(0.298 g.) on identical treatment gave 0.265 g. (84% yield) of purified 2,3-dihydroxystearic acid, m.p. 106–107°.

Preparation of 3,2-Bromohydroxystearic Acid (VI) and Its Ethyl Ester.—A solution of 1 g. of 2,3-epoxystearic acid (V) in 30 cc. of 0.3 *N* dry hydrogen bromide in ether, was allowed to stand for two days and then washed with water and evaporated. The residue (1.33 g., m.p. 44–56°) was separated by fractional recrystallization from petroleum ether and acetone, into 0.45 g. (36% yield) of 3,2-bromohydroxystearic acid (m.p. 83–84°), and 0.51 g. (38% yield) of ethyl 3,2-bromohydroxystearate (m.p. 53–53.5°). The bromohydroxystearic acid melted at 86–86.3° after further crystallizations from a mixture of acetone and petroleum ether.

Anal. Calcd. for $C_{18}H_{35}O_3Br$: C, 57.0; H, 9.31; Br, 21.1. Found: C, 56.4; H, 9.24; Br, 20.9.

Confirmation of the structure of the ethyl ester of VI (obtained above) was afforded by its preparation from esterification of VI (0.028 g.) with 10 cc. of absolute ethanol containing 0.2 cc. of concentrated sulfuric acid. The yield of crude ethyl ester after refluxing the reaction mixture for three hours, was 0.029 g. (96% yield), m.p. 52–53°.

Anal. Calcd. for $C_{20}H_{39}O_3Br$: C, 58.9; H, 9.65; Br, 19.6. Found: C, 59.5; H, 9.94; Br, 19.7.

Acetylation of 3,2-Bromohydroxystearic Acid (VI) and Its Ethyl Ester.—A solution of 0.05 g. of VI in 3 cc. of acetyl chloride was refluxed for one hour and then diluted with water and extracted with ether. Evaporation of the ether gave 0.055 g. of crude 3,2-bromoacetoxystearic acid, m.p. 74–78°. Further crystallizations of the crude from acetone and petroleum ether raised the m.p. to 82–83°. Mixed melting point with IV (m.p. 84.5°) gave no depression.

Treatment of 0.1 g. of the ethyl ester of 3,2-bromohydroxystearic acid (m.p. 53–53.5°) for one hour with 3 cc. of boiling acetyl chloride, gave 0.11 g. of gummy solid, which, after several crystallizations from petroleum ether (at −35°), gave small spherical crystalline clumps of ethyl 3,2-bromoacetoxystearate, m.p. 40.5–41°.

Anal. Calcd. for $C_{22}H_{41}O_4Br$: C, 58.8; H, 9.20; Br, 17.8. Found: C, 59.5; H, 9.51; Br, 17.9.

2-Hydroxystearic Acid from 3,2-Bromohydroxystearic Acid (VI).—A solution of 0.014 g. of VI in 10 cc. of alcohol was shaken for two days with hydrogen and Adams platinum oxide catalyst at 3 atmospheres pressure. The reaction mixture was then saponified at 37° with potassium hydroxide, acidified, and extracted with ether. The ether was evaporated to give 0.01 g. (90% yield) of crude 2-hydroxystearic acid, m.p. 83–84°. One crystallization from ethanol raised the m.p. to 84–85°. The m.p. of this material was depressed on admixture with 3-hydroxystearic acid (m.p. 90–90.2°) and with the isomeric 2,3-epoxystearic acids, but not with 2-hydroxystearic acid (m.p. 90–90.5°).

Conversion of the 2,3-Bromoacetoxystearic Acids to the Isomeric 2,3-Dihydroxystearic Acids.—A solution of 0.22 g. of 2,3-bromoacetoxystearic acid (I) and 0.23 g. of silver acetate in 3 cc. of acetic acid, was refluxed for 12 hours. The mixture was then treated with hydrochloric acid and extracted with ether. The ether extract was concentrated and the oily residue so obtained was saponified with aqueous potassium hydroxide and then acidified and extracted with ether. Evaporation of the ether gave a residue (m.p. 121–122°) which was washed with petroleum ether and crystallized from ethanol to give 0.132 g. (80% yield) of 2,3-dihydroxystearic acid, m.p. 125–125.5°.

A solution of 0.3 g. of 2,3-bromoacetoxystearic acid (III) and 0.3 g. of silver acetate in 3 cc. of acetic acid on similar treatment, gave 0.22 g. of solid (m.p. 116–118°), which was separated by fractional recrystallizations from acetone, petroleum ether and alcohol into 0.144 g. (64% yield), m.p. 122–124°, of the high-melting 2,3-dihydroxystearic acid isomer and 0.061 g. of material melting at 99–102°. Further crystallizations of the latter from mixtures of acetone and petroleum ether gave 0.020 g. of white solid, m.p. 100–103° which was probably the low-melting 2,3-dihydroxystearic acid isomer (since its m.p. was not depressed on admixture with an authentic sample. Its mixed melting point with the 2,3-dihydroxystearic acid of m.p. 126° was 99–109°).

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Approaches to Total Synthesis of Adrenal Steroids. I. 3-Ethoxy-1,3-pentadiene

BY LEWIS H. SARETT, ROBERT M. LUKES, GEORGE I. POOS, JAMES M. ROBINSON, ROGER E. BEYLER, JOHN M. VANDEGRIFT AND GLEN E. ARTH

The preparation of 3-ethoxy-1,3-pentadiene and its Diels–Alder reactions with benzoquinone and toluquinone are described. The benzoquinone adduct may be reduced catalytically to 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione (XIII). The latter is smoothly reduced with lithium aluminum hydride to 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1β,4β-diol (XIV).

Introduction to a Group of Papers

It is evident from consideration of formula A[1] that in any successful synthetic approach to the adrenal hormones, those reactions which generate linkages between rings will be stereospecific. The AB ring juncture does not offer a stereochemical problem, the angular methyl group at C_{10} being taken arbitrarily as above the plane of the nucleus and the double bond destroying asymmetry at C_5. Nor does any theoretical problem exist in introducing a 4,5-double bond into saturated intermediates with the AB juncture either *cis*[2] or *trans*.[3] On the other hand, the difficulties in establishing the *anti-trans* relationship between the three centers C_{10}, C_9 and C_8 are very real. Several approaches have involved the reduction of an 8,9-double bond, either as such or as part of an aromatic Ring C. That this reduction does not lead predominantly to compounds with the *anti* relationship of C_{10} and C_9 has been demonstrated by Cornforth and Robinson[4] in their fundamental investigations. In order to avoid the stereochemical uncertainties which in many ap-

(1) A review of the data upon which this structure is based is presented by R. B. Turner in Fieser and Fieser's "Natural Products Related to Phenanthrene," Third Edition, Reinhold Publishing Corp., New York, N. Y., 1949.

(2) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

(3) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(4) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 676 (1946); *Nature*, **160**, 737 (1947).

proaches attend the introduction of carbon atoms 10, 9 and 8, we have embarked upon a route in which the steric disposition of these centers may be assigned with reasonable certainty.

This approach is based upon the stereospecific course of the Diels–Alder reaction and proceeds through a suitably substituted *cis*-1-methyl-2-ketoperhydronaphthalene, representing the eventual Rings B and C of formula A. The preparation of 1-methyl-2-ketoperhydronaphthalene itself and its 6-methoxy and 6-carbomethoxy derivatives each presumably consisting of *cis*-isomers and their conversion to alicyclic materials of the 4b-methylperhydrophenanthrene series (stereochemical configuration incompletely known) has been described.[5,6] Instances in which the potential Rings B and C are partially unsaturated are more numerous. Cornforth and Robinson[4] have synthesized 2-keto-5-methoxy-1,2,3,4-tetrahydronaphthalene and have shown that the anticipated reactivity of its conjugate base toward methyl iodide and (sequentially) toward diethylaminobutanone methiodide[7] leads smoothly to the hexahydrophenanthrene. Grob and Jundt[8] and Grob and Wicki[9] prepared 1-methyl-2-keto-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene and thence the derived hexahydrophenanthrene, the latter through an improved Robinson–Mannich procedure. Most recently Wilds, Ralls, Wildman and McCaleb[10] disclosed the synthesis of an enol of 5-methyloctahydronaphthalene-1,6-dione from which a 4b-methyl-1,2,3,4,-4b,5,6,7,8,8a,9,10-dodecahydrophenanthrene-1,7-dione was obtained after condensation with methyl vinyl ketone and partial reduction.

While those approaches which proceed through a β-tetralone lend themselves to introduction of the potential C_{10} methyl group through the ready formation of a carbanion between the carbonyl group and aromatic ring, a comparably smooth methylation of a β-decalone is scarcely to be anticipated. The preparation of a 1-methyl-2-ketoperhydrophenanthrene by the reaction of 3-ethoxypentadiene with a *p*-benzoquinone or a substituted cyclohexene-1,4-dione has therefore been undertaken.[11]

3-Ethoxy-1,3-pentadiene and its Reactions

Although 2-alkoxybutadienes and their reactions with dienophiles have been amply catalogued in the literature,[12] 3-ethoxypentadiene (IV) is new. An adaptation of the catalytic pyrolysis used by Dykstra[13] and by Norris, Verbanc and Hennion[14] to prepare compounds of the former type served in the present case. The requisite 1,3,3-triethoxypentane (III) was obtained by either of two methods: A, through reaction of penten-3-one with ethyl orthoformate and ethanol,[15] and B, from β-ethoxypropionaldehyde *via* 1-ethoxypentan-3-ol (I) and 1-ethoxypentan-3-one (II). In agreement with the reported behavior of the oxyprenes,[13] IV showed little tendency to polymerize under ordinary conditions. A typical and violent polymerization occurred with maleic anhydride; with a catalytic amount of iodine, dimerization, as well as polymerization, occurred. The diene, after fractionation through a small Vigreux column, consisted of both geometrical isomers, the ratio varying somewhat with each batch but ordinarily favoring the active isomer.[16,17]

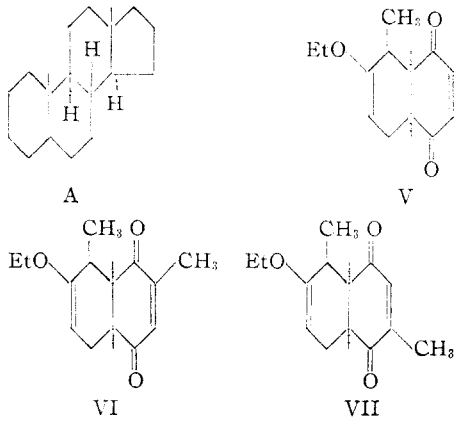
$$CH_3CH_2MgBr + C_2H_5OCH_2CH_2CHO \longrightarrow CH_3CH_2CHOHCH_2CH_2OC_2H_5 \longrightarrow$$
I

$$CH_3CH_2COCH_2CH_2OC_2H_5 \longrightarrow$$
II

$$CH_3CH_2C(OC_2H_5)_2CH_2CH_2OC_2H_5$$
III

$$CH_3CH_2COCH{=}CH_2 \longrightarrow CH_3CH{=}C(OC_2H_5)CH{=}CH_2$$
IV

Benzoquinone reacted exothermally with IV, giving 5-methyl-6-ethoxy-1,4,4aα,5,8,8aα-hexahydronaphthalene-1,4-dione (V).[18] Toluquinone added to the diene with similar alacrity, affording the isomeric 2,8-dimethyl-7-ethoxy- (VI) and 2,5-dimethyl-6-ethoxy-1,4,4aα,5,8,8aα-hexahydronaphthalene-1,4-dione (VII) isomers in a ratio of 3:1.[19]



In order to make available a set of derivatives for comparison with degradation products of more complex adducts a proof of structure of (VI) and (VII) was required. The adducts were dehydrogenated readily with benzoquinone at 100–150° to isomeric naphthoquinones (VIII and IX) which proved the pair positional isomers and eliminated the isomeric

(5) R. Robinson and F. Weygand, *Nature*, 386 (1941).

(6) J. G. Cook and R. Robinson, *ibid.*, 391 (1941).

(7) E. C. Du Feu, F. J. McQuillin and R. Robinson, *ibid.*, 53 (1937).

(8) C. A. Grob and W. Jundt, *Helv. Chim. Acta*, **31**, 1691 (1948).

(9) C. A. Grob and H. Wicki, *ibid.*, **31**, 1706 (1948).

(10) A. L. Wilds, J. W. Ralls, W. C. Wildman and K. E. McCaleb, THIS JOURNAL, **72**, 5795 (1950).

(11) The condensation of piperylene and of 2-ethoxybutadiene with benzoquinone was described by Grob and Wicki,[9] during the course of the present work.

(12) See "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Chapter 1, Vol. 4 (M. Kloetzel), Chapter 2, Vol. 4 (H. Holmes) and Chapter 3, Vol. 5 (L. Butz) for reviews.

(13) H. B. Dykstra, THIS JOURNAL, **57**, 2255 (1935).

(14) R. O. Norris, J. J. Verbanc and G. F. Hennion, *ibid.*, **60**, 1159 (1938).

(15) M. Maire (*Bull. soc. chim.*, [4] **3**, 280 (1908)) reported the conversion of pentene-3-one to its ketal by reaction with ethyl orthoformate in the absence of ethanol.

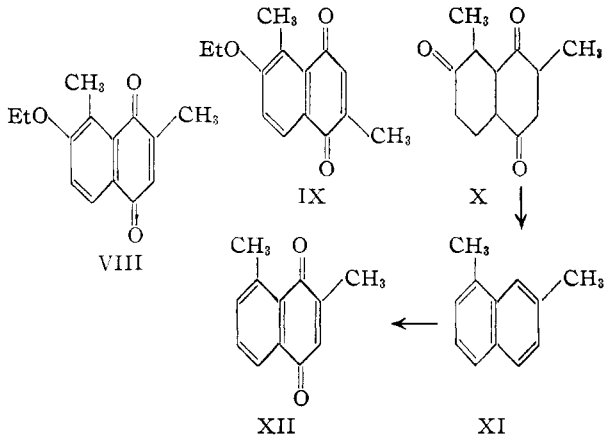
(16) R. F. Robey, C. E. Morrell and H. K. Wiese, THIS JOURNAL, **63**, 627 (1941).

(17) D. Craig, *ibid.*, **65**, 1006 (1943).

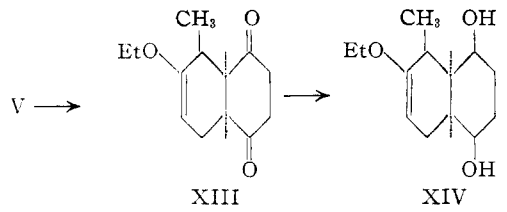
(18) Assignment of configuration to the C_5 methyl group will be discussed in a subsequent paper.

(19) *Cf.* M. Tishler, L. F. Fieser and N. L. Wendler, THIS JOURNAL, **62**, 2870 (1940), who determined that the corresponding piperylene-toluquinone adducts are formed in a 1:1 ratio.

angular methyl structures.[20] Reduction of the adducts with zinc and acetic acid[21] was accompanied by hydrolysis of the enol ether linkages leading to dimethylperhydronaphthalenetriones. Proof of the methyl positions was obtained by catalytic reduction of the trione (X) from the more abundant adduct (VI) to the triol followed by dehydration–dehydrogenation over palladium–charcoal to 1,7-dimethylnaphthalene (XI), identified as the oxidation product 2,8-dimethyl-1,4-naphthoquinone (XII).[22,23]



The reduction of Diels–Alder adducts such as 1,4,4a,5,8,8a-hexahydronaphthalene-1,4-dione to the 1,2,3,4,4a,5,8,8a-octahydro derivatives has been accomplished in several instances[21,24] by the zinc–acetic acid procedure of Albrecht.[25] Since this method does not permit the retention of an enol ether linkage, the partial catalytic reduction[26] of V was investigated and found to proceed very smoothly to 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione (XIII) provided that a neutral catalyst was used. Raney nickel which had been thoroughly washed with water, with alcohol, and with benzene and finally stored under ethyl acetate proved to be the safest catalyst. The octahydronaphthalenedione (XIII) had the expected sensitivity to acids. Under very mild conditions of hydrolysis it yielded 5-methylperhydro-(4aα,8aα)-naphthalene-1,4,6-trione. Alkaline alumina caused a facile rearrangement of XIII to the two *trans*-isomers.



(20) The relative unreactivity of the double bond bearing the methyl group has been discussed by M. Orchin and L. W. Butz (*J. Org. Chem.*, **8**, 509 (1943)) and by M. Tishler, L. F. Fieser and N. L. Wendler, ref. 19.

(21) *Cf.* K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).

(22) An authentic sample of this quinone for comparison was kindly furnished us by Professor Fieser.

(23) O. Kruber and W. Schade, *Ber.*, **69**, 1722 (1936).

(24) *Cf., e.g.*, C. K. Chuang and C. T. Han, *ibid.*, **68**, 876 (1935).

(25) W. Albrecht, *Ann.*, **348**, 31 (1906).

(26) *Cf.* C. F. H. Allen, A. Bell, J. H. Clarke and J. E. Jones, THIS JOURNAL, **66**, 1617 (1944).

The reduction of the diketo enol ether XIII with lithium aluminum hydride proceeded in a highly stereospecific sense, yielding 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1β,4β-diol[27,28] (XIV).

Experimental

1,3,3-Triethoxypentane (III). Method A.—A mixture of 154 g. of penten-3-one,[29] 370 g. of ethyl orthoformate and 380 g. of absolute alcohol (redistilled from magnesium ethoxide) was treated with 200 mg. of hydrogen chloride in 2 cc. of absolute ethanol. After standing at room temperature for four days, the solution was treated with an additional 400 g. of absolute ethanol and 200 mg. of hydrogen chloride. At the end of an additional ten days, the hydrogen chloride was neutralized with sodium methoxide, the alcohol and excess orthoformate distilled at 20–60° (10 mm.), and the residue distilled at 58–62° (0.2 mm.); yield of 1,3,3-triethoxypentane: 298 g. (85.6%). Redistillation gave a sample b.p. 67° (1.5 mm.), n^{25}D 1.4170; $n^{27.5}$D 1.4161.

Anal. Calcd. for $C_{11}H_{24}O_3$: C, 64.66; H, 11.85. Found: C, 64.91; H, 12.01.

Method B.—Ethylmagnesium bromide was prepared from 158.2 g. (6.5 moles) of magnesium in 1500 cc. of absolute ether with 715 g. of ethyl bromide in the usual manner. A solution of 510 g. (5.0 moles) of β-ethoxypropionaldehyde[30] in 500 cc. of ether was added to the stirred and cooled Grignard solution over a period of 1.5 hours. After standing at room temperature overnight, the magnesium salts were decomposed by gradual addition of 1070 cc. of saturated aqueous ammonium chloride solution with stirring and cooling. The granular magnesium salts were then filtered, and the ether removed from the filtrate, finally under aspirator vacuum. Distillation of the residue yielded 561 g. (86.3%) of 1-ethoxypentan-3-ol, b.p. 53–55° (0.1 mm.), n^{25}D 1.4202.

A solution of 606 g. of sodium dichromate in 450 cc. of water was treated with a mixture of 468 cc. of concentrated sulfuric acid and 220 cc. of water with cooling and stirring. The chromic acid solution was then added over a five-hour period to 581 g. of 1-ethoxypentan-3-ol, the mixture being maintained at 10–20° with stirring and external cooling. Five portions of 300 cc. each of benzene were added during the oxidation to keep the mixture fluid. At the end of the oxidation, sufficient water was added to dissolve the chromium salts, the benzene layer separated and the aqueous layer extracted with two portions of 500 cc. of petroleum ether (30–60°). The combined benzene and petroleum ether extracts were washed with three 100-cc. portions of water, with 100 cc. of saturated aqueous sodium bicarbonate solution, again with water and dried over sodium sulfate. The solvents were removed through a short fractionating column under aspirator vacuum and the residual product distilled at 45° (0.3 mm.), giving 454 g. (79.5%) of 1-ethoxypentan-3-one; n^{25}D 1.4119.

Treatment of 1-ethoxypentan-3-one with ethyl orthoformate, absolute ethanol and hydrogen chloride and separation of the product by fractional distillation as described in Method A above gave 62% of 1,3,3-triethoxypentane, the physical characteristics of which were identical with the above-described product.

3-Ethoxy-1,3-pentadiene (IV).—An 87.5-g. portion of 1,3,3-triethoxypentane (III) was added dropwise to a 125-cc. Claisen flask immersed in an oil-bath maintained at 155°. At the start of the addition the flask contained 100 mg. of powdered, fused potassium acid sulfate, and over the nine

(27) Presentation of evidence on the basis of which the configurational assignments have been made is deferred to a subsequent paper in this series.

(28) The system of indices adopted in this group of papers bases the configuration of substituents at all asymetric centers on the methyl group attached to C_5 in our perhydronaphthalene series and to C_{10} in the steroids. The β-index implies a *cis*- or *syn*-relationship to the methyl group and to this extent is analogous to the widely used convention of Fieser and Fieser (*Experientia*, **4**, 285 (1948)). Hydrogen atoms at bridgeheads are also considered as substituents and are assigned indices accordingly.

(29) M. Maire, *Bull. Soc. Chim.*, [4] **3**, 265 (1908).

(30) The commercially available product of Carbide and Carbon Corp. was redistilled, b.p. 80–83° (155 mm.).

hours required for addition of the triethoxypentane a fresh 100-mg. charge was added each hour. The material which distilled, during the pyrolysis, and which contained the crude 3-ethoxy-1,3-pentadiene, ethanol, and other pyrolysis products was collected in a chilled flask containing 20 cc. of 10% potassium carbonate. At the end of the pyrolysis 250 cc. of Skellysolve A was added to the distillate, the mixture was shaken well, and the aqueous layer was separated. The organic layer was washed with two 250-cc. portions of 2.5% potassium carbonate to remove the ethanol and was dried overnight over anhydrous magnesium sulfate. It was then filtered, and the Skellysolve was distilled slowly through a 12"-Widmer column. The residue was distilled *in vacuo*, that portion boiling at 56–67° (92 mm.) being collected. This distillate was redistilled through the same column, 3-ethoxy-1,3-pentadiene being collected at 57° (89 mm.); yield 20 g. (42%); $n^{21}D$ 1.4480; $n^{24}D$ 1.4430. For analysis a middle cut was taken from a twice-distilled sample; $n^{17.5}D$ 1.4517; λ_{max} 230 mμ, E_{mol} 13150.

Anal. Calcd. for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.05; H, 10.90.

The refractive index and ultraviolet absorption served only as rough criteria of the purity of the diene. If one assumes by analogy with the case of piperylene[15,16] that the component of the mixture which is active in the Diels–Alder reaction is the isomer in which the hydrogen and ethoxyl are *trans*, then the content of the latter in preparations such as that described above ranged from 50–80%. After reaction of the diene with excess benzoquinone (*vide infra*), the unreacted part of the initial diene mixture could be separated by distillation *in vacuo* and had $n^{24}D$ 1.4460 and $n^{24}D$ 1.4480 in two typical experiments. A sample of this material showed no appreciable reaction with benzoquinone after 24 hours at room temperature.

5-Methyl-6-ethoxy-1,4-naphthoquinone.—A mixture of 2.0 g. of benzoquinone, 2.0 g. of 3-ethoxypentadiene and 5.0 cc. of toluene was heated on the steam-bath for 20 hours. The solution was cooled, decanted from quinhydrone, concentrated to dryness *in vacuo* and chromatographed over acid-washed alumina. 5-Methyl-6-ethoxy-1,4-naphthoquinone was eluted with 9:1 petroleum ether–ether; yellow needles from methanol, m.p. 155°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.20; H, 5.59. Found: C, 72.36; H, 5.53.

5-Methyl-6-ethoxy-1,4,4aα,5,8,8aα-hexahydronaphthalene-1,4-dione (V).—A suspension of 4.3 g. of benzoquinone in 7.0 g. of 3-ethoxypentadiene was shaken in a stoppered flask until the quinone dissolved (about 15 minutes) and the temperature of the mixture rose to 50–60°. After standing at room temperature overnight, the solution was cooled to 0° and the supernatant liquid decanted from the dense crystalline precipitate of adduct. The latter was washed with cold petroleum ether, powdered and left *in vacuo* (0.5 mm.) to remove excess benzoquinone. The residue (6.2 g.) was recrystallized by dissolving in methanol at 40° and quickly cooling to *ca.* −30° in a Dry Ice-bath. The pale yellow crystals then melted at 69–70°. They were stable at 0° for several months but showed decomposition at room temperature in less than a week. They were attacked instantaneously by acid and alkali and were unstable to alumina.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.05; H, 7.39.

A by-product which was obtained in small amount when benzoquinone (25.5 g.) was allowed to react with a particularly active sample of ethoxypentadiene (43.9 g.) at 65–75° was the **bis-adduct**, colorless prisms very sparingly soluble in methanol, m.p. 175–178°.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.00; H, 7.93. Found: C, 72.50; H, 8.01.

2,8-Dimethyl-7-ethoxy-1,4,4aα,5,8,8aα-hexahydronaphthalene-1,4-dione (VI) and 2,5-Dimethyl-6-ethoxy-1,4,4aα,-5,8,8aα-hexahydronaphthalene-1,4-dione (VII).—Ethoxypentadiene (8.4 g.) and toluquinone (5.0 g.) were mixed at room temperature and allowed to react exothermally without cooling. After several hours, unused diene was decanted from the product and the crystals were washed with cold petroleum ether. This material amounted to 5.5 g. and was largely the higher-melting isomer (VI). Solvent, unused diene and toluquinone were removed under vacuum at low temperature from the mother liquors to yield 2.9 g. of a mixture of VI and the lower-melting isomer (VII). Total yield 8.4 g. (90%). The isomers were separated by fractional crystallization from ether–petroleum ether (5:1) and ethanol; VI, m.p. 103.5–105.5°; VII, m.p. 78–79°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.76; H, 7.75. Found: VI: C, 71.95; H, 7.80; VII: C, 72.09; H, 7.58.

An Isomeric 2,8-Dimethyl-7-ethoxy-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-dione.—In one experiment, small quantities of the ethoxypentadiene and toluquinone, after standing at room temperature for a month gave a third isomer, m.p. 83–84°. A *trans*-2,8-dimethyl-7-ethoxyhexahydronaphthalene-1,4-dione structure was assigned on the basis of oxidation with benzoquinone to 2,8-dimethyl-7-ethoxy-1,4-naphthoquinone.

Anal. Found: C, 71.46; H, 7.55.

2,8-Dimethyl-7-ethoxy-1,4-naphthoquinone (VIII). A.—A mixture of 0.33 g. of VI (m.p. 103–105°) and 1.3 g. of benzoquinone was heated at 100° for seven hours. Excess benzoquinone was removed *in vacuo* and the residue triturated with benzene–petroleum ether (3:1) to separate insoluble quinhydrone. Evaporation of solvent left 0.32 g. of crude product which crystallized from methanol as yellow needles, m.p. 122–123°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.12. Found: C, 72.52; H, 6.11.

B.—A mixture of 110 mg. of the isomeric 2,8-dimethyl-7-ethoxy-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-dione (m.p. 83–84°) and 550 mg. of benzoquinone was held at 155° for 15 minutes and worked up as above. The product melted at 122–123° and did not depress a sample of the dimethylethoxynaphthoquinone prepared by oxidation of VI.

2,5-Dimethyl-6-ethoxy-1,4-naphthoquinone (IX).—Benzoquinone (0.90 g.) and VII (0.35 g., m.p. 77.5–78.5°) were heated at 150–155° for 20 minutes. The reaction mixture was worked up as in A to yield 0.13 g. of product. Purification by methanol recrystallization gave yellow needles, m.p. 156°.

Anal. Found: C, 73.21; H, 6.30.

Reduction-Hydrolysis. A. 2,8-Dimethylperhydronaphthalene-1,4,7-trione (X).—A solution of 0.99 g. of VI in 20 cc. of 95% acetic acid was treated portion-wise at room temperature with 4.0 g. of zinc dust over a one-hour period. Acetone was added to the reaction mixture and the solids were separated by filtration. The filtrate was evaporated to dryness *in vacuo*, the solid residue was dissolved in benzene and the benzene solution washed with aqueous sodium bicarbonate. Removal of the benzene gave 0.83 g. (94%) of crystalline product. After several crystallizations from benzene, the colorless product melted at 132–135°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.62; H, 7.90.

Treatment of 75 mg. of X with 0.5 cc. of 5 *N* sulfuric acid at 100° for ten minutes followed by chromatography of the ether extract over acid-washed alumina gave 2 mg. of an isomeric 2,8-dimethylperhydronaphthalene-1,4,7-trione, m.p. 108–110°.

Anal. Found: C, 68.86; H, 7.42.

B. 2,5-Dimethylperhydronaphthalene-1,4,6-trione.—Zinc–acetic acid reduction of VII (1.37 g.) by the above procedure gave 1.05 g. (86%) of the trione. After recrystallization from benzene–petroleum ether, the product melted at 164–166.5°.

Anal. Found: C, 69.27; H, 7.66.

Treatment of 75 mg. of this material with 5 *N* sulfuric acid followed by chromatography gave 5 mg. of an isomeric 2,5-dimethylperhydronaphthalene-1,4,6-trione melting at 122–126°.

Anal. Found: C, 68.93; H, 8.29.

Conversion of X to 1,7-Dimethylnaphthalene (XI).—A solution of 1.24 g. of 2,8-dimethylperhydronaphthalene-1,4,7-trione in 25 cc. of ethanol shaken with 1.0 g. of platinum oxide absorbed the theoretical quantity of hydrogen at room temperature in 1.5 hours. Catalyst and solvent were removed, leaving the triol as a thick gummy residue.

The crude triol and 0.70 g. of 10% palladium–carbon were slowly heated to 265° and then allowed to reflux (bath temp. 265–275°) for 45 minutes. The cooled reaction mixture was triturated with ether and the ether solution was

washed with 4 *N* sodium hydroxide and then water. Solvent was removed and the crude oily product distilled to give 210 mg. (23%) of crude 1,7-dimethylnaphthalene, $n^{24.5}D$ 1.5923.

For identification 200 mg. of the hydrocarbon was oxidized with 0.77 g. of chromium trioxide in 3.8 cc. of 80% acetic acid at 60° for one hour. The reaction mixture was diluted with water and extracted with ether. After removal of the solvent, there was obtained 48 mg. of 2,8-dimethyl-1,4-naphthoquinone (XII) as yellow needles. The analytical sample melted at 133.5–135.5°, after three crystallizations from methanol (lit.[23] m.p. 135–135.5°) and did not lower on admixture with an authentic sample.[22]

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; N, 5.41. Found: C, 77.50; H, 5.33.

5-Methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione (XIII).—Raney nickel (1.5 tsp. of the benzene-washed preparation, which had been allowed to stand under ethyl acetate for six days) was added to a solution of 72.0 g. of 5-methyl-6-ethoxy-1,4,4aα,5,8,8aα-hexahydronaphthalene-1,4-dione in 550 cc. of benzene. The solution was shaken under 40 p.s.i. of hydrogen for one hour, at which time the addition of hydrogen had reached 98% of theory and the reaction had nearly stopped. The catalyst was removed by filtration, the benzene solution concentrated to 150 cc. and the crystalline product filtered and washed with 9:1 petroleum ether–ether. The mother liquors were concentrated nearly to dryness *in vacuo* and additional product was separated by crystallization from cold ether; total yield, 67.0 g., m.p. 118–122°. For analysis a sample was recrystallized from ether; m.p. 120–122°.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.22; H, 8.17. Found: C, 70.04; H, 8.41.

5-Methylperhydro-(4aα,8aα)-phenanthrene-1,4,6-trione.—A sample (100 mg.) of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione was dissolved in 1.0 cc. of 50% aqueous acetic acid. The solvents were immediately removed *in vacuo* at room temperature and the residue crystallized from ethyl acetate; m.p. 146–148°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.29; H, 7.51.

5-Methyl-6-ethoxy-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1,4-dione. (trans-isomers).—A solution of 215 mg. of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione (m.p. 118–122°) in 15 cc. of benzene was passed through a column of 25 g. of (alkaline) alumina. An additional 200 cc. of benzene was passed through the column, the eluates collected and evaporated to dryness *in vacuo*. The crude crystalline residue (201 mg.) was separated by fractional crystallization from Skellysolve C and from ethanol into two major components, m.p. 138–139° and m.p. 74.5–76°.

Anal. Found (isomer of m.p. 138–139°): C, 70.13; H, 8.01. (Isomer of m.p. 74.5–76°): C, 69.91; H, 7.75.

5-Methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1β,4β-diol (XIV).—To a solution of 2.5 g. of lithium aluminum hydride in 100 cc. of absolute tetrahydrofuran was added 4.8 g. of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione in 50 cc. of the same solvent. The suspension was stirred at room temperature overnight, excess lithium aluminum hydride destroyed by dropwise addition of 5 cc. of water with stirring, and inorganic salts then separated by filtration through Super-cel.

The filtrate was concentrated *in vacuo* at a maximum temperature of 20° and the residue crystallized from absolute ether; yield: 3.9 g.; m.p. 115–120°. The dihydroxy enol ether was extremely sensitive to acids and to moisture. Recrystallization from solvents not completely free of either lowered the melting point to *ca.* 105°.

For analysis a sample was recrystallized from acetonitrile; m.p. 115–120°.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.98; H, 9.81. Found: C, 68.98; H, 9.98.

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Approaches to Total Synthesis of Adrenal Steroids. II. 2,5- and 3,5-Dicarbomethoxy-5-methylcyclohexene-1,4-dione as Dienophiles

BY ROGER E. BEYLER AND LEWIS H. SARETT

2,6-Dicarbomethoxy-2-methylcyclohexane-1,4-dione (VI) was synthesized from dimethyl 2-furfurylidenemalonate (I) *via* dimethyl α-carbomethoxy-α-methyl-γ-ethylenedioxypimelate (IV). 2,5-Dicarbomethoxy-2-methylcyclohexane-1,4-dione (IX) was obtained by partial methylation of dimethyl succinosuccinate. Both dicarbomethoxymethylcyclohexanedione isomers yielded the corresponding cyclohexenediones (VII) and (X) by bromination and dehydrobromination and these reacted readily with 3-ethoxy-1,3-pentadiene.

Cyclic 1,4-diketones containing an intercurrent double bond arise from addition of dienes to 1,4-benzoquinones and like the latter may themselves function as dienophiles, though more weakly.[1] The potential usefulness of the substituted monocyclic cyclohexene-1,4-diones in a synthetic approach such as that sketched in the introduction to this series of papers is evident. Particular members of this class which appeared to hold both a practical and a didactic interest are the isomeric esters, 2,5- (X) and 3,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione (VII). Each of these compounds has been synthesized and its reactions with certain 1,3-dienes, particularly 3-ethoxy-1,3-pentadiene,[2] investigated.

A procedure based upon the furacrylic acid rearrangement[3] was employed for the synthesis of 2,6-dicarbomethoxy-2-methylcyclohexane-1,4-dione (VI). Dimethyl 2-furfurylidenemalonate (I) with methanolic hydrogen chloride yielded 50% of dimethyl α-carbomethoxy-γ-ketopimelate (II) as a

(1) See, for example, K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).

(2) See Part I, THIS JOURNAL, **74**, 1393 (1952).

(3) W. Marckwald, *Ber.*, **20**, 2811 (1887).