Condensed Cyclobutane Aromatic Compounds. XXVIII. α-Bromo Derivatives of Benzocyclobutenone

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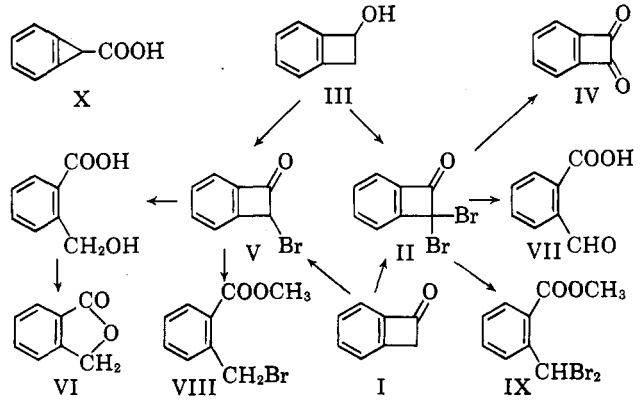
Received May 12, 1964

α-Bromobenzocyclobutenone and α,α-dibromobenzocyclobutenone are obtained by the reaction of either benzocyclobutenol or benzocyclobutenone with N-bromosuccinimide. Both bromo ketones are cleaved by base to give *o*-disubstituted benzenes exclusively. It has been demonstrated, in the case of methoxide ion, that cleavage of the four-membered ring precedes displacement or hydrolysis of the α-halogen of the ketones.

Benzocyclobutenone (I) has been reported to undergo base-catalyzed ring cleavage under mild conditions to afford a mixture of *o*-toluic acid and phenylacetic acid.[1] As part of a broad program to study the effect of substituents on the direction of cleavage of the four-membered ring of benzocyclobutenones, we have synthesized the two α-brominated benzocyclobutenones and investigated th eactions of these compounds with potassium hydroxi and with sodium methoxide.

α,α-Dibromoben ocyclobutenone (II) was obtained in good yield (61%) by the reaction of benzocyclobutenone with an excess of N-bromosuccinimide. The dibromo ketone (II) was prepared even more conveniently by the treatment of benzocyclobutenol (III) with 4 equiv. of N-bromosuccinimide; this reaction is undoubtedly a combined oxidation and bromination process. The structure of ketone II was confirmed by its reaction with silver trifluoroacetate, followed by water, which afforded benzocyclobutenedione (IV).[2]



α-Bromobenzocyclobutenone (V) was obtained by the reaction of either benzocyclobutenone or benzocyclobutenol with a limited quantity of N-bromosuccinimide. It was advantageous to stop the bromination at a stage at which unbrominated ketone I remained in the reaction mixture; in this way the formation of a difficultly separable mixture of the monobromo ketone (V) and the dibromo ketone (II) was avoided.

The reaction of α-bromobenzocyclobutenone with excess aqueous potassium hydroxide afforded *o*-hydroxymethylbenzoic acid (isolated as phthalide, VI) in almost quantitative yield. Mandelic acid, the end product resulting from cleavage of the bond between the carbonyl carbon and the aromatic ring, was not found in the reaction mixture. The reaction of α,α-dibromobenzocyclobutenone with excess aqueous base gave similar results; *o*-phthalaldehydic acid (VII) was the sole cleavage product obtained.

The reaction of the monobromo ketone (V) and of the dibromo ketone (II) with *equimolar* amounts of sodium methoxide in methanol gave, respectively, methyl α-bromo-*o*-toluate (VIII) and methyl α,α-dibromo-*o*-toluate (IX). The isolation of the bromo esters VIII and IX in good yield indicates that attack of methoxide ion upon the carbonyl group of V or II, followed by cleavage of the C-1,2 bond of the benzocyclobutene system, is a considerably faster process than the displacement of halogen by methoxide in the bromo ketones. Indeed, it may be noted that carbonyl attack by methoxide in V or II must also be a more rapid process than the reaction of methoxide ion with the highly reactive benzylic bromides VIII and IX formed as cleavage products.

The formation of only derivatives of *o*-xylene by base cleavage of the bromo ketones V and II implies that neither the unknown benzocyclopropenecarboxylic acid (X) nor any derivative of this acid is produced as an intermediate in the cleavage reactions. Benzocyclopropenes might have been expected as Favorskii rearrangement products of V or II; the failure of such compounds to be formed attests to the unusual strain present in the benzocyclopropene system.[3]

Experimental[4]

Benzocyclobutenone (I).—The following procedure for the oxidation of benzocyclobutenol to benzocyclobutenone gave better results than that described previously.[1] A solution of benzocyclobutenol (2.0 g.) in ether (20 ml.) was stirred for 2 hr. at room temperature with a solution of sodium dichromate dihydrate (1.7 g.) and sulfuric acid (1.3 ml.) in water (7 ml.). The neutral product was worked up in the usual manner; the crude oil was distilled under reduced pressure to give benzocyclobutenone (1.27 g., 67%). The ultraviolet spectrum, which was not reported previously,[1] showed the following maxima in ethanol: λ_{max} 208 mμ (log ε 4.19), 242 (4.17), 285 (3.60), 293 (3.60).

2,2-Dibromobenzocyclobutenone (II). A. From Benzocyclobutenol.—Benzoyl peroxide (0.20 g.) was added to a refluxing solution of benzocyclobutenol[1] (1.00 g.) in carbon tetrachloride (65 ml.) containing suspended N-bromosuccinimide (6.00 g.). A vigorous exothermic reaction began immediately. The mixture was refluxed for a total time of 1 hr., cooled, and diluted with 30–60° petroleum ether (15 ml.); the precipitated succinimide (3.90 g.) was removed by filtration. Evaporation of the filtrate gave a residue which was crystallized from petroleum ether to give colorless prisms of dibromo ketone II (1.3 g., 60%), m.p. 77–78°. The ultraviolet spectrum (ethanol) showed the following maxima: λ_{max} 213 mμ (log ε 4.78), 247 (4.08), 292 (3.63), 298 (3.63), shoulders at 330 (2.34) and 3.44 (2.08). Infrared

(1) M. P. Cava and K. Muth, *J. Am. Chem. Soc.*, **82**, 652 (1960).

(2) (a) M. P. Cava and D. R. Napier, *ibid.*, **79**, 3606 (1957); (b) M. P. Cava, D. R. Napier, and R. J. Pohl, *ibid.*, **85**, 2076 (1963).

(3) For the first report of the synthesis of a benzocyclopropene derivative, see R. Anet and F. A. L. Anet, *ibid.*, **86**, 525 (1964).

(4) Analyses were performed by A. Bernhardt, Mulheim. Melting points are uncorrected.

carbonyl absorption was observed (KBr) as a strong band at 5.60 and a weaker but sharp band at 5.47 μ.

Anal. Calcd. for $C_8H_4Br_2O$: C, 34.78; H, 1.45; Br, 57.97. Found: C, 35.01; H, 1.59; Br, 57.91.

B. From Benzocyclobutenone.—A mixture of benzocyclobutenone[1] (0.300 g.), N-bromosuccinimide (1.20 g.), benzoyl peroxide (0.06 g.), and carbon tetrachloride (10 ml.) was refluxed for 4 hr. The reaction mixture was worked up as described above (A) to afford 2,2-dibromobenzocyclobutenone (0.418 g., 61%), m.p. 74–78°.

2-Bromobenzocyclobutenone (V). A. From Benzocyclobutenol.—Benzoyl peroxide (0.500 g.) was added to a refluxing solution of benzocyclobutenol (4.00 g.) in carbon tetrachloride (190 ml.) containing suspended N-bromosuccinimide (19.20 g.). A vigorous exothermic reaction began immediately. The mixture was refluxed for a total time of 25 min., cooled, and diluted with petroleum ether (50 ml.); the precipitated succinimide (12.30 g.) was removed by filtration. Evaporation of the filtrate gave a residue which was purified by chromatography on alumina (Woelm, grade II, acidic), using benzene as the eluent. The oily fractions from the column (1.266 g.) were combined and recrystallized from petroleum ether to give colorless prisms of monobromo ketone V (1.824 g., 28%), m.p. 82–84°. The ultraviolet spectrum (ethanol) showed the following maxima: λ_{max} 210 mμ (log ϵ 4.47), 245 (3.92), 288 (3.55), 295 (3.55), shoulders at 320 (2.41) and 345 (2.10). Infrared carbonyl absorption was observed (KBr) as a strong band at 5.72 and a weaker band at 5.59 μ.

Anal. Calcd. for C_8H_5BrO: C, 48.76; H, 2.55; Br, 40.57. Found: C, 48.66; H, 2.49; Br, 40.44.

B. From Benzocyclobutenone.—A mixture of benzocyclobutenone (0.822 g.), N-bromosuccinimide (1.33 g.), benzoyl peroxide (0.050 g.), and carbon tetrachloride (20 ml.) was refluxed for 0.5 hr. The reaction mixture was worked up as described above (A) to afford 2-bromobenzocyclobutenone (0.575 g., 42%), m.p. 82–84°.

Benzocyclobutenedione (IV) from 2,2-Dibromobenzocyclobutenone (II).—A solution of dibromo ketone II (0.050 g.) and silver trifluoroacetate (0.150 g.) in benzene (2.5 ml.) was stirred overnight at room temperature. Excess aqueous sodium chloride was added, and the mixture was filtered after stirring for a short time. Evaporation of the dried benzene layer, followed by crystallization of the residue from methylene chloride–petroleum ether, gave the diketone IV as yellow crystals (0.020 g., 85%), m.p. 131–132°. The diketone obtained was identical (infrared and mixture melting point) with authentic material.[2]

Cleavage of Bromo Ketones II and V with Methanolic Sodium Methoxide. A. Cleavage of Dibromo Ketone II.——2,2-Dibromobenzocyclobutenone (0.300 g.) was dissolved in dry methanol (9 ml.) containing sodium methoxide (0.069 g.). After 24 hr. at room temperature the solution was evaporated to dryness and the residue was extracted with ether. Evaporation of the etheral extract gave methyl α,α-dibromo-*o*-toluate (0.278 g., 83%), m.p. 49°; the melting point of the crude ester was raised by sublimation to 51° (lit.[5] m.p. 51.5–52.5°). The material was identical (infrared and mixture melting point) with an authentic sample.[5] Acidification of the ether-insoluble residue from the base-cleavage reaction afforded α,α-dibromo-*o*-toluic acid (0.060 g.), m.p. 175°, identical in all respects with an authentic sample.[5]

B. Cleavage of Monobromo Ketone V.—2-Bromobenzocyclobutenone (0.300 g.) was dissolved in dry methanol (9 ml.) containing sodium methoxide (0.90 g.). After 5 hr. at room temperature the solvent was removed under vacuum at 30°, and the residue was extracted with ether. Evaporation of the ethereal extract gave methyl α-bromo-*o*-toluate (0.306 g., 87%) as an oil which solidified (m.p. 27–29°) after cooling to −78°. Recrystallization from petroleum ether afforded large prismatic crystals of the pure ester, m.p. 31–32° (lit.[5] m.p. 32.5°). The material was identical (infrared and mixture melting point) with an authentic sample.[5]

Cleavage of Bromo Ketones II and V with Aqueous Potassium Hydroxide. A. Cleavage of Dibromo Ketone II.—2,2-Dibromobenzocyclobutenone (0.263 g.) was stirred at room temperature for 9 hr. with 10% aqueous potassium hydroxide (8 ml.). The clear solution was cooled, acidified with hydrochloric acid, and allowed to stand for 12 hr. The colorless crystalline residue that remained after evaporation of the solution to dryness was extracted with ether–benzene. Evaporation of the solvent gave phthalaldehydic acid (0.145 g., 94%), identical (infrared and mixture melting point) with an authentic sample.

B. Cleavage of Monobromo Ketone V.—2-Bromobenzocyclobutenone (0.223 g.) was stirred at room temperature for 9 hr. with 10% aqueous potassium hydroxide (8 ml.). The clear solution was cooled, acidified with hydrochloric acid, and allowed to stand for 12 hr. Colorless crystals of phthalide (0.110 g.), m.p. 70°, were filtered from the solution. Additional phthalide (0.018 g.) was obtained by ether extraction of the mother liquor (total yield: 0.128 g., 81%). The material was identical (infrared, v.p.c., and mixture melting point) with an authentic sample.

Acknowledgment.—We should like to thank the National Science Foundation for a grant in support of this work.

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Steroids Containing Ring A Aromatic. IX. Reduction of 1-Methoxy-4-methyl-1,3,5(10)-trienes and 17β-Hydroxy-4-methylestra-1,3,5(10)-triene[1]

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Received May 22, 1964

The reduction of 17β-hydroxy-1-methoxy-4-methylestra-1,3,5(10)-triene with lithium in ethylamine or liquid ammonia was shown to yield 17β-hydroxy-4-methylestra-1,3,5(10)-triene and a monoene, 17β-hydroxy-4ξ-methylestr-5(10)-ene. The monoene was also obtained by the reduction of 17β-hydroxy-4-methylestra-1,3,5(10)-triene by lithium in ethylamine. In addition, evidence is provided for the formation of an unstable, unconjugated diene, which aromatizes to 17β-hydroxy-4-methylestr-1,3,5(10)-triene. Similarly, 1-methoxy-4-methyl-19-norpregna-1,3,5(10)-trien-20-one was converted to 4-methyl-19-norpregna-1,3,5(10)-trien-20-one.

In the course of certain investigations, we had the opportunity to study the Birch reduction[3] of 17β-hydroxy-4-methylestra-1,3,5(10)-triene[4] (Ia) and 17β-hydroxy-1-methoxy-4-methylestra-1,3,5(10)-triene[5] (Ib). Instead of obtaining the expected nonconjugated methoxydiene from Ib, products of demethoxylation and ring reduction were formed.

Reduction of Ib was realized with excess lithium in

(1) (a) Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1964, Abstracts, p. 39 S. (b) This work was supported by Grants A5326 and CAO4663-06 from the U. S. Public Health Service. (c) Part VIII: E. Caspi, P. K. Grover, and Y. Shimizu, *J. Am. Chem. Soc.*, **86**, 2463 (1964).

(2) Recipient of Public Health Service Research Career Program Award CA-K3-16614 from the National Cancer Institute.

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