terial was obtained by an analogous procedure in 19% yield and recrystallized from ethanol-ether to yield white crystals, m.p. 155° dec. Ultraviolet spectrum. Methanol, λ_{max} 296 mμ, ϵ_{max} 13,000.

Anal. Calcd. for $C_9H_{12}Cl_3N_5O_2$: C, 32.89; H, 3.68. Found: C, 33.14; H, 3.94.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE INSTITUTE OF INDUSTRIAL MEDICINE, NEW YORK UNIVERSITY MEDICAL CENTER]

Epoxidation and Cyclization of Squalene[1]

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The epoxidation of squalene, isosqualene and tetracyclosqualene was examined. It is shown that epoxidation of squalene with peracetic acid proceeds stepwise. Di-, tetra- and hexaepoxysqualenes and diepoxytetracyclosqualene were isolated and studied. Some of the lead tetraacetate cleavage products of the diols derived from these epoxides were identified.

In a recent report from this laboratory[3] the isolation and identification of squalene and isosqualene from cigarette smoke condensate was described. In view of the possibility that epoxides of squalene and isosqualene, which may also be present in cigarette smoke, may exhibit biological activity, these compounds were prepared. The rate of epoxidation of squalene and the preparation and examination of squalene epoxides are described in this report. These compounds are currently being examined for carcinogenic activity to mouse skin. In the course of this work isosqualene and tetracyclosqualene were prepared and some properties and reactions of these compounds were studied.

Raymond[4] utilized the autoxidation of benzaldehyde to epoxidize a number of unsaturated compounds including squalene. The products of the epoxidation were not isolated or identified.

Some studies on the rate of the peracetic acid oxidation of squalene were carried out in our work. Squalene was epoxidized at −12° with chloroform as solvent. Two moles of peracid are consumed within fifteen minutes; another two moles of peracid are consumed only after two hours. For consumption of the last two moles of peracid it was necessary to allow reaction to proceed at 3° overnight.

Squalene was then treated with two, four, and six moles of peracetic acid in three experiments. The diepoxy product could not be purified as such. The crude product was catalytically hydrogenated and then purified by molecular distillation. The product had the correct analysis for diepoxyoctahydrosqualene. From the other two experiments there were obtained a tetra- and a hexaepoxysqualene. Tetraepoxysqualene absorbed two moles of hydrogen to give a product which had the correct analysis for tetraepoxytetrahydrosqualene. The crude epoxides showed in their infrared absorption spectra weak bands in the hydroxyl and carbonyl regions indicative of impurities. The pure distilled epoxides showed no absorption in the 3 μ and 6 μ regions but showed bands between 7.95 and 8.08 μ characteristic for 1,2-epoxides.[5] Other infrared bands which are known to be characteristic for 1,2-epoxides[6−8] *e.g.*, at 11.0, 11.7 and 12.1 μ, do not appear in the squalene epoxides.

Early attempts to purify the epoxides by chromatography on acid washed alumina or on florisil were unsuccessful. The chromatographed products were usually viscous yellow sirups which showed intense hydroxyl (3 μ) and carbonyl (5.8 μ) absorption in the infrared spectra.

Epoxidation of squalene with six moles of perbenzoic acid gave a product which from its elementary analysis was a mixture of the tetra- and hexaepoxides. The product decomposed on vacuum distillation but by molecular distillation gave a liquid tetraepoxide. The hexaepoxide could not be obtained in pure form by the perbenzoic acid oxidation. Carbonyl, hydroxyl and aromatic absorption in the infrared spectrum of the crude products suggested oxirane ring opening to hydroxybenzoate structures and possibly rearrangement reactions to keto-carbonyl–containing products. Filler and co-workers[9] studied the nature of these side reactions in the epoxidation of 1-substituted cyclohexenes.

Because of the difference in the rate of consumption of two, four, and six moles of peracid it became of interest to examine the partly epoxidized prod-

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(5) H. Tschamler and R. Leutner, *Monatsh.*, **83**, 1502 (1952).

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(8) M. L. Brey and P. Tarrant, *J. Am. Chem. Soc.*, **79**, 6533 (1957).

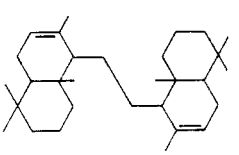
(9) R. Filler, B. R. Camara and S. M. Naqvi, *J. Am. Chem. Soc.*, **81**, 658 (1959).

ucts in more detail. Several workers[10-12] have reported poor yields of tetrahydroxystearic acid from the hydrolysis of the corresponding epoxy compound. With monoepoxy compounds, quantitative yields are usually obtained. Similarly, it was found in the present work that when the squalene epoxides were treated with aqueous acid, products were obtained which from their infrared absorption spectra contained carbonyl impurities. The viscous, resinous products could not be purified and were cleaved directly with aqueous lead tetraacetate. The aldehydes and ketones obtained were examined by paper chromatography of their 2,4-dinitrophenylhydrazones and by the ultraviolet absorption spectra of the eluted spots. Quantitative recovery studies on the 2,4-dinitrophenylhydrazones of acetone and formaldehyde using these procedures showed that these derivatives can be recovered quantitatively. Hexaepoxysqualene gave only 10% of the expected yield of acetone. The hydrogenated di- and tetraepoxides each gave in different experiments 5 to 8.5% yields of acetone, assuming that in these two epoxides the double bonds at the ends of the squalene molecule were epoxidized. Both the di- and tetraepoxides gave traces of formaldehyde. Both these epoxides gave prominent high R_F spots suggesting the presence of the 2,4-dinitrophenylhydrazones of long chain carbonyl compounds. These results do not exclude the possibility that the di- and tetraepoxides are mixtures in which different double bonds have been epoxidized. Such random epoxidation appears unlikely because of the rate data. The double bonds in squalene are all the same [C—CH=C(CH_3)—C, *trans*] and should be equally susceptible to epoxidation. On the other hand, the double bonds at the ends of the squalene molecule may be more accessible and therefore epoxidize more rapidly. A similar observation was made in a study of the epoxidation of linolenic acid.[10b] In linolenic acid, the double bonds are in the 1,4-position from each other and in squalene they are in the 1,5-position. One would not expect considerable electronic effects from an epoxide group in diepoxylinolenic acid or in di- or tetraepoxysqualene upon the rate of epoxidation of the remaining double bonds in these compounds. Such electronic interaction probably does account for the epoxidation of 1,3-butadiene to give exclusively a monoepoxide.[13,14]

Using Heilbron's procedure[15] isosqualene was obtained in this study from the isomeric hexachlorosqualanes by treatment with pyridine. The products were the same from both the hexachlorosqualanes by refractive indices and infrared spectra. It was found in this work that hexachlorosqualane is also readily dehydrohalogenated on a column of activated alumina to give a product which is very similar to isosqualene by its infrared absorption spectrum and refractive index. The absence of cyclized materials in isosqualene was established by quantitative hydrogenation with a rhodium-on-alumina catalyst (with platinum as a catalyst hydrogenation was much slower). Six moles of hydrogen were absorbed. Iodine values also indicated six double bonds, *i.e.*, very little or no cyclized material is present. Squalane obtained by the hydrogenation of squalene was identical in infrared spectrum, density, and refractive index with that obtained from isosqualene.

A pure hexaepoxide of isosqualene could not be obtained. The product invariably decomposed on attempted molecular distillation. The crude epoxide was treated with dilute sulfuric acid and then cleaved with lead tetraacetate. Paper chromatography of the 2,4-dinitrophenylhydrazones indicated the presence of both formaldehyde and acetone. This result is expected from the infrared data concerning the positions of the double bonds in isosqualene.[16]

In the course of his studies, Heilbron[15] found that squalene on treatment with 98% formic acid gave a new viscous high boiling liquid, named tetracyclosqualene, which from its iodine absorption was concluded to have only two double bonds. Büchi[17] proposed structure I for this compound.



I

In our experiments, it was found that tetracyclosqualene absorbs two moles of iodine and in a quantitative hydrogenation, two moles of hydrogen were absorbed. A Kuhn-Roth analysis gave 2.5 carbon-methyl groups. Low carbon-methyl values were also obtained for squalene and isosqualene by Dauben and co-workers.[16] Epoxidation of tetracyclosqualene with peracetic acid gave a viscous oil which had the correct analysis for diepoxytetracyclosqualene.

The infrared absorption spectrum shows only very weak carbon-carbon double bond absorption in the 6 μ region. A band at 12 μ is suggestive of trisubstituted ethylenic structures. There is no

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(11) A. F. Mackay and A. R. Bader, *J. Org. Chem.*, **13**, 75 (1948).

(12) T. G. Green and T. P. Hilditch, *Biochem. J.*, **29**, 1552 (1935).

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(15) I. M. Heilbron, E. D. Kamm, and W. M. Owens, *J. Chem. Soc.*, 1630 (1926).

(16) W. G. Dauben, H. L. Bradlow, N. K. Freeman, D. Kritchevsky, and M. Kirk, *J. Am. Chem. Soc.*, **74**, 4321 (1952).

(17) See L. Ruzicka, *Experientia*, **9**, 357 (1953).

absorption at 11.25 μ, suggesting the absence of terminal methylene structures.

Further information about the structure of tetracyclosqualene was obtained by comparison of the NMR spectra of squalene and tetracyclosqualene in carbon tetrachloride solution. The spectrum of squalene shows the signals from the three types of protons in this molecule at 95 (=C—CH_3), 118 (=C—CH_2—) and 300 cps. (=CH) relative to tetramethylsilane as internal reference. Tetracyclosqualene showed peaks at 93, 116, and 300 cps. due to the same three types of protons and in addition a peak at 57 cps. which is ascribed to the methyl protons of the grouping: $H_3C—\overset{|}{\underset{|}{C}}—$. These data are consistent with the proposed structure for tetracyclosqualene, but this does not exclude the possibility that other double bond isomers are present.

Treatment of isosqualene with formic acid under the same conditions used for the cyclization of squalene[15] gave a product which was indistinguishable from tetracyclosqualene by its spectra, physical, and chemical properties.

In the course of this work a sample of the 2,4-dinitrophenylhydrazone of levulinaldehyde was required. Attempts to prepare levulinaldehyde from 2-methylfuran by acid hydrolysis[18] led mainly to resinous products. A convenient method for the preparation of levulinaldehyde was by the hydrogenation of acetylacrolein. This substance could be readily prepared from 2-methylfuran *via* 2,5-dimethoxy-2,5-dihydro-2-methylfuran.[19,20]

EXPERIMENTAL

All melting points are corrected; boiling points are uncorrected.

Squalene. Commercial squalene (Eastman Kodak Co., 90% squalene) was chromatographed on activated alumina, eluted with petroleum ether (b.p. 30–60°), and distilled in vacuum. The fraction boiling at 188–190°/0.2 mm. (reported,[16] b.p. 213°/1 mm.) was collected; n_D^{25} 1.4904, d^{25} 0.8670, $(R)_D$ 134.92; $(R)_D$ calcd. for $C_{30}H_{50}$, 6 C=C: 137.92 (reported[15] n_D^{20} 1.4965, d^{18} 0.8596, $(R)_D$ 139.6–139.9; n_D^{20} 1.4962[16]). Squalene prepared in this manner absorbed 5.9 moles of hydrogen.[21]

Isosqualene. (a) *Pyridine method.* Isosqualene was prepared from a mixture of the hexachlorosqualanes,[15] chromatographed on activated alumina, and distilled in vacuum under nitrogen. The product, n_D^{25} 1.4890 (reported,[15] n_D^{20} 1.4990), absorbed 5.1 moles of iodine and in a quantitative hydrogenation 6 moles of hydrogen were absorbed.

(b) *Alumina method.* One gram of hexachlorosqualane[15] (mixture of isomers) was dissolved in a minimum of chloroform and chromatographed on activated alumina with petroleum ether (b.p. 30–60°) as eluent. A number of colored bands rapidly developed at the top of the column and a colorless oil was eluted. The product, 0.51 g. (81% yield), was distilled in vacuum under nitrogen, n_D^{25} 1.4902.

Anal. Calcd. for $C_{30}H_{50}$: C, 87.66; H, 12.26. Found: C, 87.35; H, 12.44.

This material absorbed 6 moles of hydrogen and its infrared and ultraviolet absorption spectra were identical with that of isosqualene prepared by the pyridine method.

Tetracyclosqualene. Squalene was cyclized with 98% formic acid as described by Heilbron.[15] The dark brown crude product was chromatographed on activated alumina using petroleum ether (b.p. 30–60°) as eluent. The residue from the eluate was distilled in vacuum under nitrogen to give a 58% yield of a colorless viscous oil, b.p. 204–210°/0.4 mm., n_D^{25} 1.5088, d^{25} 0.943, $(R)_D$ 129.5. $(R)_D$ calcd. for $C_{30}H_{50}$, 2 C=C: 131.00 [reported,[15] b.p. 230–232°/3 mm., n_D^{15} 1.5211, d^{15} 0.9359, $(R)_D$ 133.2].

Anal. Calcd. for $C_{30}H_{50}$: C, 87.66; H, 12.26; 6 C—CH_3: 21.95%. Found: C, 87.77; H, 12.37; Kuhn-Roth: 9.719 mg. required 6.00 ml. 0.01*N* sodium hydroxide, 9.27% C—CH_3, 2.5 C—CH_3 groups. The product absorbed 2.0 moles of hydrogen and 1.7 moles of iodine.

Cyclization of isosqualene. Isosqualene was cyclized with formic acid and the product worked up as described above for squalene. The light yellow viscous product, n_D^{25} 1.5083, absorbed 2 moles of hydrogen and 2 moles of iodine in double bond estimations. The infrared absorption spectrum was identical with that of tetracyclosqualene.

Catalytic hydrogenation of squalene and isomers. Squalene, isosqualene, and tetracyclosqualene were all rapidly hydrogenated at atmospheric pressure. The catalyst-compound ratio was 2:1. The hydrogenation products were purified by chromatography on activated alumina followed by vacuum distillation. All three products were colorless oils. The products were as follows: (a) *Squalane:* obtained from squalene with the absorption of 6 moles of hydrogen, n_D^{25} 1.4462, d^{25} 0.8076, $(R)_D$ 139.3; $(R)_D$ calcd. for $C_{30}H_{62}$: 140.74 [reported[22]: n_D^{20} 1.4534, d^{20} 0.810; $(R)_D$ 140.9]. (b) *Squalane:* obtained by the hydrogenation of isosqualene with the absorption of 6 moles of hydrogen, n_D^{25} 1.4470, d^{25} 0.8121, $(R)_D$ 138.5. (c) *Tetrahydrotetracyclosqualene:* obtained from tetracyclosqualene, with the absorption of 2 moles of hydrogen, n_D^{25} 1.4968, d^{25} 0.9452, $(R)_D$ 128.0, $(R)_D$ calcd. for $C_{30}H_{54}$: 131.94.

Tetraepoxysqualene. A chloroform solution of perbenzoic acid, 307 ml. (0.181 mole; 0.0815 g. of perbenzoic acid/ml.) was added slowly to 10 g. (0.024 mole) of squalene in 10 ml. of chloroform cooled in an ice bath. The temperature was kept below 20°. After the addition was completed, the mixture was allowed to stand at 0° for 17 hr. The reaction mixture was washed with cold 5% sodium hydroxide and then with cold water. The chloroform solution was dried over anhydrous sodium sulfate, filtered, and the solvent removed at room temperature. The pale yellow oil was distilled in a Hickman type molecular still at 2 microns with a bath temperature of 100°. A clear mobile oil was obtained.

Anal. Calcd. for $C_{30}H_{50}O_4$:. C, 75.85; H, 10.61. Found: C, 76.07; H, 10.80.

Tetraepoxytetrahydrosqualene. Squalene, 2 g. (0.00488 mole), was dissolved in 100 ml. of chloroform and cooled to −10°. Peracetic acid,[23] 4 ml. (0.0195 mole) saturated with sodium acetate was added with vigorous shaking. The peracid was added at such a rate that the temperature did not rise above −10°. The addition required 1 hr. Shaking and cooling was then continued for 30 min. at −10° and between −5° and 0° for another 15 min. The reaction mixture was washed well with cold 5% aqueous sodium bicarbonate

(18) C. Harries, *Ber.*, **31**, 37 (1898).

(19) N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.*, **1**, 619 (1947).

(20) D. G. Jones, Brit. Patent **595,041**, Nov. 25, 1947; *Chem. Abstr.*, **42**, 2992 (1948).

(21) Except where stated otherwise catalytic hydrogenations were carried out in tetrahydrofuran or dioxane with 5% rhodium-on-alumina (Baker and Co., Inc.) as catalyst.

(22) I. M. Heilbron, T. P. Hilditch, and E. D. Kamm, *J. Chem. Soc.*, 3131 (1926).

(23) The peracetic acid used in this work was purchased from Becco Chemical Division, Food Machinery and Chemical Corp., and contained 380 g./l. of peracetic acid in glacial acetic acid.

solution and then with cold water. The chloroform solution was dried over anhydrous sodium sulfate and the chloroform removed at room temperature. A colorless oil, 1.8 g., was obtained. The crude epoxide was hydrogenated in dioxane with Adams catalyst and distilled at 0.1 mm., bath temperature 230°.

Anal. Calcd. for $C_{30}H_{54}O_4$: C, 75.22; H, 11.36. Found: C, 75.39; H, 11.37.

Diepoxyoctahydrosqualene. Squalene, 2 g. (0.00488 mole), was dissolved in 100 ml. of chloroform and the solution cooled to −10°. Peracetic acid, 1.95 ml. (0.00975 mole), saturated with sodium acetate was added slowly and with stirring to the squalene at −10°. After the addition was complete, the mixture was agitated for an additional 5 min. The reaction mixture was extracted twice with cold 10% aqueous sodium bicarbonate solution and washed with cold water. The chloroform solution was dried over anhydrous sodium sulfate and the solvent removed at room temperature. Two grams of a clear oil was obtained. One gram of the crude squalene epoxide was hydrogenated in dioxane with platinum as catalyst; 4.0 moles of hydrogen were absorbed. The product was chromatographed on florisil, and distilled from a molecular still at 1 micron, bath temperature 100°.

Anal. Calcd. for $C_{30}H_{58}O_2$: C, 79.89; H, 12.96. Found: C, 79.96; H, 13.09.

Diepoxytetracyclosqualene. Tetracyclosqualene, 2 g. (0.00488 mole), in 200 ml. of chloroform was cooled to −10° and peracetic acid, 1.95 ml. (0.00975 mole), saturated with sodium acetate added slowly and with stirring at −10°. The mixture was allowed to stand at 0° for 24 hr. The reaction mixture was washed first with cold 10% aqueous sodium bicarbonate and then with water. The chloroform solution was dried over anhydrous sodium sulfate and the solvent removed at room temperature. The oily product, 1.7 g., was distilled in vacuum at 0.4 mm., bath temperature 250°, to give a viscous colorless oil.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.33; H, 11.38. Found: C, 81.21; H, 11.30.

Hexaepoxysqualene. Squalene, 5.1 g. (0.0125 mole), was dissolved in 500 ml. of chloroform, cooled to −10° and 15 ml. of peracetic acid (0.075 mole), saturated with sodium acetate, was added dropwise and with stirring. The mixture was agitated for 1 hr. at −10° and then stirred at 4° for 24 hr. The solution was washed with aqueous sodium bicarbonate and then with water, and dried over anhydrous sodium sulfate. Removal of the solvent left 5.3 g. of crude epoxide. The material was purified by molecular distillation at a bath temperature of 150°. A pale yellow oil was obtained.

Anal. Calcd. for $C_{30}H_{50}O_6$: C, 71.07; H, 9.94. Found: C, 72.03; H, 9.93.

Rate of epoxidation of squalene. Experiment A. One gram of squalene (0.0025 mole) dissolved in 50 ml. of chloroform was cooled to −5° in an ice-salt mixture and 4.0 ml. of peracetic acid (0.0195 mole), saturated with sodium acetate, added in one portion with stirring. The temperature increased to −3° and was maintained at this temperature. Aliquot portions were titrated at regular intervals for moles of peracid consumed. The results are given in Table I.

TABLE I

RATE OF EPOXIDATION OF SQUALENE WITH PERACETIC ACID

Experiment A (−3°)		Experiment B (−12°)	
Reaction time, min.	Moles peracid used per mole of squalene	Reaction time, min.	Moles peracid used per mole of squalene
3	4.76	3	1.26
16	5.18	12	1.86
47	5.60	37	2.20
108	5.70	58	2.40
130	5.80	115	3.45
148	6.02	136	3.81
		186	4.50
		900[a]	6.20

[a] Allowed to react at 3° after 186 min.

Experiment B. One gram of squalene (0.0025 mole) was dissolved in 150 ml. of chloroform and cooled to −12°; 1.0 ml. (0.005 mole) of peracetic acid, saturated with sodium acetate, was added with stirring. Aliquot portions were titrated at regular intervals. When 2 moles of peracid per mole of squalene was consumed another 1.0 ml. of peracid was added and the consumption of peracid followed by titration. When 4 moles of peracid were consumed, the last 2 moles of peracid were added. The rate of epoxidation decreased and the mixture was allowed to react at 3°. The results are shown in Table I.

Cleavage of squalene epoxides. All three of the squalene epoxides were hydrolyzed with aqueous sulfuric acid, cleaved with lead tetraacetate, and the aldehydes and ketones examined as follows:

(a) *Acid hydrolysis of epoxide.* Five hundred milligrams of the epoxide, dissolved in 10 ml. of benzene, was refluxed with stirring in the presence of 10 ml. of 15% aqueous sulfuric acid for 5 hr. This procedure was found necessary in order to obtain a minimum of rearrangement products as evidenced by the infrared spectra. After cooling, the benzene layer was separated and the aqueous layer extracted with benzene (2 × 10 ml.).

(b) *Lead tetraacetate cleavage of diols.* The combined benzene solutions were added to the calculated amount of lead tetraacetate in 20 ml. of water and stirred at 100° under reflux for 2 hr. The aldehydes and ketones were then steam-distilled directly into the calculated amount of 2,4-dinitrophenylhydrazine hydrochloride in aqueous-ethanolic solution. When the steam distillation was complete, the mixture in the receiver was heated to boiling, cooled, and extracted with benzene. The benzene extract was chromatographed on paper.

(c) *Paper chromatography of 2,4-dinitrophenylhydrazones.* The derivatives were chromatographed on Whatman No. 1 chromatographic paper using a system similar to that employed by Meigh.[24] After the application of the spots, the paper was allowed to equilibrate in the chromatography tank for 12 hr. in the presence of the developing solvent. The chromatograms were automatically started[25] and developed with a saturated solution of methanol in cyclohexane by the ascending technique. The spots were detected by their visible color, eluted with dioxane, and their ultraviolet absorption spectra determined in dioxane. Concentrations were determined by relating peak intensities of the longest wave-length band in the ultraviolet absorption spectrum with that of a solution of known concentration of the authentic compound. Where necessary, bands were rechromatographed. All solvents used were spectroscopically pure. The R_F values of the derivatives of known aldehydes and ketones are given in Table II.

In an attempt to determine the presence of levulinaldehyde and succindialdehyde derivatives, another chromatographic system was required because both these derivatives and the reagent showed zero R_F with the cyclohexane-methanol system. With hexane-ether-methanol (20:30:1)[26] as developing solvent, the reagent showed R_F 0.45 but the levulinaldehyde and succindialdehyde derivatives still remained at the origin. The concentrations of these two components were therefore not determined. The yields of acetone from the squalene epoxides are given in Table III.

Preparation of levulinaldehyde-2,4-dinitrophenylhydrazone. 2-Methylfuran was treated with bromine in methanol at −7° according to the procedure outlined by Clauson-Kaas

(24) D. F. Meigh, *Nature*, **170**, 579 (1952).
(25) B. L. Van Duuren, *Anal. Chem.*, **32**, 732 (1960).
(26) I. Martin, *Chem. & Ind. (London)*, 1439 (1958).

TABLE II

*R*F VALUES OF 2,4-DINITROPHENYLHYDRAZONES

2,4-DNP of	*R*F Value: Cyclohexane-methanol	*R*F Value: Hexane-ether-methanol (20:30:1)
Formaldehyde	0.25	—
Acetaldehyde	0.27	—
Isobutyraldehyde	0.53	—
Acetone	0.45	—
Tiglaldehyde	0.40	—
Levulinaldehyde	0.0	0.0
Succindialdehyde	0.0	0.0
2,4-DNP-reagent	0.0	0.45

TABLE III

YIELDS OF ACETONE FROM CLEAVAGE OF SQUALENE EPOXIDES

Epoxide	Percentage Yield of Acetone on Basis of 2 Moles of Acetone Per Mole of Epoxide
Diepoxyoctahydrosqualene	5.1, 8.5
Tetraepoxytetrahydrosqualene	5.0, 6.5
Hexaepoxysqualene	10.0

and Limborg[19] to give 2,5-dimethoxy-2,5-dihydro-2-methylfuran, b.p. 60–63°/20 mm. (reported[19] b.p. 46–56°/8 mm.). Hydrolysis of this product with dilute sulfuric acid gave 3-acetylacrolein[19] which gave a red crystalline 2,4-dinitrophenylhydrazone, m.p. 270–271° dec. from pyridine-ethanol [reported for 3-acetylacrolein,[27] m.p. 269° dec.]. Ultraviolet in dioxane: λ_{max} 404 mμ, ϵ_{max} 16,000; λ_{max} 450 mμ, ϵ_{max} 15,220. The crude acetylacrolein was hydrogenated with Adams' catalyst in tetrahydrofuran. One mole of hydrogen was absorbed. After filtration and removal of solvent the residue was converted directly to a 2,4-dinitrophenylhydrazone. The yellow needles were recrystallized from pyridine-ethanol, m.p. 233° (reported[28] m.p. 234–235°). Ultraviolet in dioxane: λ_{max} 350 mμ, ϵ_{max} 7530; λ_{max} 420 mμ, ϵ_{max} 4530.

Anal. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.38; H, 3.51; N, 24.36. Found: C, 44.73; H, 3.64; N, 24.28.

Spectra. Infrared absorption spectra were measured with a Baird double-beam instrument with sodium chloride optics. Spectra were obtained of 5% solutions in chloroform and 5% solutions in carbon disulfide. In addition, spectra of liquids were determined qualitatively as thin films of pure liquids and spectra of solids were obtained from potassium bromide pellets.

Ultraviolet absorption spectra were obtained on a Process and Instruments automatic recording unit with a Beckman DU spectrophotometer.

NMR spectra were recorded and interpreted by Varian Associates, Palo Alto, Calif. Carbon tetrachloride was used as solvent with added tetramethylsilane as internal standard. Both the spectra reported were obtained at 60 M.C.

Acknowledgment. The authors are indebted to Dr. Norton Nelson for his interest and encouragement in this work and to Mr. C. A. Joseph for technical assistance.

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(27) K. G. Lewis, *J. Chem. Soc.*, 1083 (1956).

(28) H. Inoue, *Pharm. Bull. (Japan)*, 1, 401 (1953); *Chem. Abstr.*, **49**, 10908 (1955).

[CONTRIBUTION FROM THE RESEARCH DIVISION, ARMOUR AND CO.]

Preparation of New Derivatives of Synthetic Estrogens *via* the Claisen Rearrangement[1]

EMIL KAISER AND ELLEN GUNTHER

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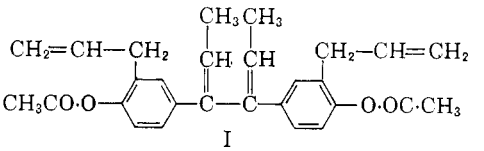
The preparation of 3,3′-diallyldienestrol diacetate from 3,4-bis(4-hydroxyphenyl)-3,4-hexanediol is described. In the course of this synthesis, it was demonstrated that the migratory aptitude of substituents affected the competition between pinacol rearrangement and dehydration in the treatment of a pinacol with acetyl chloride.

The recently reported[2] growth-promoting activity of 3,3′-diallyldiethylstilbestrol and 3,3′-diallylhexestrol[3] in ruminants made it desirable to synthesize other diallyl derivatives of synthetic estrogens. The preparation of 3,3′-diallyldienestrol diacetate (I) was of special interest as its parent compound, dienestrol diacetate, is in use as a poultry growth promotant.



I

The synthesis of I was originally planned to start with 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) and proceed through the dehydration product of this pinacol, the dienestrol diallyl ether, to the 3,3′-diallyldienestrol and by subsequent acetylation to I.

By analogy with the dehydration of 3,4-bis(4-acetoxyphenyl)-3,4-hexanediol (IIc) to dienestrol diacetate,[4] we expected to obtain the dienestrol

(1) Presented at the 136th meeting of the American Chemical Society, Atlantic City, N. J., Sept. 13–18, 1959.

(2) O. O. Thomas, R. R. Woodward, J. T. Doty, and J. R. Queensberry, *J. Animal Sci.*, **18**, 1498 (1959); I. A. Dyer and A. T. Ralston, *J. Animal Sci.*, **18**, 1499 (1959).

(3) E. Kaiser and J. J. Svarz, *J. Am. Chem. Soc.*, **68**, 636 (1947).