

(CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN)

Formation of Nortricyclene Derivatives by Bromination of *exo*-2,5-Methylene-1,2,5,6-tetrahydrobenzoic Acids

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Bromination of several derivatives of *exo*-2,5-methylene-1,2,5,6-tetrahydrobenzoic acid in aqueous bicarbonate solution forms derivatives of 3-bromonortricyclene, as well as rearranged bromolactones, bromohydrins, etc. This novel reaction is interpreted as a type of *trans* elimination. Iodolactonization has been used as a method for removing the *endo* isomer from a mixture of *endo* and *exo* isomers and as a method for the analysis of such mixtures.

The Diels-Alder reaction of *trans*-2-phenylethene-1-sulfonic acid derivatives with cyclopentadiene forms a mixture of stereoisomers A and B. The percentage of *endo*-sulfo isomer (B) was determined quantitatively by bromosulfonation in neutral aqueous solution.² In an extension of this study to *trans*-cinnamic acid derivatives,³ bromolactonization was found to be inapplicable, since not only did the *endo*-acids I form neutral bromolactones as expected, but also the *exo*-acids II formed neutral material as well as the expected acidic bromination products. In the present paper, it is demonstrated that some *exo*-bicyclo[2,2,1]-5-heptene-2-carboxylic acids are converted in part to bromonortricylenes by bromine in aqueous bicarbonate; a minor amount of rearranged bromolactone is formed in some cases.

Acrylic acid adds to cyclopentadiene to give primarily *endo*-2,5-methylene-1,2,5,6-tetrahydrobenzoic acid (III) contaminated by the *exo* isomer IV.⁴ The percentage of *exo* isomer may be increased by alkaline isomerization of the *endo*-methyl ester, followed by saponification.⁴ In the present work, it was found that the isomerized acid was a mixture containing about 60% *exo*- and 40% *endo*-acids. Pure *exo*-acid could not be obtained by crystallization of the mixture, but after removal of the *endo* contaminant as the iodolactone by treatment with iodine in aqueous bicarbonate solution,⁵ the *exo* isomer was readily crystallized in pure form. The iodolactonization did not affect the *exo*-isomer, hence it was possible to show that the original crude *endo*-acid was about 75% *endo* and 25% *exo*.

The known⁴ bromolactone Va formed readily from III in 74% yield. However, when the pure *exo* isomer IV was brominated by the same procedure (aqueous bicarbonate), the acidic bromohydrins and dibromides were accompanied by 3-bromonortricyclene VI and a rearranged bromolactone Vb in respective yields up to 8 and 6%. The acidic material was usually glassy, but in one case a pure crystalline bromohydrin acid (VII or an isomer) was isolated. The structure of VI was proved by comparison with an authentic sample. The identity of Vb was inferred by its non-identity with Va, by the similarity of its infrared spectrum and that of Va, and by analogy to the case considered below.

(1) Eastman Kodak Fellow, 1953-1954. Abstracted from the Ph.D. Dissertation of C. D. V., University of Michigan, 1955.

(2) C. S. Rondestvedt, Jr., and J. C. Wygant, *THIS JOURNAL*, **73**, 5785 (1951); *J. Org. Chem.*, **17**, 975 (1952).

(3) C. S. Rondestvedt, Jr., and C. D. Ver Nooy, *THIS JOURNAL*, **77**, in press (1955).

(4) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett and R. Armstrong, *ibid.*, **72**, 3116 (1950); especially footnote 9.

(5) E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 2315 (1954).

Attention was then turned to the stereoisomeric 3,6-methylene-1,2,3,6-tetrahydrophthalic acids. The *endo*-*cis* form VIII is known to give the bromolactonic acid IX,⁶ while the *trans* isomer X forms a different bromolactonic acid XI.^{6,7} Bromination of the *exo*-*cis*-acid XII has been reported to give only a poorly characterized mixture.⁸ The anhydride of XII has been brominated in non-polar solvents⁹⁻¹¹ to form dibromides, while the *exo* adducts of furan and maleic anhydride or maleic acid have been brominated in aqueous solution.^{12,13} When we brominated XII in aqueous bicarbonate medium, the bromonortricyclenecarboxylic acid XIII was formed in 22-36% yield. Both XIII and its amide exhibited strong infrared absorption at 12.2-12.5 μ ; it has been shown previously that nortricyclene derivatives exhibit strong absorption in the 12.0-12.5 μ region.^{4,14} The structure of XIII was established by reductive dehalogenation to the known solid nortricyclene-3-carboxylic acid (XIV) which was identical with an authentic sample.⁴ A second product was a bromolactonic acid which was neither IX nor XI. It was identified by reductive dehalogenation to the known lactonic acid XV, identical with authentic samples prepared in two different ways. The structure XVI is consistent with these observations.

The remainder of the bromination product of XII was a mixture of stereoisomeric dibromides and bromohydrins, judging from the neutral equivalents. These were not investigated in detail.

The *exo*-carboxyl adducts II of cinnamic acid and *p*-nitrocinnamic acid with cyclopentadiene were prepared from the mixed adducts by removal of the *endo* isomers by iodolactonization.³ They formed the corresponding nortricyclene derivatives XVII in about 65% yields when brominated in bicarbonate solution. Both exhibited characteristic nortricyclene absorption in the 12-12.5 μ region. They were accompanied by acidic dibromides and/or bromohydrins.

Discussion

The nortricyclene system is not well known. It has been formed by the action of N-bromosuccinimide

(6) K. Alder and G. Stein, *Ann.*, **504**, 247 (1933).

(7) H. Kwart and L. Kaplan, *THIS JOURNAL*, **76**, 4078 (1954).

(8) Reference 6, p. 230.

(9) H. Kwart and L. Kaplan, *THIS JOURNAL*, **75**, 3356 (1953).

(10) D. Craig, *ibid.*, **73**, 4889 (1951).

(11) (a) P. D. Bartlett and A. Schneider, *ibid.*, **68**, 6 (1946); (b) J. A. Berson, *ibid.*, **76**, 5748 (1954).

(12) R. B. Woodward and H. Baer, *ibid.*, **70**, 1161 (1948).

(13) J. A. Berson and R. Swidler, *ibid.*, **75**, 1721 (1953); **76**, 4057 (1954); J. A. Berson, *ibid.*, **76**, 4069 (1954).

(14) E. R. Lippincott, *ibid.*, **73**, 2001 (1951).

formation, and (4) the *exo* location of the carboxyl group would prohibit lactonization. Further work will be necessary to confirm this assignment.

The reactivities of halonium ions differ markedly. A bromonium ion, which forms bromolactone or bromonortricyclene, depending upon the carboxyl configuration, is evidently a much more energetic species than an iodonium ion, which can form iodolactone but not idonortricyclene. This fact is of considerable value in separating *endo* and *exo* isomers and forms the basis of a convenient analytical method for mixtures of the two.³

We are extending this investigation to other electrophilic reagents¹⁸ and other bicyclic systems in order to establish the scope of this ring closure.

Experimental¹⁹

endo-2,5-Methylene-1,2,5,6-tetrahydrobenzoic Acid (III).—A sample was prepared by the method of Alder²⁰; b.p. 121.5° (9 mm.), n_D^{25} 1.4934 (reported⁴ b.p. 118.5–120.5° (5.7 mm.), n_D^{25} 1.4931). A sample was recrystallized several times from petroleum ether (30–40°) by cooling in Dry Ice; m.p. 45.7–46.2° (reported m.p. 39°²⁰ and 44.1–45.0°⁴). A sample of the distilled adduct before crystallization (12.50 g., 0.0905 mole) was treated with iodine in aqueous bicarbonate solution,³ and it formed 17.67 g. (74%) of oily iodolactone; the aqueous layer upon acidification deposited 2.91 g. (23%) of crystalline *exo* acid. Roberts⁴ reported that the crude adduct contained 10% *exo* isomer on the basis of infrared analysis involving the impure "*exo*" isomer as a reference compound.

The known bromolactone was prepared from crude *endo*-acid by bromination in aqueous bicarbonate solution. After crystallization from petroleum ether (60–75°), it melted at 67.5–68.5° (reported⁴ 64.8–65.9°). The yield was 56% based upon total acid, 74% on the actual *endo* content.

exo-2,5-Methylene-1,2,5,6-tetrahydrobenzoic Acid (IV).—The crude acid was prepared as described by Roberts,⁴ b.p. 77° (0.3 mm.) (reported, 103.5–104° (22 mm.)). In a separatory funnel, 55.6 g. (0.403 mole) of crude acid was neutralized with 10% sodium hydroxide solution. Then 10 g. of sodium bicarbonate was added, followed by excess iodine solution (about 300 ml.). The dark oil was extracted with three portions of ether, and the ether extract was washed with 10% sodium thiosulfate and dried over calcium chloride. The ether was evaporated (the last traces at 20 mm.), leaving 44.6 g. (42%) of yellow iodolactone which solidified on standing. The crude yield in a duplicate run was identical. It was recrystallized by dissolving in ethyl acetate, treating with Norit, and diluting with petroleum ether (60–75°). White crystals formed on chilling; m.p. 58–59°, unchanged after a second crystallization.

Anal. Calcd. for $C_8H_8O_2$: C, 36.39; H, 3.44. Found: C, 36.63; H, 3.51.

The aqueous layer from the iodolactonization was treated with 10% sodium thiosulfate solution, acidified, and extracted with three portions of ether. The ether was washed with water and 1% sodium thiosulfate solution, dried with calcium chloride, and evaporated. The crude crystalline acid (34.0 g., 61%) was distilled, b.p. 89° (0.25 mm.) (reported⁴ b.p. 103.5–104° (2.2 mm.)). The product was crystallized from petroleum ether (30–40°) by cooling in a Skau tube in Dry Ice. The white solid melted at 44–45°

(reported⁴ 32.5–35°). The melting point was unchanged by another crystallization or by sublimation, but it was depressed strongly on admixture of III.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.43; H, 7.29.

exo-3,6-Methylene-1,2,3,6-tetrahydro-*cis*-phthalic Acid (XII).—The corresponding anhydride was prepared by isomerization of the *endo-cis* isomer as described by Craig¹⁰; m.p. 141.5–142° after three crystallizations (reported^{6,10} 142–143°). The anhydride was boiled with water for 15 min. The hydrate crystallized upon cooling; m.p. 147–148° dec. (reported m.p. 148° dec.^{6,11} and 153–154° dec.¹⁰), neut. equiv. 100 (calcd. 100). The hydrate lost its water when heated for 30 min. at 0.5 mm.; the anhydrous acid melted at 159–160° dec. (reported¹⁰ 161–162° dec.).

endo-2-Phenyl-3,6-methylene-1,2,3,6-tetrahydro-*exo*-benzoic Acid (IIa).—The pure *exo*-acid was prepared from the mixed Diels–Alder adduct by removing the *endo* isomer by iodolactonization.³

endo-2-*p*-Nitrophenyl-3,6-methylene-1,2,3,6-tetrahydro-*exo*-benzoic Acid (IIb).—The pure *exo*-acid was prepared from the mixed adduct by removing the *endo*-isomer by iodolactonization.³

Bromination of *exo*-2,5-Methylene-1,2,5,6-tetrahydrobenzoic Acid (IV).—In a 300-ml. 3-necked flask, 9.60 g. (0.07 mole) of IV was neutralized to phenolphthalein with sodium hydroxide solution, and 100 ml. of 5% sodium bicarbonate solution and water were then added to make a volume of about 250 ml. Bromine, 11 g., was added with vigorous stirring until a tinge of yellow persisted. The mixture was cloudy with some insoluble heavy oil. It was extracted with three portions of ether, and the extracts were dried with calcium chloride and evaporated at reduced pressure. The tan oil, 0.65 g., slowly deposited 0.17 g. of solid (Vb) which was collected and washed with petroleum ether (60–75°). The residual oil obtained from the filtrate and washings was largely 3-bromonortricyclene (VI) (crude yield 0.48 g., 4%). After two distillations, b.p. 70–71° (18 mm.), n_D^{25} 1.5220 (reported⁴ b.p. 70–74.5° (19 mm.), n_D^{25} 1.5269). The infrared spectrum of this material and that of a sample of VI prepared by N-bromosuccinimide bromination of norbornylene⁴ were almost identical, except that a weak hydroxyl band was present in the former spectrum, indicating that some hydrolysis had occurred. Carbon–hydrogen analysis reinforced this belief. Highest purity could not be obtained with the quantities at hand.

The above solid (bromolactone Vb, crude yield 1.1%), was dissolved in ethyl acetate and diluted with petroleum ether (60–75°) to give white crystals, m.p. 87.5–88.5°. The melting point was raised to 89.0–89.5° by a second crystallization. This melting point was depressed to 40–55° on admixture with Va.

Anal. Calcd. for $C_8H_8O_2Br$: C, 44.26; H, 4.18. Found: C, 44.43; H, 4.20.

The aqueous layer after the original ether extraction was acidified and extracted continuously with ether for 24 hr. After drying and distilling the ether, the residue was 13.5 g. of a light brown glass, neut. equiv. 261 (calcd. for bromohydrin, neut. equiv. 235; for dibromide, neut. equiv. 298).

In other experiments with pure IV, the yields of VI were as high as 8% and of Vb as high as 6%. When crude IV (the 60:40 mixture) was brominated, the yield of VI varied from 1.5–4%. Vb could not be isolated, but Va was found (30–33% yield based on crude IV, 75–82% based on the 40% of III actually present in crude IV) by distillation of the crude oil followed by crystallization from ethyl acetate–petroleum ether (60–75°); m.p. 67.5–68.5°, undepressed by a sample (m.p. 67.5–68.5°, reported 64.8–65.9°) prepared as described by Roberts.⁴

In one experiment with crude IV, in which the aqueous layer was acidified carefully and allowed to stand, a crystalline product, m.p. 125–127°, separated. After two recrystallizations from ethyl acetate–petroleum ether (60–75°), it melted at 132.5–133.0°. The yield was 13.8% based on crude IV, 23% based on the 60% of pure IV actually present, if the structure is assumed to be bromohydrin VII or a stereoisomer.

Anal. Calcd. for $C_8H_{10}O_3Br$: C, 40.87; H, 4.72; neut. equiv., 235. Found: C, 40.72; H, 4.67; neut. equiv., 235.

Bromination of *exo*-3,6-Methylene-1,2,3,6-tetrahydro-*cis*-phthalic Acid (XII).—In a 300-ml. 3-necked flask, 5.00

(18) M. Gates and S. P. Malchick, *THIS JOURNAL*, **76**, 1378 (1954); H. M. Walborsky and D. F. Loncrini, *ibid.*, **76**, 5397 (1954); H. Kwart and W. G. Vosburgh, *ibid.*, **76**, 5400 (1954). These workers have studied hydroxylation, and have observed rearrangement. Perhaps IV and XII will form nortricyclene derivatives upon treatment with a peracid.

(19) Microanalyses by Anna Griffin, University of Michigan, by Spang Microanalytical Laboratory, Plymouth, Mich., and Micro-Tech Laboratories, Skokie, Ill. Melting points are uncorrected. Infrared spectra were taken on a Perkin–Elmer model 21 spectrophotometer as capillary films or as Nujol mulls (for solids); we are indebted to Masao Yoshimine for obtaining the curves.

(20) K. Alder, *et al.*, *Ann.*, **514**, 197 (1934).

g. (0.025 mole) of XII monohydrate was neutralized to phenolphthalein with sodium hydroxide solution; 2.0 g. of sodium bicarbonate and water to make 200 ml. were added. With vigorous stirring, 4.0 g. of bromine was added dropwise. The exothermic reaction was terminated when a tinge of yellow persisted. The clear solution was acidified slowly with dilute hydrochloric acid and allowed to stand in the refrigerator. The oily solid crystallized, m.p. 120–200°. It was sublimed at 100° (0.1–0.5 mm.), giving a white solid (XIII), m.p. 121.5–123.5°, in yields of 22–36%. (In one experiment, the pure acid separated during the acidification in 30% yield.) Two recrystallizations from ethanol–water gave white plates, m.p. 123.0–123.5°. Its infrared spectrum showed strong absorption at 12.20 and 12.55 μ .

Anal. Calcd. for $C_8H_9O_2Br$: C, 44.26; H, 4.18; neut. equiv., 217. Found: C, 44.19; H, 4.31; neut. equiv., 216.

The amide was prepared by refluxing the acid with thionyl chloride and pouring the mixture onto ice-cold concd. ammonium hydroxide solution. The solid was recrystallized from ethanol–water and benzene–petroleum ether (60–75°) as white plates, m.p. 117.0–117.5°. The infrared spectrum had the characteristic absorption at 12.25 μ .

Anal. Calcd. for $C_8H_{10}ONBr$: C, 44.41; H, 4.79. Found: C, 44.46; H, 4.66.

The bromo acid XIII (1.0 g.) was hydrogenolyzed by stirring under hydrogen with 4 g. of sodium carbonate, 3 g. of fresh Raney nickel, and 75 ml. of water for 15–30 min. at room temperature. The mixture was acidified and extracted with ether, giving 0.5 g. of oil which, after sublimation, melted at 51–53°. This product was identical with 3-nortricyclenecarboxylic acid²¹ as shown by mixture melting point and comparison of the infrared spectra.

The residue from which XIII had been sublimed varied in amount and melted over a wide range (190–235°). In one run as described, 1.36 g. (25%) of XIII was obtained as sublimate, and the crystalline residue weighed 2.32 g., m.p. 190–235°, neut. equiv. 171. Continuous ether extraction of the aqueous solution from which the crude acid had been filtered produced an additional 2.36 g. of a colorless glass, neut. equiv. 195. These by-products are thought to be mixtures of dibromides (neut. equiv. 171), bromohydrins (neut. equiv. 140) and bromolactones (neut. equiv. 261).

In one experiment with 0.15 mole of XII, 12.0 g. of acidic material separated from the acidified solution. The solid nortricyclene derivative was isolated by sublimation. The aqueous solution was concentrated, and 1.1 g. (3%) of crystalline rearranged bromolactonic acid (XVI) separated. The analytical sample was crystallized from methanol–water, m.p. 212.5–213.0°. In another run, the yield of XVI was 11%.

Anal. Calcd. for $C_8H_9O_3NBr$: C, 41.40; H, 3.47; neut. equiv., 261. Found: C, 41.30; H, 3.56; neut. equiv., 261.

Authentic XI was prepared from *trans*-3,6-methylene-1,2,3,6-tetrahydrophthalic acid (X) by bromination in bicarbonate solution. The white solid (from ethyl acetate–petroleum ether (60–75°) or hot water) melted at 183.5–184.5° (reported 186°), neut. equiv. 256 (calcd. 261). It depressed the melting point of XVI to 162°, and the infrared spectra have many differences. No nortricyclene derivative was found.

Authentic IX was prepared from the *endo-cis* isomer VIII (m.p. 191–192° dec., reported 178–179°⁸ and 193–194°¹⁰) by bromination in aqueous bicarbonate solution. It melted at 158–160° after vacuum drying (reported 157°⁶, 155.5–157°⁷), neut. equiv. 263 (calcd. 261), and it depressed the melting point to XVI to 140°. The infrared spectra were different. No nortricyclene was detected.

Hydrogenolysis of the bromolactonic acids IX and XVI

in aqueous sodium carbonate with Raney nickel as described above produced the same lactonic acid XV, m.p. 199.5–200.5°, which was identical with a sample prepared by lactonization of VIII as described by Alder and Stein; m.p. 199.5–200.5° (reported²² 203°).

In one experiment, the crystalline residue (m.p. 190–235°) from the sublimation of XIII, 1.15 g., was refluxed for 2 hr. with acetic anhydride. The mixture was evaporated at 20 mm. to remove volatile materials. The residue was dissolved in ether and extracted with two portions of sodium bicarbonate solution. The aqueous layer was acidified and evaporated in an air jet, giving 0.35 g. of XVI, m.p. 209–211°. The ether was evaporated and the residual oil was dissolved in 50% aqueous acetone and warmed on the steam-bath for 2 hr. After treatment with Norit, the solution was evaporated, giving 0.85 g. of white solid, softens at 210°, decomp. about 240°. After two recrystallizations from water–ethanol, there was obtained 0.5 g. of a white solid, m.p. 255–256° dec., possibly an acetoxy-bromobicyclo[2,2,1]heptanecarboxylic acid. It was recovered unchanged after boiling with dilute acid. No acidic products were formed upon attempted deacetylation by treatment with excess tetraisopropyl titanate. It was not investigated further.

Anal. Calcd. for $C_{11}H_{13}O_6Br$: C, 41.14; H, 4.08; neut. equiv., 321. Found: C, 41.06, 41.26; H, 3.44, 3.59; neut. equiv., 269.

Bromination of *endo*-2-Phenyl-3,6-methylene-1,2,3,6-tetrahydro-*exo*-benzoic Acid (IIa).—In a separatory funnel, 2.14 g. (0.01 mole) of IIa was neutralized with sodium hydroxide solution, and 10 ml. of 5% sodium bicarbonate solution was added. Then 1.6 g. (0.01 mole) of bromine in water was added until a faint color persisted. The precipitated oil was extracted with ether, and the solution was dried with calcium chloride and evaporated. The residue, 1.63 g. (64%), of crude, oily solid XVIIa, was crystallized by dissolving it in ethyl acetate, treating with Norit, and diluting with five volumes of petroleum ether (30–40°). Upon cooling in Dry Ice, white plates separated, m.p. 52–53°, unchanged by a second crystallization. The infrared spectrum of pure XVIIa showed prominent absorptions at 12.20, 12.40 and 12.55 μ .

Anal. Calcd. for $C_{13}H_{13}Br$: C, 62.66; H, 5.26. Found: C, 62.62; H, 5.22.

The aqueous layer was acidified and extracted with ether. After drying and evaporating the ether (100° (20 mm.)), 1.03 g. of a dark glass remained, neut. equiv. 335, 300 on different samples. It is probably a mixture of dibromide (neut. equiv. 373) and bromohydrin (neut. equiv. 310).

Bromination of *endo*-2-*p*-Nitrophenyl-3,6-methylene-1,2,3,6-tetrahydro-*exo*-benzoic Acid (IIb).—In a 40-ml. centrifuge tube, 0.568 g. of IIb was dissolved in about 2 ml. of ethanol and neutralized with sodium hydroxide solution. Then 10 ml. of 5% sodium bicarbonate solution and 5 ml. of water were introduced. Bromine water was added until a faint yellow color persisted. The light yellow precipitate weighed 0.424 g. (66%), m.p. 116–118°. After recrystallization from methanol–water, it melted at 118.5–119.0°. A 72% yield of XVIIb was obtained in another run. Its infrared spectrum exhibited prominent absorption at 12.4 μ .

Anal. Calcd. for $C_{13}H_{12}O_3NBr$: C, 53.08; H, 4.11; N, 4.76; Br, 27.17. Found: C, 53.08, 52.84; H, 4.21, 4.07; N, 4.89; Br, 27.34.

The aqueous filtrate was acidified and extracted twice with ether. The extract was dried and evaporated (100° (20 mm.)), leaving 0.222 g. of a yellowish, glassy solid, neut. equiv. 335 (calcd. for bromohydrin, 355).

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(21) A sample was kindly furnished by Dr. John D. Roberts.

(22) K. Alder and G. Stein, *Ann.*, **514**, 22 (1934).