In order to determine whether there is an increase in volume when these liquids are mixed to form the azeotrope, as is to be expected since there are positive deviations from Raoult's law, the specific gravity was determined and from this the volume of a given weight of the azeotrope calculated. This volume was found to be 4% greater than that calculated assuming ideal behavior.

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The C-12 Position of the Carbonyl Group in Hecogenin

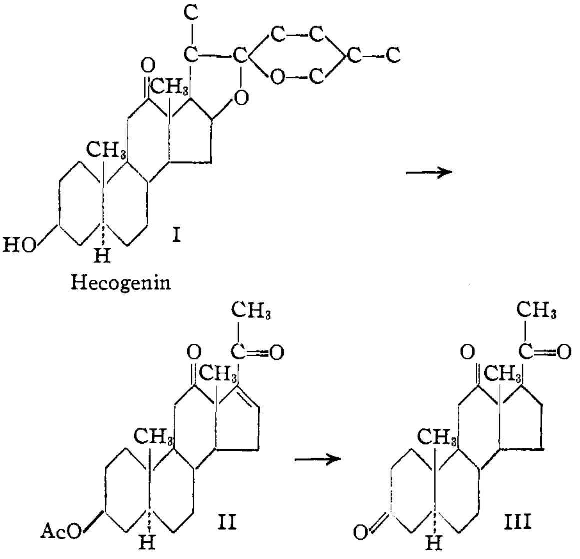
BY R. B. WAGNER, JAMES A. MOORE AND ROBERT F. FORKER

The current interest in cortisone for rheumatoid arthritis has stimulated great interest in the 12-ketosapogenins as possible starting material for its synthesis. The position of the carbonyl group in these substances has been assigned as a result of a systematic elimination of the other possible positions.[1]

It is now possible to give more direct proof for the C-12 oxygen in hecogenin (1) and related sapogenins by converting hecogenin to *allo*-pregnan-3,12,20-trione (III) identical with an authentic sample prepared from 12(α)-acetoxyprogesterone. Treatment of the oxidation product from pseudohecogenin diacetate with a hot aqueous methanolic solution of potassium carbonate followed by acetylation leads to 16-*allo*-pregnen-3(β)-ol-12,20-dione acetate (II). This substance (II) shows an ultraviolet absorption maximum in alcohol at λ230 mμ, log ε 3.93, typical for α,β-unsaturated systems. It is noteworthy that the peak is shifted from the position $\lambda^{\text{alc}}_{\text{max}}$ 238–240 mμ, log ε 3.9 exhibited by other 16-pregnen-20-ones containing no oxygen at C-12.[1a] Catalytic hydrogenation followed by hydrolysis and mild chromic acid oxidation gives *allo*-pregnan-3,12,20-trione (III). For purposes of comparison, this material and its C-5 isomer have been prepared from degradation products of desoxycholic acid.[2]

Previous efforts for converting hecogenin to this key substance (III) resulted in a product whose structure was not definitely settled.[1,2] Marker has stated that this material is 17-hydroxy-*allo*-pregnan-3,12,20-trione arising by the addition of water to the unsaturated ketone system.[3]

Acknowledgments.—We gratefully acknowledge a generous gift of hecogenin from Merck and Company. We thank Parke, Davis and Company for their help.



I

Hecogenin

II (tentative)

III *allo*-Pregnan-3,12,20-trione

Experimental

16-*allo*-Pregnen-3(β)-ol-12,20-dione Acetate.—To a solution of 2 g. of pseudohecogenin diacetate in 30 ml. of acetic acid was added a solution of 1.2 g. of chromic anhydride in 10 ml. of 80% acetic acid. After the reaction mixture had stood at 25° for ninety minutes, it was diluted with water and the product was extracted with ether. The ethereal solution was washed free from acetic acid and evaporated. The residue dissolved in 16 ml. of hot methanol was treated with 1 g. of potassium carbonate in 10 ml. of hot water, adding additional water to cause a turbid solution. The total time of heating on the steam-bath was ten minutes. The hydrolysis mixture was immediately diluted with cold water and ether extracted. The ethereal solution was dried and evaporated to dryness. The residue was acetylated with a hot pyridine–acetic anhydride mixture and finally crystallized from ether–pentane, m. p. 173–176°; 345 mg. Recrystallization from ether–methanol gave needles, m. p. 177–179°, $[\alpha]^{20}_{D}$ +126° and $[\alpha]^{20}_{5461}$ +159° (dioxane), $[\alpha]^{27}_{D}$ +138° and $[\alpha]^{27}_{5461}$ +177° (chloroform), absorption maximum at 227–230 mμ (log ε 3.93 in ethanol).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.2; H, 8.7. Found: C, 73.9; H, 8.6.

***allo*-Pregnan-3,12,20-trione from Hecogenin.**—The 16-pregnene compound from above, 300 mg., in 200 ml. of ether containing a few drops of acetic acid was shaken with hydrogen and Adams catalyst at forty-five pounds pressure for four hours. This treatment removed the conjugated unsaturated ketone system as shown by the absence of an absorption maximum at λ 230 mμ in the crude product. After hydrolyzing with 2% alcoholic potash in the usual manner, it was oxidized for two hours at room temperature with 0.6 g. of chromic anhydride in acetic acid. The excess oxidizing agent was destroyed with methanol and the acetic acid was removed in vacuum. The residue was extracted with ether and the ethereal solution was washed with water, 10% sodium hydroxide, water and evaporated. The crystalline residue was crystallized from ether to give almost pure material, m. p. 206–208°; yield, 105 mg. Recrystallization from ether gave crystals, m. p. 207–209°, $[\alpha]^{28}_{D}$ +180° and $[\alpha]^{28}_{5461}$ +225 (chloroform). These properties are in good agreement with those of *allo*-pregnan-3,12,20-trione described below. A mixture gave no melting point depression.

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(1) Marker and co-workers, THIS JOURNAL, **69**, 2167 (1947).

(1a) FOOTNOTE ADDED IN PROOF: Ultraviolet absorption data for the pregnene compound from a second 12-ketosapogenin is in agreement with the lower maximum. In view of these data, formula II may not be the exact representation. On the other hand, any assignment must be closely related to account for the formation of *allo*-pregnan-3,12,20-trione (III). The nature of this unsaturated system is under further study.

(2) Wagner, Moore and Forker, THIS JOURNAL, **71**, 3856, 4159 (1949).

(3) Marker, *ibid.*, **71**, 2656, 4149 (1949).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.2. Found: C, 76.0; H, 9.2.

allo-**Pregnan-3,12,20-trione from Desoxycholic Acid.**—Using essentially the procedures described in the literature,[4-7] desoxycholic acid was converted to 3(α)-hydroxy-12(α)-acetoxypregnan-20-one, m. p. 205–206°, $[\alpha]^{25}_{\mathrm{D}}$ +150° in acetone (literature[7]: m. p. 208–210°, $[\alpha]_{\mathrm{D}}$ +151 ± 6° in acetone) and then to 12(α)-acetoxyprogesterone,[6] m. p. 181°, $[\alpha]^{26}_{\mathrm{D}}$ +215° and $[\alpha]^{26}_{5461}$ +259° in chloroform, absorption maximum at 240 mμ (log ε 4.14 in ethanol).

To 500 mg. of 12(α)-acetoxyprogesterone dissolved in 60 ml. of absolute ethanol was added 6 g. of sodium during fifty minutes at steam-bath temperature. The reaction mixture was diluted with ether and the ethereal solution was washed and evaporated to dryness. The residue was then oxidized with 1.14 g. of chromic anhydride in 114 ml. of acetic acid at room temperature for twelve hours. The reaction mixture was processed as described above for the product from hecogenin to give crude material from ether, m. p. 185–194°, wt. 120 mg. Recrystallization from aqueous methanol gave *allo*-pregnan-3,12,20-trione as needles, m. p. 206–208°, $[\alpha]^{23}_{\mathrm{D}}$ +184° and $[\alpha]^{23}_{5461}$ +224° (chloroform), no maximum at λ 240 mμ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.2. Found: C, 76.0; H, 8.9.

The reduction was also accomplished with hydrogen and Adams catalyst in acetic acid at room temperature and three atmospheres for five hours. After hydrolyzing with 2% alcoholic potash and oxidizing with chromic acid as described above, the product was crystallized from ether, m. p. and mixed m. p. with above, 206–208°.

Pregnan-3,12,20-trione.—For purposes of comparison with the above isomeric substance, this compound was prepared by the oxidation of pregnan-3(β)-ol-12,20-dione with chromic anhydride in acetic acid at room temperature for forty minutes. The product was crystallized successively from ether, aqueous methanol and then acetone, m. p. 204–206°, $[\alpha]^{26}_{\mathrm{D}}$ +181°, and $[\alpha]^{26}_{5461}$ +225° in chloroform (literature for pregnan-3,12,20-trione[7]: m. p. 201–202°; $[\alpha]^{17}_{\mathrm{D}}$ +182 ± 7°, $[\alpha]^{17}_{5461}$ +218 ± 8° in acetone). A mixture with the above isomeric substance showed a melting point depression of 36°.

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(4) Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1938).

(5) Miescher, *et al.*, *Helv. chim. Acta*, **27**, 1815 (1944); **28**, 1252 (1945).

(6) Shoppee and Reichstein, *ibid.*, **24**, 351 (1941).

(7) Reichstein and von Arx, *ibid.*, **23**, 747 (1940).

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Identification of Free Radicals by Radio-halogens in the Radiolysis of Hydrocarbons[1]

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Recent work in these laboratories on the photolysis and radiolysis of alkyl iodides,[2] in which radioactive iodine was used to demonstrate the high efficiency of reactions of the type

$$R\cdot + I_2 \longrightarrow RI + I$$

has suggested the use of radioactive halogens as a general method of detecting and identifying free radicals. By using molecular halogens of high specific activity in systems where such radicals are generated one may expect to be able to observe unweighable but radiochemically detectable amounts of the halides corresponding to the free radicals formed. Subsequent addition and fractionation of appropriate carrier substances, followed by activity determinations, will give an estimate of the types and relative amounts of radicals formed.

We have tested this procedure in a number of systems, producing free radicals both by absorption of light and ionizing radiations. The accompanying figure shows the result of gamma irradiation of a solution of approximately 4 mg. of highly active[3] iodine in 5 cc. of purified *n*-pentane. After exposure, excess iodine was extracted and 10 cc. each of methyl, ethyl, *n*-propyl, *n*-butyl and *n*-amyl iodides added. These carriers were fractionated in a glass-packed Todd column, taking 2-cc. cuts. The activity of each fraction was measured in a liquid cell Geiger counter. Both the activity and boiling point of each fraction are indicated in the figure. The purest fractions corresponding to each carrier are labeled.

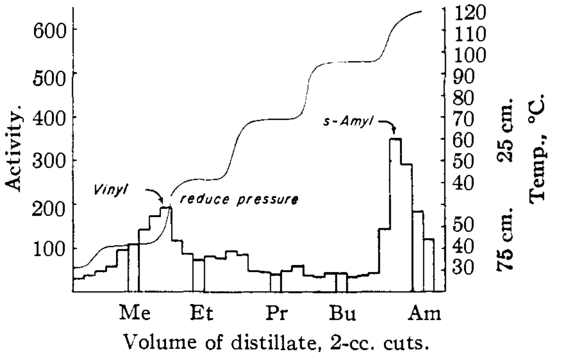

Fig. 1.—Radiolysis of *n*-pentane (liquid) + I_2^*.

It is apparent from the data that considerable proportions of the lower alkyl iodides were formed, corresponding to rupture of the pentane molecule, radical or ion. At least two intermediate peaks appear. These must correspond to active species for which no carrier was added. From the sequence of these in the distillation curve they have been tentatively identified as vinyl iodide and *s*-amyl iodide.

This technique is also being applied to the photobromination of hydrocarbons and here again fragmentation of the carbon chain appears to be significant. In the photobromination of gaseous *n*-pentane with visible light at 80°, the ratio of all lower bromides to amyl bromides appears to be approximately 30:70. This ratio remains unchanged over a thirty-fold change in the ratio of bromine and pentane pressures, which indicates that the production of the lower bro-

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[1] Reported at the 116th meeting of the American Chemical Society, Atlantic City, N. J., September 19–23, 1949.

[2] R. H. Schuler, Dissertation, University of Notre Dame, 1949.

[3] Activity due to 8-day I^{131}, obtained from U. S. Atomic Energy Comm., Oak Ridge, Tenn.