chloric acid, and the solution was then evaporated to dryness *in vacuo*. Water was added to the residue, and the evaporation repeated, this operation being done several times. The glue-like mass was treated with a minimum of warm water for solution (5 ml.). It was found that the amino acid could best be isolated from this solution by titration with lithium hydroxide, and making use of the solubility of lithium chloride in alcohol. The solution was treated dropwise with concentrated lithium hydroxide solution as long as a test portion did not give a precipitate with several volumes of ethanol (*p*H 2.5–3). Ten volumes of ethanol then were added slowly during 20 minutes, and the liquid filtered and left to stand, when the amino acid gradually separated as crystalline grains. After five hours, the product was filtered, washed with ethanol and dried (weight 1.65 g.). The filtrates, on standing overnight, gave an additional 150 mg. The total yield was 1.80 g. or 74%. This was the best yield obtained in several runs, the difficulty being in adjusting the amount of lithium hydroxide used. If too much of the alkali is employed, an amorphous high-melting product precipitates before the amino acid separates, while if too little lithium hydroxide is added, some of the amino acid remains in solution after alcohol is added. The amorphous product may be the monolithium salt of the β-methylglutamic acid.

The methylglutamic acid was recrystallized by adding 3–4 volumes of alcohol and seed to its concentrated aqueous solution. The highest m.p. observed, after several recrystallizations, was 169.5–170.5°.

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.72; H, 6.83. Found: C, 44.58; H, 6.72.

Both the amino acid and the high-melting substance gave purple colors on warming with a dilute aqueous acetic acid solution of ninhydrin.

N-Benzoyl-β-methylglutamic Acid Monohydrate.—The amino acid was benzoylated by the procedure of Bullerwell, Lawson and Morley,[6] as used for glutamic acid, giving a white, crystalline, hydrated, benzoyl derivative. This compound was recrystallized several times from water for analysis. On heating, it melted at 114–116°, with partial solidification above 120°, forming the anhydrous acid which melted about 142°.

Anal. Calcd. for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.01. Found: C, 54.82; H, 5.83.

N-Acetyl-α-carbethoxyglutamic Acid Diethyl Ester.—The addition of ethyl acrylate to ethyl acetamidomalonate was carried out in a manner similar to that used for the crotonate. The reactants were mixed more slowly and the product was extracted by ether after the steam distillation. Evaporation of the ether solution left a pasty solid; 43.4 g. (0.2 mole) of the acetamidomalonate gave 51 g. of product or 80.4% yield. This ester was best recrystallized from ether–petroleum ether (2:1). After three recrystallizations, it had m.p. 81–82.5°. The analysis indicated that a carbethoxy group was not lost in the condensation.

Anal. Calcd. for $C_{14}H_{23}NO_7$: C, 52.997; H, 7.26. Found: 52.67; H, 6.77. Calcd. for $C_{11}H_{19}NO_5$ (decarbethoxylated product): C, 53.88; H, 7.76.

(6) R. A. F. Bullerwell, A. Lawson and H. V. Morley, *J. Chem. Soc.*, 3283 (1954).

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An Explosion during the Preparation of Neopentyl Alcohol

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The preparation of neopentyl alcohol as recently described[1] has been repeated successfully many times in this Laboratory. Recently, however, a violent explosion occurred during a run. Investigation revealed that the explosion undoubtedly took place after the acetone peroxide which had been removed by suction filtration was allowed to be sucked dry on the funnel. The suction flask was unharmed but much damage resulted from the explosion. Accordingly, when this preparation is carried out as described,[1] care should be taken that the solid peroxide be kept moist and destroyed with care. Preferably, an alternate procedure which avoids the formation of acetone peroxide should be used.

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Preparation of Modified Squalenes

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There is considerable evidence that cholesterol plays an important, if ambiguous, role in the development of atherosclerosis.[1] Recent progress in the elucidation of the biogenesis of cholesterol has demonstrated that the hydrocarbon squalene is the most efficient precursor to cholesterol yet discovered.[2] It was our purpose to prepare modified squalenes in the hope that these compounds would act as metabolic antagonists to the endogenous syntheses of cholesterol. The reduction of the serum cholesterol concentration should have a beneficial effect on the severity of the atherosclerotic lesions.

It was shown recently that the hydrocarbon regenerated from squalene hexahydrochloride has a different structure from the natural squalene.[3] This can be differentiated from the natural material in biological systems.[4] We have investigated the preparation of squalene hexahydrobromides and particularly the effect of peroxide on the mode of addition of hydrogen bromide. It was hoped that materials more closely analogous to natural squalene could be regenerated from squalene hexahydrobromides of approxpiate structure. For example, a "squalene" differing from natural squalene in the position of one of the double bonds possibly could function as a metabolic antagonist to squalene utilization. We repeated the experiment of Heilbron and co-workers[5] and found, as these workers had foreshadowed, that a mixture of hexahydrobromides results when squalene is treated with hydrogen bromide in acetone solution. This mixture is rather readily separated by fractional crystallization into isomers melting at 112–114, 135–138, and 151–153°. Schmidt[6] reports the isolation of two hexahydrobromides, m.p. 116–118° and 136–138° from synthetic squalene. The infrared spectra of these isomers were similar, but distinctly different. When the hydrogen bromide reaction was run in the presence of 0.02 mole % of ascaridole a different result was obtained. A single hexahydrobromide

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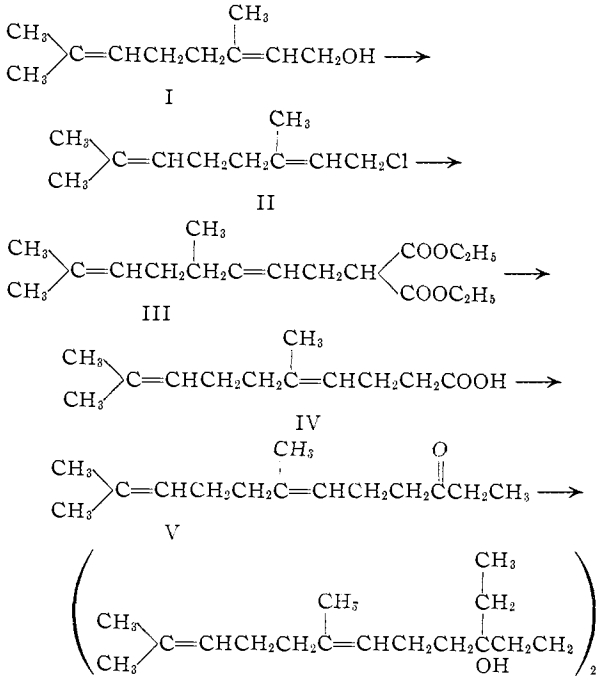
(2) R. G. Langdon and K. Bloch, THIS JOURNAL, **74**, 1869 (1952).
(3) W. G. Dauben, H. L. Bradlow, N. K. Freeman, D. Kritchevsky and M. Kirk, *ibid.*, **74**, 4321 (1952).
(4) R. G. Langdon and K. Bloch, *J. Biol. Chem.*, **202**, 77 (1953).
(5) I. M. Heilbron, E. D. Kamm and W. M. Owens, *J. Chem. Soc.*, 1630 (1926).
(6) J. Schmidt, *Ann.*, **547**, 115 (1941).

melting at 114–117° was isolated in lower yield. This compound had an essentially identical infrared spectrum to the 112–114° isomer isolated in the first experiment. It appeared as if the use of peroxide did not give a significantly different mode of addition but inhibited secondary reaction pathways. Since a markedly different hexahydrobromide was not prepared, the dehydrobromination of these materials was not studied.

Another possibility for the preparation of a squalene antagonist was suggested by the antimetabolic relationship of methionine and ethionine. If a compound could be prepared which differed from squalene by the addition of methylene groups in branched methyl groups, it might function in metabolic blockage. A modification of the Schmidt squalene synthesis[6] as outlined was studied for the preparation of such a material.



The preparation of geranylacetic acid (IV) followed the literature descriptions.[7,8] The ethyl homogeranyl ketone V was new and could be obtained in good yield by the alkylation of geranylacetyl chloride with diethylcadmium. The Barbier reaction of V with 1,4-dibromobutane and magnesium followed the course described by Schmidt for his squalene synthesis. Dauben and Bradlow[9] had observed that the squalene preparation according to Schmidt contained hydroxylated material. The dehydration conditions used by these workers appeared to be rather severe and we chose to carry out the dehydration by the Darzens procedure, a method demonstrated to retain structural integrity.[10] This method was successful and the desired bismethylsqualene (VI) was obtained as a pale yellow oil, b.p. 201–203° (0.05 mm.), $n^{25}D$ 1.4950. The infrared absorption spectrum was very similar to that of natural squalene except for some absorption at 11.18 μ. This result indicated some unsymmetrical dialkylethylene structures were present.[11] The spectrum was more similar to that of natural squalene than to the spectrum of "squalene" regenerated from the squalene hexahydrohalides.

Acknowledgment.—We are indebted to R. T. Nicholson for the preparation of the geranylacetic acid and to R. T. Dillon and his staff for the analytical data.

Experimental

Squalene Hexahydrobromide.—Natural squalene (Distillation Products Industries squalene (90%) was distilled, b.p. 215–220° (0.7 mm.).

Anal. Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.57; H, 12.37; IR (3% in chloroform), 5.96, 6.90, 7.24, 8.98, 10.12, 11.88 μ.

Following the method of Heilbron, *et al.*,[5] from 30 g. of squalene there was obtained 40 g. of solid hexahydrobromide. The majority of this material dissolved in one l. of boiling acetone. Cooling gave 20 g. of colorless crystalline solid, m.p. 112–114°.

Anal. Calcd. for $C_{30}H_{56}Br_6$: Br, 53.50. Found: Br, 53.14; IR (KBr disk), 5.86, 7.26, 7.66, 8.76, 11.56, 13.44 μ.

Treatment of the undissolved material with a second liter of boiling acetone effected partial solution. Cooling of the filtered solution yielded 3.7 g. of colorless solid, m.p. 135–138°.

Anal. Found: Br, 52.86; IR (KBr disk), 5.86, 7.26, 7.66, 8.78, 11.56, 13.44μ.

Crystallization of the acetone-insoluble material from benzene gave 1.8 g., m.p. 151–153°.

Anal. Found: Br, 53.30; IR (KBr disk), 5.86, 7.25, 7.67, 8.76, 8.98, 11.56, 13.44 μ.

An identical experiment except that 0.21 ml. of ascaridole was added gave 25 g. of crude product. This dissolved in 750 ml. of boiling benzene and yielded on cooling 18 g. of material, m.p. 114–117°.

Anal. Found: Br, 53.09; IR (KBr disk), 5.86, 7.26, 7.66, 8.78, 11.56, 13.44 μ.

7,11-Dimethyl-6,10-dodecadien-3-one (V).—A solution of 19.63 g. (0.10 mole) of geranylacetic acid (b.p. 111–115 (0.4 mm.), $n^{25}D$ 1.4710; Forster and Cardwell[8] give b.p. 179° (19 mm.), $n^{21}D$ 1.4739) in 200 ml. of dry ether was treated with one drop of pyridine and 10 ml. (16 g.) of thionyl chloride. The suspension was swirled occasionally at room temperature for 3 hours. The ether was removed by distillation at reduced pressure. The resulting oil was dissolved in 100 ml. of dry benzene and the benzene removed by distillation at reduced pressure. The benzene addition and removal was repeated. The yellow colored acid chloride was dissolved in 125 ml. of benzene. A solution of diethylcadmium in benzene–ether was prepared by the general method of Cason[12] from 12.16 g. of magnesium, 60 g. of ethyl bromide, 500 ml. of ether and 46 g. of anhydrous cadmium chloride. The majority of the ether was removed by distillation and 250 ml. of dry benzene added. The acid

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chloride solution was added to the stirred diethylcadmium mixture over the course of one hour at room temperature. A one-hour reflux period was employed after the addition was completed. The cooled suspension was treated with ice and 2% hydrochloric acid. The benzene layer and one benzene extract were combined and washed twice with water, twice with dilute sodium hydroxide solution and once with water. The benzene solution was dried over anhydrous sodium sulfate and evaporated at reduced pressure. The residual oil was distilled. Three fractions were collected: (1) b.p. 137–139° (1.5 mm.), wt. 1.0 g., $n^{25}D$ 1.4678; (2) b.p. 140–150° (1.5 mm.), wt. 14.9 g., $n^{25}D$ 1.4674; (3) b.p. 134–145° (1.5 mm.), wt. 0.9 g., $n^{25}D$ 1.4678. The residue in the distilling flask weighed 2.7 g. The yield was 16.8 g. (81%).

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.71; H, 11.37; IR (3% in chloroform), 5.84, 6.88, 7.26, 8.92, 10.20, 11.20, 11.88 μ.

A second run on a 0.158-mole scale gave 25.9 g. (78%), b.p. 152–158° (2.5 mm.), $n^{25}D$ 1.4672. **The semicarbazone** of the ketone was crystallized from petroleum ether (60–68°), m.p. 86–89°.

Anal. Calcd. for $C_{15}H_{27}ON_3$: C, 67.88; H, 10.26; N, 15.83. Found: C, 68.73; H, 10.05; N, 15.69.

2,6,19,23-Tetramethyl-10,15-diethyltetracosa-2,6,10,14,-18,22-hexaene (VI).—This reaction followed the directions of Schmidt[6] for the conversion of geranylacetone to squalene. A mixture of 3.87 g. of magnesium, 25.9 g. of 7,11-dimethyl-6,10-dodecadien-3-one and 16.8 ml. of 1,4-dibromobutane (b.p. 83–84° (14 mm.), $n^{25}D$ 1.5.73) was heated and then 83 ml. of ether added. A vigorous reaction took place. The crude Barbier product (29 g.) was dissolved in 150 ml. of pyridine, the solution cooled to 0°, and 12 ml. of thionyl chloride added. A considerable separation of pyridine hydrochloride was observed. After one hour at 0°, the dark brown colored reaction mixture was poured into dilute hydrochloric acid. The suspension was extracted with ether. The ethereal solution was washed with dilute hydrochloric acid, once with water, twice with dilute sodium hydroxide solution (strong color development), once with sodium sulfite solution and twice with water. The ethereal solution was dried over anhydrous sodium sulfate, the ether evaporated, and the oil distilled. Five fractions were taken: (1) b.p. 38–63° (2.5 mm.), wt. 4.64 g.; (2) b.p. 100–152° (1.0–3.0 mm.), wt. 8.14 g.; (3) b.p. 160–215° (2.5 mm.), wt. 3.88 g.; (4) b.p. 220–238° (1.2 mm.), wt. 8.30 g.; (5) b.p. 218–234° (0.8 mm.), wt. 2.78 g. Fractions 4 and 5 were combined and distilled. Four fractions were collected: (1) b.p. 140–192° (0.05 mm.), wt. 2.99 g.; (2) b.p. 192–200° (0.05 mm.), wt. 2.90 g., $n^{25}D$ 1.4943; (3) b.p. 201–203° (0.05 mm.), wt. 2.80 g., $n^{25}D$ 1.4950; (4) b.p. 201–208° (0.05 mm.), wt. 1.36, $n^{25}D$ 1.4963. Fraction 3 was taken for analysis.

Anal. Calcd. for $C_{32}H_{54}$: C, 87.59; H, 12.41. Found: C, 87.47; H, 12.36; IR (3% in chloroform), 6.90, 7.26, 11.18, 11.90 μ.

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The Preparation and Cyclization of Substituted Acetoacetanilides

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In connection with other work in progress it became necessary to synthesize a number of hitherto unreported α- and phenyl-substituted acetoacetanilides, and from these the corresponding 4-methylcarbostyrils. The former were prepared by previously described alkylations of acetoacetanilide[1,2] and by acetoacetylation of aromatic amines,[3] the latter by cyclodehydration of the acetoacetanilides with sulfuric acid, either slowly by standing at room temperature[1] or more rapidly by heating at 75–100°.[2,4]

The chief obstacle encountered was effecting the ring closure of acetoacetanilides substituted by a benzyl or phenyl group. Previous workers state either that such compounds could not be cyclized,[1,2] that they could not be characterized after cyclization,[5] or that cyclization proceeded only with concomitant sulfonation of a phenyl group.[6] The single instance of success reported is by Kaslow and Hayek,[7] who describe the preparation of 4-methyl-6-phenylcarbostyril by heating 4-phenylacetoacetanilide in mineral oil to 275°, or in unsatisfactory yield by the use of phosphoric acid (methods which did not accomplish the desired result when applied to our compounds); however, they found both these and conventional procedures failed with 2-phenylacetoacetanilide.

In order to circumvent both the comparative difficulty of ring closure and the ease of sulfonation that such behavior implies, aqueous rather than the usual concentrated sulfuric acid was employed as a cyclodehydrating agent. Thus, with an excess of 74% sulfuric acid at 96° for a half-hour, α-acetyl-β-phenylpropionanilide gave an excellent (89%) yield of 3-benzyl-4-methylcarbostyril. 2-Methylacetyl-β-phenylpropionanilide and α-acetyl-γ-phenylbutyranilide were likewise cyclized in the same way.

Although this apparently general method could not be fruitfully applied to 2-phenylacetoacetanilide, the latter compound was eventually cyclodehydrated by refluxing with phosphorus pentoxide in xylene, albeit in very low (8.5%) yield. The closely related α-methyl-2-phenylacetoacetanilide, however, resisted cyclization in this fashion or by any other procedure employed.

Our results are summarized in Tables I and II. Unless otherwise noted, all compounds cited gave negative ferric chloride tests and were crystallized from aqueous ethanol, whence they separated as colorless or white needles. Melting points are uncorrected.

Experimental

3-Benzyl-4-methylcarbostyril.—α-Acetyl-β-phenylpropionanilide[1] (4.0 g.) was mixed with 50 ml. of 74% sulfuric acid (conveniently prepared by combining two volumes of concentrated sulfuric acid with one volume of water). The mixture was heated at 96° for 0.5 hr. The anilide gradually dissolved, giving an orange-red solution; toward the end of the reaction period a yellow solid began to precipitate. The mixture was poured into 200 ml. of cold water, and the residue which formed filtered off and washed with cold water. Recrystallization from a benzene–ethanol mixture gave white needles melting at 238–240°. Further crops were obtained by successive concentrations and refrigeration of the mother liquor from the first crystallization. The total yield of product was 3.3 g. (89%).

3-Benzyl-4,8-dimethylcarbostyril.—2-Methyl-α-acetyl-β-phenylpropionanilide (2.0 g.) and 40 ml. of 74% sulfuric acid were heated on a steam-bath for 1.5 hours. There were two phases present at all times, and the mixture became deep red as the reaction proceeded. The mixture was stirred occasionally during the heating period. It was

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