[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, UNITED STATES DEPARTMENT OF AGRICULTURE]

The Synthesis of Condensed Ring Compounds. V. The Dianhydride of a Steradiene-6,7,11,12-tetracarboxylic Acid[1]

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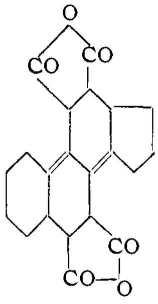
The object of this investigation is the synthesis of compounds needed for a study of the metabolism of steroids in animals, particularly of nonbenzenoid steroids with the substituents found in the hormones and of their possible biogenetic precursors. These substituents include a 3-hydroxyl or keto group, a 10-methyl group, an 11-hydroxyl or keto group, a 13-methyl group, and a 17-hydroxyl or keto group. Steroids with known relative configurations at all the asymmetric carbon atoms are sought.

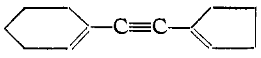
A dienyne double addition reaction was recently[2] described which makes possible the synthesis of compounds with two carbon rings more than are contained in the reactants. A preliminary report[3] has been made of the synthesis of a steradiene tetracarboxylic dianhydride by means of this reaction. This compound, probably a derivative of 8(14),9-steradiene (I), has anhydride groups at positions 6,7 and 11,12 but lacks other substituents. A detailed description of its preparation and some of its reactions are reported here.

The steradiene dianhydride was prepared by heating maleic anhydride and 1-cyclohexenyl-1'-cyclopentenylacetylene (II) together in sealed tubes at temperatures ranging from 100° to 150°. The reaction did not go at 70°. It appears that temperatures are required of the order of magnitude necessary for the addition of maleic anhydride to hindered diene systems such as that of ergosterol. Since the system C—C≡C—C in the dienyne II is linear, considerable distortion of the molecule appears to be necessary before it could add maleic anhydride. On this basis the relatively high temperature required perhaps becomes understandable. The highest yield of dianhydride obtained was 25%; it was usually 15%. The empirical process is: $2C_4H_2O_3 + C_{13}H_{16} \rightarrow C_{21}H_{20}O_6$. There is formed along with the crystalline dianhydride, $C_{21}H_{20}O_6$, and in quantity two times as much, an amorphous solid, soluble in aqueous potassium hydroxide. This material, which may or may not contain steroids, is being investigated further.

The carbon skeleton of the dianhydride adduct was demonstrated by its conversion to the known compound, 16,17-dihydro-15-cyclopenta[a]-phenanthrene (III), by heating with palladium-charcoal, with or without calcium hydroxide.



I



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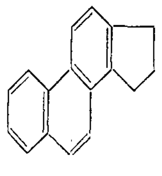

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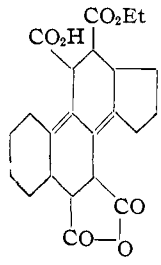

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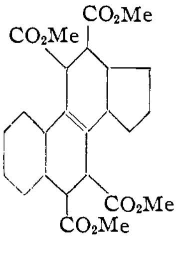
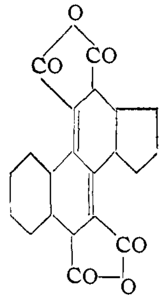


V



VI

On heating the steradiene dianhydride with ethanol a monoethyl ester was formed in good yield and a diethyl ester in lesser yield. The monoester must be IV or one of its three isomers. The formation of the monoester surprised us, but preferential reaction of a group at carbon 11 or 12 when the same group is available at carbon 6 or

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[1] This work was supported by an appropriation from Bankhead-Jones funds (Bankhead-Jones Act of June 29, 1935) and is part of an investigation being carried out under the Physiology of Reproduction Project, a coöperative project of the Bureau of Animal Industry and the Bureau of Dairy Industry. Not subject to copyright.

[2] Butz, Gaddis, Butz and Davis, *J. Org. Chem.*, **5**, 379 (1940).

[3] Butz, Gaddis, Butz and Davis, THIS JOURNAL, **62**, 995 (1940).

7, or the reversed preference, is not unknown in steroid chemistry, although it has not hitherto been observed with a derivative of 8(14),9-steradiene which must have a nearly planar ring system. We consider this formation of a monoester of importance because it suggests the general possibility of converting compounds symmetrically substituted with respect to rings B and C, which must always result from the dienyne double addition process, to unsymmetrically substituted compounds. At 250° a gas (ethanol) is eliminated from the monoester and the original dianhydride is regenerated.

Steradiene-6,7,11,12-tetracarboxylic acid has been prepared from the dianhydride by way of the potassium salt and the free acid has been converted to the tetramethyl ester by diazomethane.

Many attempts to catalytically hydrogenate the dianhydride gave mixtures from which it was difficult to secure pure products. The tetramethyl steradienetetracarboxylate, on the other hand, gave a dihydro product in 89% yield, when hydrogenated in acetic acid with Adams platinum oxide catalyst. We do not know the structure of the dihydro ester but we feel that the fact that the hydrogenation comes to an end sharply after two atoms have been taken up is evidence in favor of 1,4-addition leading to structure V. Such a sterene ester contains a double bond placed as in 1,2,3,4,4a,5,6,6a,7,8,9,10,10a,11,12,12a-hexadecahydrochrysene which resists catalytic hydrogenation.[4]

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA OF THE ADDUCTS[a] FROM 1,5-DIENE-3-YNES COMPARED WITH REFERENCE COMPOUNDS[b]

	$\lambda_{max.}$	ϵ
Steradiene-6,7,11,12-dianhydride[c]	2560	19000
Tetradecahydrochrysene-5,6,11,12-dianhydride	2570	23500
6a-Methyltetradecahydrochrysene-5,6,11,12-dianhydride	2540	24000
1,5-Dimethylhexahydronaphthalene-3,4,7,8-dianhydride[d]	2470	22000
Tetramethyl steradiene-6,7,11,12-tetracarboxylate	2560	22000
Tetramethyl sterene-6,7,11,12-tetracarboxylate	<2200 *ca.*	5000
1,3-Butadiene	2170	21000
3,5-Cholestadiene	2400	14000
4,6-Cholestadiene	2380	24000
6,8(14)-Cholestadiene-3,9-diol	2480	27200
2,4-Cholestadiene	2670	5500
5,7-Cholestadiene-3-ol	2700	11900
6,8-Cholestadiene-3-ol	2700	5350
6,8-Coprostadiene-3-ol	2700	4700
3,5-Octadienoic acid	2280	24000
Muconic acid (1,3-butadiene-1,4-dicarboxylic acid)	2650	25200

[a] Observations by Dr. Russell E. Davis and Mr. Harry Bastron, Bureau of Animal Industry, Beltsville. [b] Values taken from the compilation by Dimroth, *Angew. Chem.*, **52**, 545 (1939). [c] All compounds were dissolved in ethanol; therefore the values recorded for the dianhydrides really pertain to mixtures of the various ethyl esters. [d] Ref. 2.

The position and intensity of absorption in the ultraviolet region of the spectrum of the steradiene dianhydride and its tetramethyl ester are in agreement with the formulation of the structure as tetracyclic compounds containing a pair of conjugated double bonds spread over two rings. Completely suitable reference compounds with absorption data are not available for comparison since the conjugated system postulated in I is unique among known steroids in that all of the doubly bonded carbon atoms are completely substituted and participate in the formation of carbon rings. However, reference to Table I will show that there is a good reason for the assignment of structure I. In the table three other diene dianhydrides prepared by the dienyne double addition reaction are included. Two of these are tetracyclic and are described in the following communication.[5] The sterene ester prepared by hydrogenation of the steradiene ester is also included. It can be seen that there is good agreement among the data for the various diene adducts. The sterene derivative absorbs quite differently. Also the data for the synthetic steradiene derivatives agree well with those for the steradiene derivatives of the cholesterol series which have the conjugated system spread over two rings, and do not agree with the data for the derivatives with both double bonds in the same ring. These comparisons seem to exclude from consideration structures for the steradiene dianhydride containing the double bonds in a single ring.

The absorption data presented also offer an opportunity to discuss possible secondary dianhydrides resulting from tautomeric change in the primary adduct I. This structure includes two β-unsaturated carboxylic anhydride systems and, if sufficiently mobile, might be expected to pass to some extent under the conditions of formation to the α-unsaturated carboxylic acid structure

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(4) Von Braun and Irmisch, *Ber.*, **65**, 883 (1932).

(5) Joshel, Butz and Feldman, THIS JOURNAL, **63**, 3348 (1941).

VI. This seemed worth considering in spite of the fact that there are substituents at both the β and γ carbon atoms in I and that analysis of equilibrium mixtures of such α- and β-unsaturated compounds by Linstead's halogenometric methods[6] showed that the β-isomer predominates. VI contains a muconic acid system beginning with the carbonyl group at carbon 8 and extending to include the carbonyl group at carbon 11. It is very unlikely that the synthetic steradiene dianhydride has this structure, for muconic acid has an absorption maximum which compared with that of its parent compound, butadiene, is displaced more than 400 Å. toward longer wave lengths. A 7,9(11)-steradiene would be expected to exhibit maximal absorption at about 2400 Å. and further conjugation with two carbonyl groups as in VI ought to give a compound with a maximum at about 2800 Å. VI can therefore hardly represent the synthetic steradiene dianhydride.

Experimental[7]

Dianhydride of Steradiene-6,7,11,12-tetracarboxylic Acid.—Freshly distilled maleic anhydride (containing about 0.6% maleic acid) and 1-cyclohexenyl-1'-cyclopentenylacetylene[8] are heated together in a sealed tube in an atmosphere of nitrogen. The ether-insoluble part of the reaction mixture when recrystallized from ethyl acetate or dioxane yields one-third its weight of pure dianhydride, colorless, m. p. 252–255° (evacuated tube) (without decomposition).

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.5; H, 5.5. Found: C, 68.7; H, 5.6.

From one batch which was recrystallized from dioxane a second compound melting at 246–250° was isolated. Its composition is that of a monodioxanate.

Anal. Calcd. for $C_{21}H_{20}O_6.C_4H_8O_2$: C, 65.8; H, 6.2. Found: C, 65.7; H, 6.2.

The usual yield of dianhydride is 15–17%. From one batch, in addition to this amount, the dioxanate was isolated in an amount equivalent to 9% of dianhydride, making the total yield in this one run 25%. The crude ether-insoluble products are obtained in 45% yield if all is calculated as adduct from one mole of dienyne and two moles of maleic anhydride. The unpurified parts can be precipitated from the dioxane or ethyl acetate mother liquors from the dianhydride by the addition of ether. The composition of this material, which appears to be amorphous, has not been determined. It is readily soluble in dilute aqueous potassium hydroxide.

The yield of dianhydride can be increased to 20% by using dienyne which has been rendered colorless by refluxing with alcoholic potassium hydroxide. However, the losses sustained by such purification of the dienyne are so considerable that the over-all yield of steradiene dianhydride calculated on the glycol is actually reduced by this refinement.

The following reaction conditions all give the customary yield (15–17%): 9 moles of maleic anhydride, 100°, twenty-four hours; 3 moles of anhydride, 130°, four hours; 3 moles of anhydride, 150°, three hours; and 11 moles of anhydride, 100°, forty-eight hours.

The reaction apparently does not go at 70°; thus 9 moles of maleic anhydride and twenty-four or ninety hours gave no crystalline dianhydride. In these two runs respective yields of 5 and 10% of total ether-insoluble products were obtained, whereas the usual yields of material at this stage of purification are of the order of 45%. There is a suggestion that the uncharacterized by-products form at lower temperatures than the crystalline steradiene dianhydride. If this be so, these products are formed by a primary process from maleic anhydride and the dienyne and not from the steradiene dianhydride by a reaction subsequent to the dienyne double addition.

Conversion of the Steradiene Dianhydride to 15,16-Dihydro-17-cyclopenta[a]phenanthrene.—The dianhydride (0.85 g.) was mixed with 0.57 g. of palladium (12%) on charcoal and heated twenty minutes at 260–340°, followed by ninety minutes at 340–390°. A purplish fluorescent crystalline material collected in the upper part of the flask. This, together with material obtained from the charcoal mixture by steam distillation and extraction with ether (60 mg., all soluble in petroleum ether), was recrystallized from methanol. A second portion of dianhydride (0.6 g.) was heated with 0.5 g. of palladium-charcoal and 1.5 g. of calcium hydroxide, and the volatile products were crystallized from methanol. The recrystallized compounds from the two runs were combined and crystallized again from methanol; nearly colorless crystals, 25 mg., m. p. 132–133°, not depressed by mixing with an authentic specimen of 15,16-dihydro-17-cyclopenta[a]phenanthrene.[9]

Monoethyl Steradiene-6,7-anhydride-11,12-dicarboxylate IV or an Isomeric Monoester, and a Diethyl Steradiene-6,7,11,12-tetracarboxylate.—The dianhydride (2.0 g.) was refluxed with 100 ml. of dry ethanol until solution was complete (five hours). Concentration of the solution by evaporation gave a colorless compound which was recrystallized from ethanol; yield, 1.2 g., 53%; m. p. 223–230° (with evolution of gas, but without discoloration).

Anal. Calcd. for $C_{23}H_{26}O_7$: C, 66.6; H, 6.3. Found: C, 66.6; H, 6.3.

This monoester (0.61 g.) was converted to a dianhydride (0.27 g.), identical with that taken for the reaction with ethanol, by heating at 250° for ten minutes; m. p. of pyrolytic product, 240–249°, not depressed by mixing with a specimen of the original anhydride melting at 243–249° (in open capillary tube).

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.5; H, 5.5. Found: C, 68.3; H, 5.9.

The ethanol mother liquor from the monoester was taken to dryness and the residue was recrystallized successively from ethyl acetate and ethanol. This gave a diethyl ester

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[6] Baker, "Tautomerism," D. Van Nostrand Company, Inc., New York, N. Y., 1934, p. 156.

[7] All melting points are corrected.

[8] Pinkney, Nesty, Wiley and Marvel, THIS JOURNAL, **58**, 972 (1936).

[9] Kindly furnished by Dr. Erich Mosettig; Burger and Mosettig, *ibid.*, **59**, 1307 (1937).

or a mixture of diethyl esters, yellow, melting at 234–238° with decomposition; yield, 0.20 g. (8%).

Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.2; H, 7.0. Found: C, 65.3; H, 7.1.

Steradiene-6,7,11,12-tetracarboxylic Acid.—The dianhydride was dissolved in an excess of *N* potassium hydroxide at room temperature, the solution was cooled with ice, and the calculated quantity of *N* hydrochloric acid was added. The precipitate was washed well with water and then dried in a vacuum desiccator; yield 94% of a colorless acid, m. p. 231–232° (dec.).

Anal. Calcd. for $C_{21}H_{24}O_8$: C, 62.4; H, 6.0. Found: C, 61.9; H, 6.2.

This very insoluble acid can be recrystallized from dioxane, but the losses are high and a mole of dioxane is retained; m. p. 213–214° (dec.).

Anal. Calcd. for $C_{21}H_{24}O_8 . C_4H_8O_2$: C, 61.0; H, 6.5. Found: C, 60.8; H, 6.5.

The acid can also be recrystallized from aqueous acetic acid. The steradiene tetracarboxylic acid in glacial acetic acid solution absorbs bromine.

Tetramethyl Steradiene-6,7,11,12-tetracarboxylate.—A suspension of the crude tetracarboxylic acid (2 g.) in ether was treated with ethereal diazomethane from 10 ml. of nitrosomethylurethan. Solution was complete after a few minutes. The tetramethyl ester was obtained as colorless needles, m. p. 117.5–120.5°. The wide melting range is interesting. It was not changed by successive recrystallization from ether–petroleum ether, ethyl acetate-hexane, and methanol; yield, 2.0 g. (88%). The compound forms an amber-colored solution with tetranitromethane. Its ultraviolet absorption curve is very similar to that of the dianhydride in ethanol (see Table I).

Anal. Calcd. for $C_{25}H_{32}O_8$: C, 65.2; H, 7.0. Found: C, 65.2; H, 7.4.

Tetramethyl Sterene-6,7,11,12-tetracarboxylate.—A solution of 0.90 g. of the diene tetramethyl ester in 15 ml. of acetic acid with 100 mg. of Adams catalyst was shaken with hydrogen. At the end of five hours, absorption had stopped and 0.93 mole of hydrogen had been absorbed. The colorless needles which had precipitated during the reduction could be dissolved by the addition of a few ml. of acetic acid, but no further hydrogenation took place on subsequent shaking. After filtration of the catalyst and evaporation of the acetic acid in vacuum, the product was crystallized from acetone–methanol, furnishing 0.8 g. (89%) of colorless needles, m. p. 164.5–170.5°. After recrystallization from methanol, the compound exhibits a double melting point, first melting sharply at 165.4–166.0°, solidifying, and then remelting at 168–174°. The ester forms a yellow solution with tetranitromethane.

Anal. Calcd. for $C_{25}H_{34}O_8$: C, 64.9; H, 7.4. Found: C, 64.8; H, 7.5.

The ultraviolet absorption curve of this ester is quite different from that of the tetramethyl steradienetetracarboxylate (see Table I).

Acknowledgments.—Mr. Adam M. Gaddis and Dr. Eleanore W. J. Butz participated in the original preparation of the steradiene dianhydride. Mr. Melvin Goldberg prepared much of the 1-ethynylcyclohexanol and 1,1′-ethynylenecyclohexanolcyclopentanol.

Summary

A non-benzenoid steroid has been synthesized in practical yield by a series of four reactions from acetylene, cyclohexanone, cyclopentanone and maleic anhydride.

The steroid is the dianhydride of a steradiene-6,7,11,12-tetracarboxylic acid. It is probably a derivative of 8(14),9-steradiene. It has been converted to 16,17-dihydro-15-cyclopenta[a]phenanthrene, the free steradiene tetracarboxylic acid, a monoethyl ester (anhydride-ester-acid), a diethyl ester, a tetramethyl ester, and a tetramethyl dihydro (sterene) ester.

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