of acetic acid gave 170 mg (86%) of IV.

c) From III. III (1 g, 3.98 mmol) and 770 mg (4.82 mmol) of bromine, dissolved in 100 m*l* of acetic acid, were heated at 100°C for 3 hr to give 1.2 g (91%) of IV. The same reaction, but at 20°C, gave an 80% yield of IV.

d) From V. A solution of 100 mg of V in 3.5 m*l* of acetic acid was heated at 100°C for 2.5 hr. A crystalline product which separated on cooling was filtered, and the filtrate was concentrated to give an additional crop of the product. The recrystallization of the combined products from ethanol afforded 68 mg (84%) of IV. When dissolved in 1 N sodium hydroxide and allowed to stand for 1.5 hr at room temperature, V decomposed to produce IV in a fair yield.

e) From VI. A solution of 100 mg of VI in 3 m*l* of methanol containing 0.15 m*l* of 2 N sodium hydroxide was allowed to stand for 3 hr, and then the precipitate which had separated on acidification was collected and recrystallized. Yield, 30 mg (37%).

The identities of the samples obtained above have been confirmed by mixed-melting-point determinations and by infrared-spectrum comparisons. Ultraviolet spectrum (methanol): mμ (log ε), 285 (4.71), 355 (3.82), infrared spectrum (KBr) in the region above 1500 cm^{-1}: 3330, 1593, 1568, 1513 cm^{-1}.

Found: C, 40.30; H, 1.81%. Calcd for $C_{11}H_6O_2Br_2$: C, 40.03; H, 1.83%.

Acetate of IV, colorless granular crystals (recrystallized from methanol), mp 172—173°C.

Found: C, 41.90; H, 2.27%. Calcd for $C_{13}H_8O_3Br_2$: C, 41.97; H, 2.17%.

Methyl ether of IV, colorless needles (recrystallized from methanol), mp 160—161°C.

Found: C, 42.22; H, 2.21%. Calcd for $C_{12}H_8O_2Br_2$: C, 41.89; H, 2.34%.

2,2,7-Tribromo-4,5-benzocyclohepta-4,6-diene-1,3-dione (VI). *a) From IV.* A mixture of 100 mg (0.30 mmol) of IV and 2 g (12.5 mmol) of bromine was refluxed for 4 hr, the excess bromine was distilled, and then the residue was recrystallized from ethanol to afford 90 mg (73%) of yellow needles of VI melting at 132—133°C.

b) From I and III. A similar treatment of 100 mg (0.58 mmol) of I with 2 g (12.5 mmol) of bromine gave 50 mg (21%) of VI and 20 mg (10%) of IV, while the treatment of 100 mg (0.40 mmol) of III with 2 g (12.5 mmol) of bromine gave 110 mg (68%) of VI. Ultraviolet spectrum (methanol): 288 mμ, (log ε 3.77), infrared spectrum (KBr) in the region above 1500 cm^{-1}: 1710, 1692, 1591, 1569 cm^{-1}.

Found: C, 32.32; H, 1.64%. Calcd for $C_{11}H_5O_2Br_3$: C, 32.31; H, 1.23%.

Debromination of II, IV, and VI to I. The reaction was carried out in the same way as has already been described for the debromination of III to I. A solution of 300 mg (0.91 mmol) of IV in 100 m*l* of ethanol was shaken with hydrogen in the presence of 100 mg of 5% palladium chloride-charcoal and 100 mg of anhydrous sodium acetate. After 43.6 m*l* (1.84 mmol) of hydrogen had been taken up at 16°C, the catalyst was filtered, the filtrate was evaporated, and the residue was recrystallized from ethanol, giving 130 mg (83%) of I, mp and mixed mp 208.5°C (dec.). A similar treatment of II and VI with hydrogen gave I in 80% and 48% yields respectively.

Reaction of II with Hydrobromic or Hydrochloric Acid. a) II (200 mg), dissolved in 25 m*l* of acetic acid and 15 m*l* of 47% hydrobromic acid, was heated under reflux for 2.5 hr. The solution gave a positive patassium iodide - starch paper test, indicating the presence of free bromine. The solution was then concentrated, and the product was fractionally recrystallized from ethanol to give 58 mg (29%) of III and 5 mg (4%) of I.

b) The heating of 120 mg of II, dissolved in a mixture of 15 m*l* of acetic acid and 12 m*l* of 6 N hydrochloric acid for 2 hr, and the recrystallization of the product from dilute ethanol gave 70 mg (71%) of 7-chloro-6-hydroxy-2,3-benzotropone (VII) as pale yellow needles melting at 172—173°C (dec.), along with 10 mg (12%) of I. VII, ultraviolet spectrum (methanol): mμ (log ε), 245 (4.34), 283 (4.60), infrared spectrum (KBr) in the region above 1500 cm^{-1}: 3006, 1646, 1570, 1518, 1507 cm^{-1}.

Found: C, 63.77; H, 3.53%. Calcd for $C_{11}H_7O_2Cl$: C, 63.94; H, 3.41%.

Reaction of IV with Hydrochloric or Hydrobromic Acid. The reaction was carried out in the same way as above. The reaction of 200 mg of IV with 20 m*l* of 47% hydrobromic acid in 15 m*l* of acetic acid gave 130 mg (85%) of III, mp and mixed mp 243°C (dec.), while the reaction of 300 mg of IV with 15 m*l* of 6 N hydrochloric acid in 30 m*l* of acetic acid gave

5-bromo-7-chloro-6-hydroxy-2,3-benzotropone (VIII) as yellow needles (from ethanol), mp 213—214°C (dec.), yield 215 mg (83%). VIII, ultraviolet spectrum (methanol): mμ (log ε), 287 (4.73), 357 (3.93), infrared spectrum (KBr) in the region above 1500 cm^{-1}: 3306, 1590, 1566, 1514 cm^{-1}.

Found: C, 46.22; H, 2.25%. Calcd for $C_{11}H_6O_2ClBr$: C, 46.27; H, 2.12%.

During the former reaction a considerable amount of bromine was liberated; it was identified by a potassium iodide-starch paper test.

Acetate of VIII, colorless, granular crystals, mp 183—184°C.

Found: C, 48.03; H, 2.57%. Calcd for $C_{13}H_8O_3ClBr$: C, 47.66; H, 2.46%.

Reaction of VI with Hydrobromic or Hydrochloric Acid. A similar treatment of VI (400 mg) with 47% hydrobromic acid (30 m*l*) in acetic acid (50 m*l*) gave III (173 mg, 71%), while that of VI (400 mg) with 6 N hydrochloric acid (30 m*l*) in acetic acid (50 m*l*) gave VIII (100 mg, 36%).

Dehalogenation of VIII. The dehalogenation was carried out in the same manner as has been described for the debromination of II, IV, and VI. a) A solution of 300 mg of VIII in 100 m*l* of ethanol was treated with hydrogen in the presence of 150 mg of 5% palladium chloride-charcoal and 130 mg of anhydrous sodium acetate. The reaction was stopped when a molar equivalent of hydrogen had been taken up. The recrystallization of the product from ethanol gave 81 mg (31%) of III and 101 mg (47%) of VII. b) When stopped after the uptake of two molar equivalents of hydrogen, the same reaction, using 300 mg of VIII, 150 mg of 5% palladium chloride-charcoal, 260 mg of anhydrous sodium acetate, and 100 m*l* of ethanol, produced 121 mg (67%) of I. The products obtained in a) and b) were identified by a mixed-melting-point determination and by a comparison of the infrared spectra.

Oxidation of II, IV, VII and VIII. A 200-mg sample was dissolved in 20 m*l* of 0.5 N sodium hydroxide, and to this 5 m*l* of 35% hydrogen peroxide were added. After standing at 50°C for 5 hr, the solution was acidified by dilute hydrochloric acid to precipitate unreacted material (30—50% recovery), which was removed by filtration. The filtrate was extracted with ether, and the extract was evaporated to give the product. The oxidation of II and VII gave *o*-carboxycinnamic acid (mp and mixed mp 185—186°C) in 47 and 33% yields respectively, while that of IV and VIII gave phthalic acid, mp and mixed mp 200°C, in 40 and 35% yields respectively.

Bromination of 4-Bromo-6-hydroxy-2,3-benzotropone (IX) to 4,7-Dibromo-6-hydroxy-2,3-benzotropone (X) and Debromination of X to IX. These reactions were carried out exactly as has been described above for the bromination of III and for the reaction of IV with hydrobromic acid. The reaction of IX (400 mg) and bromine (300 mg) in acetic acid at 100°C for 1 hr gave X (410 mg, 78%) as pale yellow prisms (from dilute ethanol) melting at 156—157°C. X, ultraviolet spectrum (methanol): mμ (log ε), 265 (4.39), 349 (3.79), infrared spectrum (KBr) in the region above 1500 cm^{-1}: 3186, 1616, 1599, 1581, 1555, 1543, 1528 cm^{-1}.

Found: C, 39.99; H, 2.05%. Calcd for $C_{11}H_6O_2Br_2$: C, 40.03; H, 1.83%.

The reaction of X (150 mg) and 47% hydrobromic acid (20 m*l*) in acetic acid (15 m*l*) at 100°C for 2 hr produced IX (60 mg, 53%).

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