

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

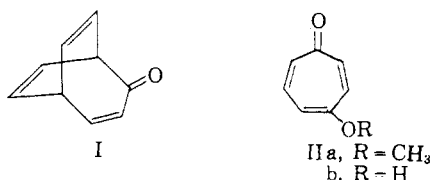
A Diels-Alder Adduct from γ -Tropolone Methyl Ether

BY O. L. CHAPMAN AND D. J. PASTO

RECEIVED OCTOBER 6, 1958

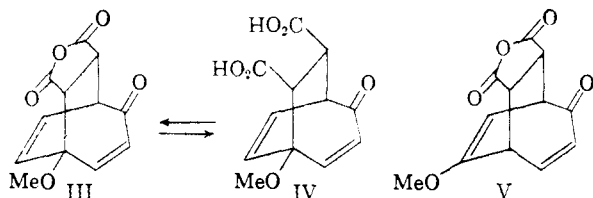
The reaction of γ -tropolone and maleic anhydride in refluxing xylene has been shown to yield a single adduct. The structure of the adduct has been shown to be VIII by hydrolysis to the diacid IV and reconversion of IV to VIII, hydrogenation and formation of a bromolactone.

As one aspect of our effort to synthesize the unsaturated ketone I, we have had occasion to prepare Diels-Alder adducts from a variety of troponeid compounds. We now wish to report the preparation and characterization of a Diels-Alder adduct of γ -tropolone methyl ether (IIa). The preparation of an adduct of IIa is of particular interest in view of the fact that the chemistry of IIa has not been investigated and that the chemical



transformations of IIb have been confined to bromination,¹⁻³ coupling with diazonium salts,¹ hydrogenation,¹ salt formation^{1,2} and methylation and benzoylation of the enolic hydroxyl function.¹

Refluxing γ -tropolone methyl ether⁴ and maleic anhydride in xylene for 6 hours gave a single crystalline adduct in 60-65% yield. No evidence of the presence of an isomeric adduct was obtained, the remainder of the product being an intractable red tar. The adduct showed infrared maxima at 5.40, 5.60 and 5.95 μ and an ultraviolet maximum at 231 $m\mu$ (8800); it did not absorb in the region (6.2 μ) characteristic of the double bond of enol ethers. Mild acid treatment of the adduct produced no change. Slightly more vigorous acid treatment gave a dibasic acid (IV, $\lambda_{max}^{95\% \text{ EtOH}}$ 232 $m\mu$ (5400)) with the same number of carbon atoms as the adduct. This eliminates any possibility of the presence of an enol ether in the adduct. Sublimation of the diacid IV gave the original adduct thus precluding rearrangement during the acid hydrolysis. These data require that the adduct have the structure III rather than V. Catalytic hydrogenation of the adduct required two moles of hydrogen. The product, a tacky, viscous liquid which could not be crystallized, showed in-



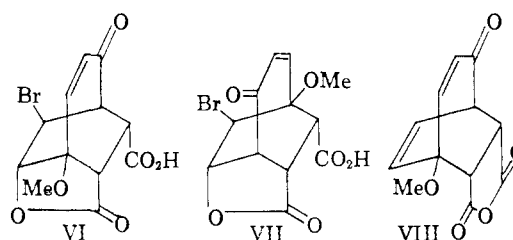
(1) T. Nozoe, T. Mukai, Y. Ikegami and T. Toda, *Chemistry & Industry*, 66 (1955).

(2) R. S. Coffey, R. B. Johns and A. W. Johnson, *ibid.*, 658 (1955).

(3) R. S. Coffey and A. W. Johnson, *J. Chem. Soc.*, 1741 (1958).

(4) J. Meinwald and O. L. Chapman, *This Journal*, 80, 633 (1958).

frared maxima at 5.40, 5.60 and 5.84 μ and no high intensity absorption in the ultraviolet. Treatment of an aqueous solution of the adduct with bromine gave a good yield of a bromolactone (5.56, 5.78 and 5.92 μ , $\lambda_{max}^{95\% \text{ EtOH}}$ 227 $m\mu$ (5700)) which must be either VI or VII. In either case the stereochemistry of the adduct must be that shown in VIII.



The conversion of VIII and structurally related compounds to derivatives of I by means of the bis-decarboxylation reaction⁵ is now being studied.

Experimental

Preparation of the Adduct III.—A solution of maleic anhydride (0.80 g.) and γ -tropolone methyl ether⁴ (1.0 g.) in 10 ml. of dry xylene (b.p. 137-140°) was refluxed gently under nitrogen for 6 hours. The solution on cooling to room temperature deposited crystalline adduct. Sublimation and recrystallization of the product from benzene-hexane gave colorless crystals (1.1 g., 64%), m.p. 184.5-185°, $\lambda_{max}^{95\% \text{ EtOH}}$ 231 $m\mu$ (8800); infrared maxima 5.40, 5.60 and 5.95 μ .

Anal. Calcd. for $C_{12}H_{10}O_6$: C, 61.54; H, 4.27. Found: C, 61.78; H, 4.51.

Evaporation of the xylene in a stream of dry nitrogen gave a red tar from which no additional adduct could be obtained by sublimation or trituration with solvents.

Hydrolysis of the Adduct.—The adduct (0.95 g.) was dissolved in 20 ml. of hot water to which a few drops of concentrated hydrochloric acid had been added. Cooling of the solution produced a solid precipitate which on recrystallization from water gave 0.95 g. of colorless crystals, $\lambda_{max}^{95\% \text{ EtOH}}$ 232 $m\mu$ (5400); infrared maxima 5.82 and 5.98 μ . These crystals appeared to lose water above 146°, sintered at 173° and melted at 185° (*cf.* melting point of the adduct, III). The product lost 5.75% of its weight on drying at 170° for 30 seconds.⁶ The very hygroscopic, anhydrous diacid IV thus obtained was analyzed immediately.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.15; H, 4.80. Found: C, 57.19; H, 4.62.

Reconversion of the Diacid IV to the Adduct III.—Sublimation (bath temperature 150°, 0.1 mm.) of the diacid IV gave a pale yellow solid. One recrystallization of this solid from benzene-hexane gave colorless crystals which had melting point and infrared and ultraviolet spectra identical to those of the adduct III.

(5) W. von E. Doering and M. Finkelstein, *J. Org. Chem.*, 23, 141 (1958); C. A. Grob, M. Ohta, E. Renk and A. Weiss, *Helv. Chim. Acta*, 41, 1191 (1958).

(6) This drying procedure was devised and performed by the Midwest Microlab, Inc., Indianapolis, Ind. Prolonged drying gave only the anhydride III.

Catalytic Hydrogenation of the Adduct.—Approximately 20 mg. of platinum oxide in tetrahydrofuran was prereduced in the usual manner. A solution of the adduct (0.4 g.) in 30 ml. of tetrahydrofuran was added. The adduct absorbed 95% of the theoretical amount of hydrogen (based on two double bonds) in 40 minutes. The hydrogenation was continued for a few hours during which time hydrogen was absorbed at a greatly reduced rate. The total hydrogen uptake was almost exactly 2 moles per mole of adduct. The product obtained by filtration and removal of the solvent under reduced pressure was a viscous, colorless liquid which could not be induced to crystallize. Sublimation of a portion of the product gave a tacky, viscous liquid which could not be crystallized. This material showed infrared maxima at 5.40, 5.60 and 5.84 μ and no high intensity absorption in the ultraviolet.

Preparation of the Bromolactone VI or VII.—The adduct (0.2 g.) was dissolved in 10 ml. of hot water, and the solution was cooled to 40°. Bromine (0.55 ml., 95% of the theoretical) was added dropwise with swirling. During the addition, the bromolactone precipitated. The mixture was chilled in ice, and the precipitate was collected and recrystallized from ethyl acetate giving 0.18 g. (63%) of crystalline bromolactone, m.p. 100.5–103°, $\lambda_{\text{max}}^{\text{EtOH}}$ 227 m μ (5700); infrared maxima: 5.56, 5.78 and 5.92 μ . It was necessary to dry the bromolactone at 100° just prior to analysis to completely remove water from the sample.

Anal. Calcd. for C₁₂H₁₁O₂Br: C, 43.52; H, 3.35. Found: C, 43.62; H, 3.44.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KANSAS, AND FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

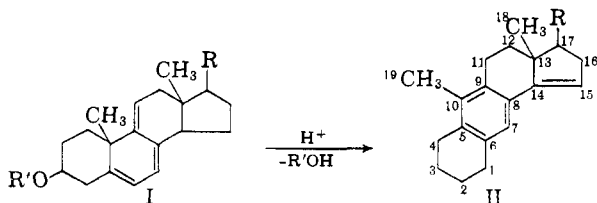
The Total Synthesis of dl-C-17 Oxygenated Anthrasteroids¹

BY ALBERT W. BURGSTAHLER² AND ERICH MOSETTIG

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dl-17-Oxo- and 17 β -hydroxyanthrasteroids (XV, R = CH₃ and II, R = OH, respectively) have been synthesized from the 4-oxo derivative (VI, R = CH₃) of 9-methyl-s-octahydroanthracene (V, R = CH₃) by application of the reaction sequence devised by Johnson, Petersen and Gutsche (ref. 8a) for the attachment of ring D in their total synthesis of equilenin.

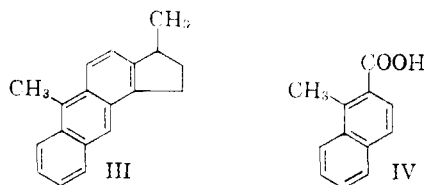
In the presence of an acid catalyst β -hydroxysteroidal-5,7,9(11)-trienes (I, R' = H) and their esters (I, R' = acyl or aroyl) undergo an interesting transformation involving dehydration, bond rearrangement and aromatization to yield unsaturated derivatives (II) of s-octahydroanthracene.³



Because of its possible implications in any abnormal steroidal metabolism which might lead to the formation of active anthracenic carcinogens in the body,⁴ the reaction has been the subject of considerable study from a chemical standpoint, especially by Nes and Mosettig and their co-workers,³ and has been designated by them as the "anthrasteroid rearrangement." With the recent demonstration⁵ of the detailed structure of these products as shown in II, rational efforts for the total synthesis of representative members of the group became feasible. Moreover, in view of various experimental difficulties involved in the preparation of certain anthrasteroids from natural sources, e.g., II, when R = OH,⁶ such a goal, if it held promise of having preparative utility, would not only be

attractive for its own sake in providing final confirmation of the structure of anthrasteroids but would also be of considerable value for the practical purpose of making these substances and their derivatives more readily accessible for further biological examination.

While studies on the total synthesis of anthrasteroids have not been described as yet by other workers, the preparation of the parent dimethylclopentenoanthracene III by a multistage route from 1-methyl-2-naphthoic acid (IV) has been reported recently.⁷ Conceivably, with appropriate modifications, this synthesis could be adapted



to the preparation of anthrasteroids; it would, however, necessarily be somewhat lengthy. In the present work, by employing a suitable preformed hydroanthracene unit, and by applying to it the elegant method of Johnson, Petersen and Gutsche⁸ for the attachment of ring D, which was used with such outstanding success in their total synthesis of equilenin, we have realized a comparatively direct synthetic pathway to C-17 oxygenated anthrasteroids.

The starting material, 9-methyl-s-octahydroanthracene (V, R = CH₃), is easily obtained from an-

(7) M. Nakazaki and S. Isoe, *Chemistry & Industry*, 43 (1958).

(1) Presented before the Division of Organic Chemistry at the 135th National Meeting of the American Chemical Society, Boston, Mass., April, 1959.

(2) Visiting Scientist, U. S. Public Health Service, N.I.H., Summer, 1958.

(3) For nomenclature, numbering convention and references, cf. W. R. Nes, J. A. Steele and E. Mosettig, *THIS JOURNAL*, **80**, 5230 (1958); see also P. Bladon, *J. Chem. Soc.*, 2176 (1955).

(4) For discussion and references, cf. ref. 3 and 6.

(5) A. W. Burgstahler, *THIS JOURNAL*, **79**, 8047 (1957).

(6) W. R. Nes, J. A. Steele and E. Mosettig, *ibid.*, **80**, 5233 (1958).

(8) (a) W. S. Johnson, J. W. Petersen and C. D. Gutsche, *THIS JOURNAL*, **69**, 2942 (1947); (b) cf. D. K. Bannerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *ibid.*, **78**, 3769 (1956). (c) For another application, see R. J. Collins and E. V. Brown, *ibid.*, **79**, 1103 (1957); also G. V. Bhide, N. L. Tikotkar and B. D. Tilak, *Chemistry & Industry*, 1319 (1957) and references cited therein.