methyl*allo*dihydrohydrocortisone BMD (XIII) and 30 cc. of 60% aqueous formic acid was heated inside a steam-cone for 30 minutes. The resulting solution was cooled and extracted with chloroform. The chloroform layer was washed with aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated *in vacuo*. The crude concentrate was dried by azeotropic distillation with benzene, and then subsequently treated for 15 minutes with 0.07 meq. of sodium methoxide in 1.0 ml. of methanol to cleave any formate esters. After neutralization with acetic acid the solution was diluted with water and extracted with chloroform. The chloroform layer was dried over sodium sulfate and concentrated *in vacuo*. The material was acetylated with acetic anhydride in pyridine under standard conditions and chromatographed on 7 g. of acid-washed alumina (Merck). The column was eluted with ether–chloroform, 7:3, to remove an unsaturated fraction, m.p. 225–235°, presumably 6α-methyl-9,11-*allo*pregnene-17α,21-diol-3,20-dione 21-acetate. Elution with ether–chloroform, 4:6, afforded 46 mg. of crude 6α-methyl*allo*pregnane-11β,17α,21-triol-3,20-dione 21-acetate (XIV). The analytical sample was crystallized from benzene, m.p. 183–186°. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.87; H, 8.92.

17α,20,20,21-Bismethylenedioxy-3-ethylenedioxy-*allo*pregnane-11-one.[16]—A suspension containing 100 mg. of the diketodioxolane V, 700 mg. of potassium hydroxide pellets, 1.0 ml. of 85% hydrazine hydrate and 10 ml. of redistilled diethylene glycol was refluxed at 170° for 30 minutes. The temperature was raised to 210° by removing low boiling components, and reflux continued for two hours. The cooled reaction mixture was diluted with water and extracted with ether. After drying the ether layer over sodium sulfate and concentrating, the crude material in benzene solution was adsorbed on 7.0 g. of acid-washed alumina (Merck). Elution with ether and crystallization from methanol yielded 40 mg. of 17α,20,20,21-bismethylenedioxy-3-ethylenedioxy-*allo*pregnane-11-one, m.p. 190–200°. The analytical sample was recrystallized from methanol, m.p. 197–201°, $[\alpha]_D$ −37°. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.20; H, 7.97.

17α,20,20,21-Bismethylenedioxy-*allo*pregnane-11β-ol-3-one.—A solution containing 30 mg. of 17α,20,20,21-bismethylenedioxy-3-ethylenedioxy-*allo*pregnane-11-one in 5 cc. of benzene dried by azeotropic distillation was added to a suspension consisting of 100 mg. of lithium aluminum hydride in 20 ml. of dry tetrahydrofuran, and refluxed for 4 hours. Excess lithium aluminum hydride was decomposed with ethyl acetate. After hydrolysis of aluminum alkoxides with 1.3 cc. of water, the organic layer was separated by filtration, and concentrated. The crude product which showed no absorption due to carbonyl in the infrared was treated with 5 cc. of acetone, containing 10 mg. of *p*-toluenesulfonic acid, at room temperature overnight. The reaction mixture was diluted with water, neutralized with aqueous sodium bicarbonate solution, and extracted with chloroform. The chloroform layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material in benzene solution was adsorbed on 5.0 g. of acid-washed alumina (Merck). Elution with ether yielded 16 mg. of 17α,20,20,21-bismethylenedioxy-*allo*pregnane-11β-ol-3-one, m.p. 205–215° after crystallization from ether. This material did not depress the melting point of an authentic[17] sample. A melting point depression was observed, however, with the A/B *cis* compound, 17α,20,20,21-bismethylenedioxy-pregnane-11β-ol-3-one.[17] Infrared analysis of these compounds confirmed the conclusions drawn from the melting point data.

Acknowledgment.—We are indebted to Dr. J. Van de Kamp and Mr. S. M. Miller for preparation of supplies of some of the intermediates used in this synthesis.

RAHWAY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, HEBREW UNIVERSITY AND THE MEDICAL RESEARCH LABORATORIES, MEDICAL CORPS, ISRAEL DEFENSE FORCES]

The Synthesis and Biological Availability of Some Lower Homologs of Cholesterol

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Several analogs of cholesterol containing shorter side-chains have been synthesized from the chloride of 3-acetoxy-etiochol-5-enic acid (II) and di-*n*-butyl-, di-*n*-pentyl- and diphenylcadmium and from pregnenolone acetate (III) and *n*-butyl-, *n*-pentyl- and phenylmagnesium bromide. In the former case, the ketones obtained were reduced, in the latter the tertiary carbinols dehydrated and subsequently hydrogenated. The structure of these dehydration products and the configuration of the hydrogenation products has been established, the latter by the observation that the analogous series of reactions with 4-methylpentylmagnesium bromide leads to cholesteryl acetate. These "unnatural" sterols show an effectiveness of at most 43% of that of cholesterol, as growth promoters of housefly larvae. No pupation occurred when these "unnatural" sterols were added to the sterile medium on which the larvae were reared.

It has been known for some time that insect larvae cannot themselves synthesize the sterols they require but have to rely on their food for the supply of these essential factors.[1,2] According to Bloch[3] and co-workers, larvae of the beetle *Dermestes vulpinus* transform acetate normally to squalene but cannot cyclize the latter to lanosterol (and cholesterol).

In the case of the housefly *Musca vicina Macq.*[4] cholesterol and sitosterol, and to a lesser extent ergosterol[5] and stigmasterol, were found effective in promoting larval growth and pupation. Also a number of minor changes of the molecular structure of cholesterol was found compatible with the biological functions of the compound, while more drastic changes destroyed its ability to regulate growth and pupation and produced either biologically inactive substances or even antagonists of the natural sterols. In particular, the removal of the sterol side chain destroyed the activity completely. In view of these effects,[6] it was thought interesting to synthesize analogs of cholesterol in which the side-chains are similar to the natural one, but shorter, and to study the biological availability of these compounds.

(1) H. Lipke and G. Fraenkel, *Ann. Rev. Entomol.*, **1**, 17 (1956).

(2) Another case recently studied is that of *Tribolium confusum* Duval; St. D. Beck and G. G. Kapadia, *Science*, **126**, 258 (1957).

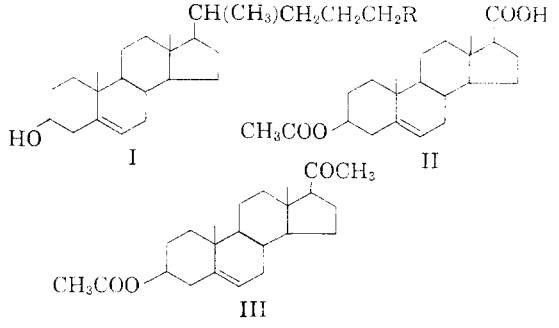
(3) R. G. Langdon and K. Bloch, *J. Biol. Chem.*, **200**, 135 (1953); R. B. Clayton and K. Bloch, *ibid.*, **218**, 319 (1956); T. T. Tchen and K. Bloch, THIS JOURNAL, **78**, 1516 (1956); K. Bloch, R. G. Langdon, A. I. Clark and G. Fraenkel, *Biochim. Biophys. Acta*, **21**, 176 (1956); J. D. Johnston and K. Bloch, THIS JOURNAL, **79**, 1145 (1957).

(4) Z. H. Levinson and E. D. Bergmann, *Biochem. J.*, **65**, 254 (1957).

(5) Ergosterol is also less active than cholesterol in promoting larval growth of the flies *Musca domestica* L. (C. S. Hammen, *Ann. Entom. Soc. Amer.*, **50**, 125 (1957)), *Lucilia sericata* Meig. (R. P. Hobson, *Biochem. J.*, **29**, 2023 (1935)) and *Phormia regina* Meig (M. Brust and G. Fraenkel, *Physiol. Zool.*, **28**, 186 (1955)).

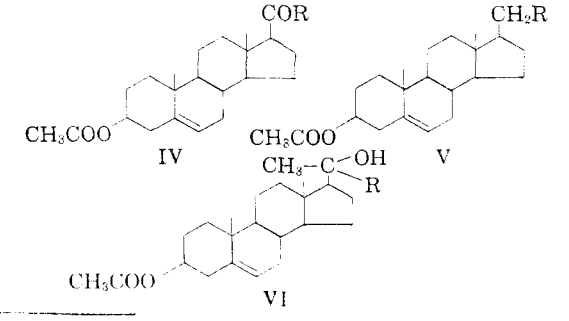
(6) J. Glover and C. Green (*Biochem. J.*, **67**, 308 (1957)) have ascribed the specificity of the sterols for many insects, which require either phyto- or zoösterols, to the fact that the intestinal membranes through which the sterols have to pass are adapted specifically to either of these sterol types.

A few syntheses of such "unnatural" sterols have been reported before. Mitui[7] has prepared 3β-hydroxy-20-*n*-butyl-pregn-5-ene (norcholesterol) (I, R = CH_3) by Clemmensen reduction of 3β-hydroxy-20-(3′-oxobutyl)-pregn-5-ene, and de Vries and Backer[8] have synthesized a number of sterols by condensation of 3-acetoxychol-5-enic acid chloride and dialkyl cadmium compounds and subsequent reduction of the ketones formed, either by the method of Wolff–Kishner or by catalytic hydrogenolysis of their thioketals. The compounds these authors describe have formula I, with R = CH_3, C_2H_5, *n*-C_3H_7, *i*-C_3H_7(cholesterol), *n*-C_4H_9, $CH_2{\cdot}C_6H_5$. de Vries and Backer have also prepared the norcholesterol I, R = CH_3, by reaction of dibutylcadmium and 3-acetoxy-bisnorchol-5-enic acid chloride and subsequent reduction of the keto-group. In this

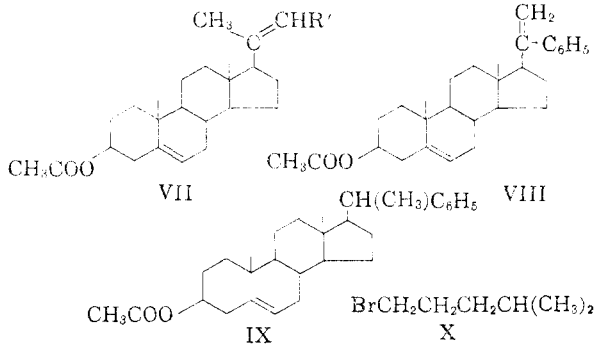


connection, the work of Woodward[9] and Kazuno[10] should be mentioned directed toward the analogous synthesis of sterols, *saturated* in the 5,6-position. Woodward treated 3-acetoxy-pregnan-20-one with isohexylmagnesium bromide and dehydrated and subsequently hydrogenated the diol so obtained. Kazuno synthesized 20-(3′-oxopentyl)-pregnane from cholanic acid amide and ethylmagnesium bromide and used the ketone for some further transformations.

In the present study, 3-acetoxyetiochol-5-enic acid (II) and pregnenolone acetate (III)[11] were used as starting materials. The chloride of II was condensed with cadmium di-*n*-butyl, di-*n*-pentyl and diphenyl and the ketone so formed (IV, R = *n*-C_4H_9, *n*-C_5H_{11}, C_6H_5) reduced by the method of Huang-Minlon. Thus, we obtained the sterols



V (R = *n*-C_4H_9, *n*-C_5H_{11}, C_6H_5). A second series of unnatural sterols was prepared by the reaction of III with the Grignard compounds from *n*-butyl bromide, *n*-pentyl bromide and bromobenzene, dehydration of the carbinols formed (VI, R = C_4H_9, C_5H_{11}, C_6H_5) to the dienes VII (R′ = C_3H_7, C_4H_9) and VIII, respectively, and catalytic hydrogenation of the dienes with platinum oxide in the presence of glacial acetic acid under conditions which do not involve the $\Delta^{5,6}$-double bond.[12] We thus obtained I (R = CH_3, C_2H_5) and IX.[13]



The Grignard reactions with pregnenolone acetate (III) were preferred to those with pregnenolone itself, as the latter formed an insoluble magnesyl derivative and, therefore, the reaction remained incomplete. The products of the Grignard reactions with III appear, of course, in deacetylated form and were re-acetylated in their crude state. The compounds were homogeneous in all cases; of the possible epimers at C_{20} only one was formed. This is at variance with the observations of Woodward[9] in his synthesis of the *saturated* cholestanol.

Two questions arose in the course of these experiments, *viz.*, (1) the structure of the dienes formed by dehydration of the carbinols VI and (2) the configuration at C_{20} resulting from the catalytic hydrogenation of these dienes. While in VIII, the dehydration product of VII, the question does not arise (indeed, the infrared spectrum shows the C–H bending bands at 910 and 990 cm.$^{-1}$, characteristic for terminal methylene groups in olefins),[14] the formula of the dienes VII is not *per se* unambiguous; they may be the isomers with terminal methylene groups (as VIII). The fact that in neither case (R′ = C_3H_7, C_4H_9) infrared bands were observed at 910 and 990 cm.$^{-1}$ indicates the correctness of formula VII. This was proven unambiguously by ozonization of VII (R′ = C_3H_7) which gave in quantitative yield butyraldehyde, identified as 2,4-dinitrophenylhydrazone. Woodward[9] in the synthesis of cholestanol has not isolated the intermediate product.

As to the configuration at C_{20} in I (R = CH_3, C_2H_5) and in IX, we satisfied ourselves that it is identical with the configuration in the natural

(7) Mitui, *Bull. Agr. Chem. Soc. Japan*, **16**, 145 (1940) (*C. A.*, **35**, 6263 (1941)).

(8) H. de Vries and H. J. Backer, *Rec. trav. chim.*, **69**, 739, 1852 (1950).

(9) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **73**, 3548 (1951); **74**, 4223 (1952).

(10) T. Kazuno, T. Okunobo and T. Shimizu, *Ann.*, **607**, 187 (1957).

(11) We are deeply indebted to Messrs. Syntex Co., Mexico, for a most generous gift of pregnenolone.

(12) E. B. Hershberg, E. P. Oliveto, C. Gerold and L. Johnson, THIS JOURNAL, **73**, 5073 (1957).

(13) We have shown that under these conditions of hydrogenation, cholesteryl acetate does not absorb hydrogen.

(14) R. N. Jones and C. Sandorfy, in "Chemical Applications of Spectroscopy," Interscience Publishers, Inc., New York, N. Y., 1956, p. 378.

sterols by showing that the application of the above synthesis to the preparation of cholesterol yielded *cholesteryl acetate*, identical in melting point (and mixed melting point), rotation and infrared spectrum with the natural product. For this purpose, III was treated with the magnesium derivative of 4-methylpentyl bromide (X); thus 3β-acetoxy-20-hydroxy-20-(4′-methylpentyl)-pregn-5-ene (VI, R = $CH_2CH_2CH_2CH(CH_3)_2$) was obtained; it was dehydrated to 3β-acetoxy-17-(α-methyl-β-(3′-methylbutyl)-vinyl)-pregn-5-ene (VII, R = $CH_2CH_2CH(CH_3)_2$)[15] and the latter was hydrogenated. Two similar syntheses of cholesterol have been reported recently, the one based on the reaction between 3-acetoxy-norchol-5-enic acid chloride and diisobutylcadmium,[16] the other (leading to cholesteryl methyl ether) starting from 3β-methoxy-bisnorchol-5-enic acid chloride and diisoamylcadmium.[17]

The utilizability of the unnatural sterols was evaluated by the method described recently[4]; however, the presence of bacteria was excluded from the larval diet by antiseptic measures. As Table I shows, all aliphatic analogs of cholesterol and its acetate support the growth of housefly larvae, although their effectiveness, measured in terms of the average weight attained by the larvae within 72 hr. of growth (t, 35°), is at most 43% of that of cholesterol.[18] The more closely the side chain of an unnatural sterol resembles that of cholesterol, the more readily the sterol appears to be utilized. A comparison of the utilization of the *unsaturated* sterols VII with that of their saturated homologs I shows that the presence of the double bond in the side chain reduces the biological availability of the sterol by 40–50%. The introduction of a hydroxyl group in the 20-position (VI) seems to affect the utilizability of the compound more than a shortening of its side chain. Replacement of the aliphatic side chain of cholesterol by an aromatic hydrocarbon radical destroys the biological availability of the resulting compounds (V, VIII, IX). No pupation occurred in the presence of the unnatural sterols. This could be due largely to the retarded growth rate which would prevent the larvae from attaining a body weight sufficient for pupation. If such an analog is fed to the larvae simultaneously with a minute amount of cholesterol (in itself insufficient for normal growth and pupation), it greatly accelerates growth and makes pupation possible. Further experiments in this direction are under way.

TABLE I

UTILIZATION OF UNNATURAL ANALOGS OF CHOLESTEROL BY HOUSEFLY LARVAE

Sterols were fed at a level of 2 mg./g. of lipid-free, aseptic diet. Utilization is expressed in terms of the average weight (E) of experimental larvae at 72 hr. of age as compared with that (C) of equiaged larvae reared with dietary cholesterol; utilization = $E/C \times 100$. Each value represents the average of 3–4 separate experiments. $t = 35 \pm 0.5°$.

Sterol added	Utilization
Cholesterol	100.0
Cholesteryl acetate	84.5
3β-Hydroxy-20-*n*-amyl-pregn-5-ene (I, R = C_5H_{11})	42.7
17-*n*-Hexyl-androst-5-ene-3β-ol (as V, R = C_6H_{13})	42.7
3β-Acetoxy-20-*n*-butyl-pregn-5-ene (as I, R = CH_3)	37.4
3β-Acetoxy-17-*n*-pentyl-androst-5-ene (V, R = C_4H_9)	30.7
3β-Acetoxy-20-hydroxy-20-*n*-amyl-pregn-5-ene (VI, R = C_5H_{11})	24.1
3β-Acetoxy-17-(α-methyl-β-butyl-vinyl)-pregn-5-ene (VII, R′ = C_4H_9)	22.2
3β-Acetoxy-17-(α-methyl-β-propyl-vinyl)-pregn-5-ene (VII, R′ = C_3H_7)	15.6
3β-Acetoxy-20-phenyl-pregn-5-ene (IX)	5.1
3β-Acetoxy-17-(α-phenylvinyl)-pregn-5-ene (VIII)	0.0
17-Benzyl-androst-5-ene-3β-ol (as V, R = C_6H_5)	3.8
None	5.1

Experimental

All optical rotations have been determined in chloroform solution at $c = 1.0$.

Pregnenolone was converted into its **acetate** III, m.p. 146–147° (from ethanol), according to Butenandt and co-workers.[19] For the preparation of **3β-acetoxy-etiochol-5-enic acid (II)** we employed the method of King[20] with some modifications. The solution of 15.6 g. of pregnenolone in 75 ml. of warm dry pyridine was cooled, 12.8 g. of iodine added and the mixture heated, with stirring, for 1 hr. on the water-bath. The stirring was continued for 12 hr. at room temperature and the precipitate collected, washed with methanol and heated at 100° for 1.5 hr. with a solution of 7.5 g. of sodium hydroxide in 250 ml. of 50% ethanol. The clear solution then was cooled and acidified and the crude acid obtained dried at 90°. It was then acetylated at room temperature (12 hr.) with 75 ml. of acetic anhydride in 75 ml. of pyridine. The solution obtained was poured onto ice and the product filtered, dried, extracted with ether (Soxhlet) and the ether solution concentrated. The residue was recrystallized from a mixture of petroleum ether and benzene and melted at 247°; yield 12 g.

The **chloride** of the acid was prepared according to Steiger and Reichstein.[21]

3β-Acetoxyetiochol-5-enyl Butyl Ketone (IV, R = C_4H_9). —To a solution of di-*n*-butylcadmium (from 0.5 g. of magnesium, 2.8 g. of butyl bromide, 1.6 g. of cadmium chloride), 3 g. of the acid chloride in 30 ml. of benzene was added and the mixture refluxed for 1 hr. Then the ether was driven off and the benzene solution heated for another 3 hr., cooled and decomposed with ice. The benzene was removed by steam distillation, the residue acidified and the product filtered. After chromatography on alumina from its benzene–petroleum ether solution, the ketone was recrystallized from methanol; needles, m.p. 100°; yield 2.5 g. (80 %); $[\alpha]^{26}D$ + 25.2°.

Anal. Calcd. for $C_{26}H_{40}O_3$: C, 78.0; H, 10.0. Found: C, 78.3; H, 10.1.

In the same manner, we prepared these compounds.

3β-Acetoxy-etiochol-5-enyl amyl ketone (IV, R = C_5H_{11}), from methanol, leaflets of m.p. 103°; $[\alpha]^{26}D$ + 25.4°; yield 75%.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.2; H, 10.1. Found: C, 77.9; H, 9.8.

(15) In this case, too, the infrared spectrum was used to establish the position of the double bond in the side chain.

(16) P. Kurath, F. M. Ganis and M. Radakowich, *Helv. Chim. Acta*, **40**, 933 (1957).

(17) A. Romeo and R. Villotti, *Ann. chim. (Rome)*, **47**, 618 (1957); (*C. A.*, **51**, 16506 (1957)).

(18) The sterol acetates and the free sterols were assumed to be equivalent, since cholesteryl acetate is known to be utilized only slightly less than cholesterol.[4] Like other insects (G. Clément and A. M. Frisch, *Compt. rend. soc. biol.*, **140**, 472 (1946)), housefly larvae undoubtedly contain an active esterase.

(19) A. Butenandt, U. Westphal and H. Cobler, *Ber.*, **67**, 1611 (1934).

(20) L. C. King, THIS JOURNAL, **66**, 1612 (1944).

(21) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).

3β-Acetoxy-etiochol-5-enyl phenyl ketone (IV, R = C_6H_5), from methanol leaflets, m.p. 142°; $[\alpha]^{26}D$ −14.8°; yield 90%.

Anal. Calcd. for $C_{28}H_{36}O_3$: C, 80.1; H, 8.6. Found: C, 79.6; H, 8.5.

3β-Acetoxy-17-*n*-pentyl-androst-5-ene (V, R = C_4H_9).—To a solution obtained from 2 g. of the ketone IV (R = C_4H_9) and 5 ml. of 95% hydrazine hydrate in 25 ml. of diethylene glycol, which had been refluxed for 30 minutes, 1.5 g. of powdered potassium hydroxide was added and the heating continued for 1.5 hr. Then the water formed was removed and the mixture refluxed again for 4 hr. The product was diluted with water and the solid product filtered and re-acetylated with 10 ml. of acetic anhydride in 10 ml. of pyridine at room temperature (12 hr.). The solution was poured into cold dilute hydrochloric acid and the product chromatographed (benzene) and recrystallized from methanol; m.p. 85°; yield 1.2 g. (60%); $[\alpha]^{26}D$ −100°.

Anal. Calcd. for $C_{28}H_{44}O_2$: C, 80.8; H, 10.9. Found: C, 81.1; H, 10.7.

17-*n*-Hexyl-androst-5-ene-3-β-ol (V, R = C_5H_{11}).—The reduction of IV (R = C_5H_{11}) was carried out as in the preceding case, but the reaction product was not acetylated. From methanol leaflets, m.p. 122–123°; $[\alpha]^{26}D$ −56.0°; yield 70%.

Anal. Calcd. for $C_{25}H_{42}O$: C, 83.8; H, 11.7. Found: C, 83.7; H, 11.6.

Analogously, we prepared **17-benzyl-androst-5-en-3-β-ol** (V, R = C_6H_5), from methanol; m.p. 165°, $[\alpha]^{26}D$ + 87.0°; yield 75%.

Anal. Calcd. for $C_{27}H_{36}O$: C, 84.8; H, 9.6. Found: C, 84.9; H, 9.8.

3β-Acetoxy-20-hydroxy-20-*n*-butyl-pregn-5-ene (VI, R = C_4H_9).—Following the method of Petrov and Stuart-Webb,[22] 3.6 g. of pregnenolone acetate (III) in 50 ml. of benzene was added to a solution of butylmagnesium bromide, prepared from 1 g. of magnesium and 5.5. g. of butyl bromide in 100 ml. of ether. The mixture was refluxed with stirring for 1 hr., the ether distilled off and the benzene solution refluxed for 4 more hr. Decomposition with ice and hydrochloric acid, extraction with benzene and concentration of the dried benzene solution gave an oil, which could be converted into a crystalline compound by trituration with petroleum ether but was directly re-acetylated with 30 ml. of acetic anhydride in 30 ml. of pyridine at room temperature (12 hr.). The product was chromatographed (benzene–petroleum ether, 9:1) and recrystallized from acetone; needles of m.p. 176°; $[\alpha]^{26}D$ −54°; yield 3 g. (75%).

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.9; H, 10.6. Found: C, 78.2; H, 10.4.

3β-Acetoxy-20-hydroxy-20-*n*-amyl-pregn-5-ene (VI, R = C_5H_{11}), from methanol, m.p. 155°; $[\alpha]^{26}D$ −57°; yield 67%.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 78.1; H, 10.1. Found: C, 78.3; H, 10.3.

3β-Acetoxy-20-hydroxy-20-phenyl-pregn-5-ene (VI, R = C_6H_5), from methanol; m.p. 185°; $[\alpha]^{26}D$ −35°; yield 73%. In this case, the product of the Grignard reaction was insoluble and was isolated by filtration, before it was re-acetylated.

Anal. Calcd. for $C_{27}H_{38}O_2$: C, 82.0; H, 9.8. Found: C, 82.2; H, 9.5.

3β-Acetoxy-20-hydroxy-20-(4′-methylpentyl)-pregn-5-ene (VI, R = $CH_2CH_2CH_2CH(CH_3)_2$), from methanol; m.p. 135°; yield 80%.

The necessary **4-methylpentanol** was prepared in 70% yield according to Huston and Agett[23] from isobutylmagnesium bromide and ethylene oxide, b.p. 145–153°, and the corresponding bromide (X) in the usual way; b.p. 150–154°; yield 80%.

3β-Acetoxy-17-(α-methyl-β-propyl-vinyl)-pregn-5-ene (VII, R′ = C_3H_7).—The alcohol VI (R = C_4H_9) was dehydrated following the method of Koechlin and Reichstein[24] by heating 2 g. of it with 30 ml. of pyridine and 4 ml. of phosphorus oxychloride for 4 hr. at 140° (bath temperature). After this time, 5 ml. of pyridine and 2 ml. of phosphorus oxychloride was added and the heating continued for 4 hr. The solution obtained was poured into a mixture of ice and hydrochloric acid and the product extracted with ether. The ethereal solution then was washed with sodium bicarbonate solution and water, dried and concentrated and the residue chromatographed (ether–petroleum ether) and recrystallized from methanol; m.p. 80°; $[\alpha]^{26}D$ −54.8°; yield 1.5 g. (83%).

Anal. Calcd. for $C_{27}H_{42}O_2$: C, 81.4; H, 10.5. Found: C, 81.3; H, 10.8.

Ozonization.—A current of ozone was passed through a solution of 1 g. of VII (R′ = C_3H_7) in 50 ml. of glacial acetic acid. This treatment was continued for 15 minutes after the first traces of unreacted ozone had appeared. Then 5 g. of zinc dust was added and the mixture heated at 80° for 30 minutes and filtered. The solution was then distilled to dryness; only in the first 8 ml. of distillate the presence of an aldehyde could be proven qualitatively. The total of these 8 ml. was then diluted with 25 ml. of water and treated with 50 ml. of the 2,4-dinitrophenylhydrazine reagent. The product was three times recrystallized from ethanol and melted at 122–123°, also on admixture of a pure specimen of the 2,4-dinitrophenylhydrazone of *butyraldehyde;* yield, quantitative. It was observed that also the specimen of the 2,4-dinitrophenylhydrazone reached the melting point of 122–123° only after three recrystallizations from ethyl alcohol. Analogously to VII (R′ = C_3H_7), the following three substances were prepared:

3β-Acetoxy-17-(α-methyl-β-butyl-vinyl)-pregn-5-ene (VII, R′ = C_4H_9), from ethanol; m.p. 90°; $[\alpha]^{26}D$ −54.2°; yield 80%.

Anal. Calcd. for $C_{28}H_{44}O_2$: C, 81.5; H, 10.6. Found: C, 81.3; H, 10.5.

3β-Acetoxy-17-(α-phenylvinyl)-pregn-5-ene (VIII), from aqueous methanol; m.p. 104°; $[\alpha]^{26}D$ + 33.2°; yield 80%.[25]

Anal. Calcd. for $C_{29}H_{38}O_2$: C, 83.2; H, 9.1. Found: C, 83.3; H, 9.0.

3β-Acetoxy-17-(α-methyl-β-(3′-methylbutyl)-vinyl)-pregn-5-ene (VII, R′ = $CH_2CH_2CH(OH_3)_2$), from methanol; m.p. 80°; yield 60%.

3β-Acetoxy-2-*n*-butyl-pregn-5-ene (I, R = CH_3).—Following the method of Hershberg, *et al.*,[12] 1 g. of the diene (VII, R = C_3H_7) in 50 ml. of pure dioxane (Analar) and 1 ml. of glacial acetic acid was hydrogenated in the presence of 0.1 g. of platinum oxide at room temperature and atmospheric pressure. It was found advantageous to add a second portion (0.05 g.) of catalyst after some time. The theoretical quantity of hydrogen (1 mole)[26] was absorbed in 8 hr. The filtered solution was diluted with water and the solid product chromatographed (ether–petroleum ether) and recrystallized from methanol; double m.p. 85° and 114°[27]; $[\alpha]^{26}D$ −49° (lit.[8] m.p. 116–117° and 129°; $[\alpha]D$ −48.8°); yield 0.8 g. (80%).

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 81.0; H, 11.0. Found: C, 81.6; H, 11.1.

Analogously, we prepared **3β-acetoxy-20-*n*-amyl-pregn-5-ene** (I, R = C_2H_5), from acetone. Double melting points 87 and 124–125°; $[\alpha]^{26}D$ −47.6°, yield 70%.

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.1; H, 11.1. Found: C, 81.1; H, 11.0.

3β-Acetoxy-20-phenyl-pregn-5-ene (IX), from methyl ethyl ketone, m.p. 232°; $[\alpha]^{26}D$ +34.5°; yield 80%.

Anal. Calcd. for $C_{29}H_{40}O_2$: C, 82.8; H, 9.5. Found: C, 83.0; H, 9.5.

Cholesteryl acetate, m.p. and mixed m.p. with an authentic specimen, 115°; $[\alpha]^{25}D$ −43.5°[28]; yield 85%.[29]

3β-Hydroxy-20-*n*-amyl-pregn-5-ene (as I, R = C_2H_5).—A solution of 0.5 g. of the acetate (I, R = C_2H_5) in 10 ml. of

(22) V. Petrov and A. Stuart-Webb, *J. Chem. Soc.*, 4675 (1956).

(23) R. C. Huston and A. H. Agett, *J. Org. Chem.*, **6**, 123 (1941).

(24) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

(25) In this case, the dehydration required a heating period of 12 (not 8) hr.

(26) By a separate experiment, the amount of hydrogen had been determined which the catalyst alone absorbs.

(27) Such double melting points—due probably to the occurrence of polymorphic modifications of the compound—also have been observed by de Vries and Backer.[8]

(28) *Cf.* R. J. Anderson, *J. Biol. Chem.*, **71**, 407 (1926/1927). D. H. R. Barton, *J. Chem. Soc.*, 1116 (1946).

(29) No trace of the C_{20}-epimer, m.p. 123–124°, $[\alpha]D$ −47.9° (*c* 0.9), recently described by K. Tsuda, R. Hayatsu, Y. Kishida and S. Akagi (THIS JOURNAL, **80**, 921 (1958)); *cf.* R. Hayatsu, *Pharm. Bull.*, **5**, 452 (1957) (*C. A.*, **52**, 9179 (1958)), was found. *Cf.* also the recent paper by F. Sondheimer and R. Mechoulam, THIS JOURNAL, **80**, 3087 (1958).

ethanol was refluxed for 3 hr. with a solution of 1 g. of sodium hydroxide in 2 ml. of water. The product, which crystallized upon cooling, was recrystallized from ethanol and melted at 132°; yield 0.3 g: $[\alpha]^{25}D$ −38.9°.

Anal. Calcd. for $C_{26}H_{44}O$: C, 83.7; H, 11.8. Found: C, 83.2; H, 11.3.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Reaction of Trialkyl Phosphites with Thiyl and Alkoxy Radicals[1]

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The reaction between mercaptans and trialkyl phosphites yielding hydrocarbons and trialkyl phosphorothionates is shown to be a free radical chain process, initiated by azobisisobutyronitrile. An analogous reaction between disulfides and trialkyl phosphites to give sulfides and trialkylphosphorothionates also occurs, induced by light and organic peroxides. Free radical chain mechanisms are proposed for both reactions involving thiyl radical attack on the phosphite to yield an intermediate phosphorus radical with an expanded valence shell. At higher temperatures the non-radical Arbuzov type reaction between phosphites and disulfides (to yield phosphorothiolates) apparently occurs as well. When di-*t*-butyl peroxide and dicumyl peroxide are allowed to react with triethyl phosphite (either thermally or photochemically) the products are triethyl phosphate and hydrocarbon mixtures arising from alkyl radical dimerization and disproportionation. The utility of these reactions for producing complex organic hydrocarbon radicals of known structure is suggested, and the extension of our observations to the interpretation of other organophosphorus reactions pointed out.

In 1956, Hoffman and co-workers[2] reported a remarkable reaction occurring between trialkyl phosphites and mercaptans at elevated temperatures or in the presence of light.

$$RSH + P(OEt)_3 \longrightarrow RH + SP(OEt)_3 \quad (1)$$

Although no suggestion was made as to mechanism, the light catalysis suggested a radical process. In a preliminary communication[3] we showed that an analogous reaction may be induced between trialkyl phosphites and alkyl disulfides

$$RSSR + P(OEt)_3 \longrightarrow RSR + SP(OEt)_3 \quad (2)$$

and proposed that both involve radical chains with the propagation steps

$$RS\cdot + P(OEt)_3 \longrightarrow RS{-}\dot{P}(OEt)_3 \quad (3)$$

$$RS{-}\dot{P}(OEt)_3 \longrightarrow R\cdot + SP(OEt)_3 \quad (4)$$

$$R\cdot + HSR \longrightarrow RH \longrightarrow RS\cdot \quad (5a)$$

or

$$R\cdot + RSSR \longrightarrow RSR + RS\cdot \quad (5b)$$

This paper describes our experimental results in more detail and also some observations on a quite analogous (but non-chain) reaction which occurs between dialkyl peroxides and triethyl phosphite to yield hydrocarbons and triethyl phosphate. In the light of our findings we have also suggested the utility of these reactions for generating complex hydrocarbon radicals of known structure, and the possible radical nature of several other reactions of trivalent phosphorus.

Results

Trialkyl Phosphite—Mercaptan Reactions.—The strongest evidence for the proposed radical chain mechanism for reaction (1) would be the demonstration that it is brought about by typical radical chain initiators. This was investigated by comparing the reaction of triethyl phosphite and isobutyl mercaptan at 69° in the presence and absence of azobisisobutyronitrile (AIBN). Using a slight excess of phosphite and no AIBN, no detectable reaction was noted in 30 minutes. In the presence of 1.84 mole % AIBN, gas evolution (isobutane) was noted in 2 minutes. Gas chromatographic analysis of the reaction mixture cooled after 2 minutes showed no mercaptan, disappearance of the expected amount of phosphite, and strong peaks of isobutane and triethyl phosphorothionate. A *minimum* kinetic chain length for reaction (1) could be calculated. From the data of Lewis and Matheson,[4] AIBN decomposes to the extent of 0.5% in 2 minutes at 69°. Assuming complete reaction and that each decomposition starts two chains, the average chain length is 100/0.0184 = 5400. This value (which is larger than that reported earlier[3]) necessarily represents a minimum since (a) the system did not reach bath temperature immediately, (b) the reaction may have been essentially complete in less than 2 minutes, and (c) chain initiation by AIBN is usually not more than 40–80% efficient.[5] Nevertheless, the very long chain nature of the reaction is clearly evident.

Photochemical Reaction of Triethyl Phosphite with Disulfides.—An important step in our formulation of the trialkyl phosphite-mercaptan reaction is (5a), attack of an alkyl radical upon the S–H bond, a process which is well established in the free radical addition of mercaptans to olefins. The analogous attack on disulfides (5b) is also known, and accounts for the appreciable transfer constants of disulfides in vinyl polymerization. In general, (5b) occurs less readily than (5a), the tranfer constants of styrene with *n*-alkyl mercaptans[6] being approximately 20 and with a variety of dialkyl disulfides, 0.005–0.03.[7] Nevertheless it seemed possible that reaction 2 could be realized

(1) Taken from the Ph.D. Dissertation of Robert Rabinowitz. Support of this work by the National Science Foundation is gratefully acknowledged.

(2) F. W. Hoffman, R. J. Ess, T. C. Simmons and R. S. Hanzel, THIS JOURNAL, **78**, 6414 (1956).

(3) C. Walling and R. Rabinowitz, *ibid.*, **79**, 5326 (1957).

(4) F. M. Lewis and M. S. Matheson, *ibid.*, **71**, 747 (1949).

(5) G. S. Hammond, J. N. Sen and C. E. Boozer, *ibid.*, **77**, 3244 (1955).

(6) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 319.

(7) R. M. Pierson, A. J. Costanza and A. H. Weinstein, *J. Polymer Sci.*, **17**, 221 (1955).