It was washed with methanol and recrystallized from a mixture of methanol and ethyl acetate; m. p. 196–199°. A mixture with diosgenin acetate, m. p. 199–200°, melted at 198–200°, and a mixture with tigogenin acetate, m. p. 202°, melted at 185–191°.

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.3; H, 9.7. Found: C, 76.5, 76.5; H, 9.7, 9.8.

A solution of 200 mg. of the acetate and 150 mg. of potassium hydroxide in 15 cc. of ethanol was boiled for thirty minutes, poured into water, and filtered. The solid was washed with water and dried. After recrystallization from aqueous acetone the product melted at 208–209°. A mixture with diosgenin, m. p. 207–209°, melted at 208–209°.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.2; H, 10.2. Found: C, 77.9, 77.9; H, 10.2, 10.2.

Sarsasapogenin from *Asparagus officinalis* (L.).—The dried and powdered root (25 lb.) was treated as described above under *Aletris*.

The crude genin from the ether extract of the hydrolysis mixture was not acetylated but was recrystallized directly from ethanol. It melted at 203–205°. When mixed with diosgenin or with tigogenin the melting point was depressed 20°. When mixed with sarsasapogenin, m. p. 203–205°, the melting point was 203–205°.

The acetate was prepared by refluxing with acetic anhydride and melted at 142° after recrystallization from ethyl acetate. When mixed with sarsasapogenin acetate, m. p. 142°, the melting point was 142°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.9; H, 10.2.

Liligenin from *Lilium rubrum magnificum*.—The wet lily bulbs (36 lb.) were ground in a food chopper and extracted with ethanol. The procedure followed that given above for asparagus root. The ether extract from the hydrolysis mixture was washed with 2 *N* sodium hydroxide solution and water. On evaporation of the ether 1.1 g. of sapogenin was obtained. After recrystallization from ethanol the product had a m. p. 245–246°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 75.1; H, 10.1.

When a solution of the substance in ethanol was treated with a solution of digitonin in ethanol, there was immediately formed a heavy white precipitate of the digitonide. It was saturated to bromine.

The acetate was prepared by refluxing with acetic anhydride, followed by crystallization from methanol, m. p. 158°.

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.33; H, 9.16.

To a solution of 400 mg. of liligenin in 30 cc. of glacial acetic acid at 25° was added a solution of 600 mg. of chromic anhydride in 10 cc. of 80% acetic acid. The mixture stood for thirty minutes at room temperature. It was poured into water and extracted with ether. The ethereal solution was washed with dilute sodium carbonate and the acidic material precipitated with dilute hydrochloric acid. The acid could not be crystallized. There was no neutral fraction left in the ether after extraction with sodium carbonate.

Summary

Diosgenin and sarsasapogenin have been obtained from the roots of *Aletris farinosa* (L.) and *Asparagus officinalis* (L.), respectively. A new steroidal sapogenin has been obtained from bulbs of a Japanese lily.

STATE COLLEGE, PENNA. RECEIVED JULY 24, 1940

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CVIII. The Preparation of Dihydroandrosterone and Related Compounds from Diosgenin and Tigogenin

BY RUSSELL E. MARKER

Androsterone has the *epi* configuration of the C-3 hydroxyl group and is of the *allo* series.[1] We have shown[2,3] that the oxidation of 20-keto-pregnane compounds with Caro's acid is a convenient method of preparing androstanol-17 compounds. By this method androstanol-17(α), *etio*-cholanediol-3(α),17(α), Δ^5-androstenediol-3,17 and testosterone have been prepared.[3]

In order to apply the same procedure to the preparation of dihydroandrosterone, *allo*-pregnanol-3(α)-one-20 was required. This was made by the method of Marker and Rohrmann.[4] Tigogenone, obtained by the oxidation of tigogenin from diosgenin, was reduced with aluminum isopropylate and the tigogenin in the product was separated as the digitonide. The residual product was *epi*-tigogenin. It gave an acetate and was reconverted to tigogenone on oxidation with chromic acid.

When *epi*-tigogenin was heated with acetic anhydride at 200° it gave pseudo-*epi*-tigogenin, a substance analogous to the other pseudo sapogenins previously reported from this Laboratory.

(1) Ruzicka, Goldberg, Meyer, Brunnger and Eichenberger, *Helv. Chim. Acta*, **17**, 1395 (1934).

(2) Marker), Rohrmann, Wittle, Crooks and Jones, THIS JOURNAL, **62**, 650 (1940).

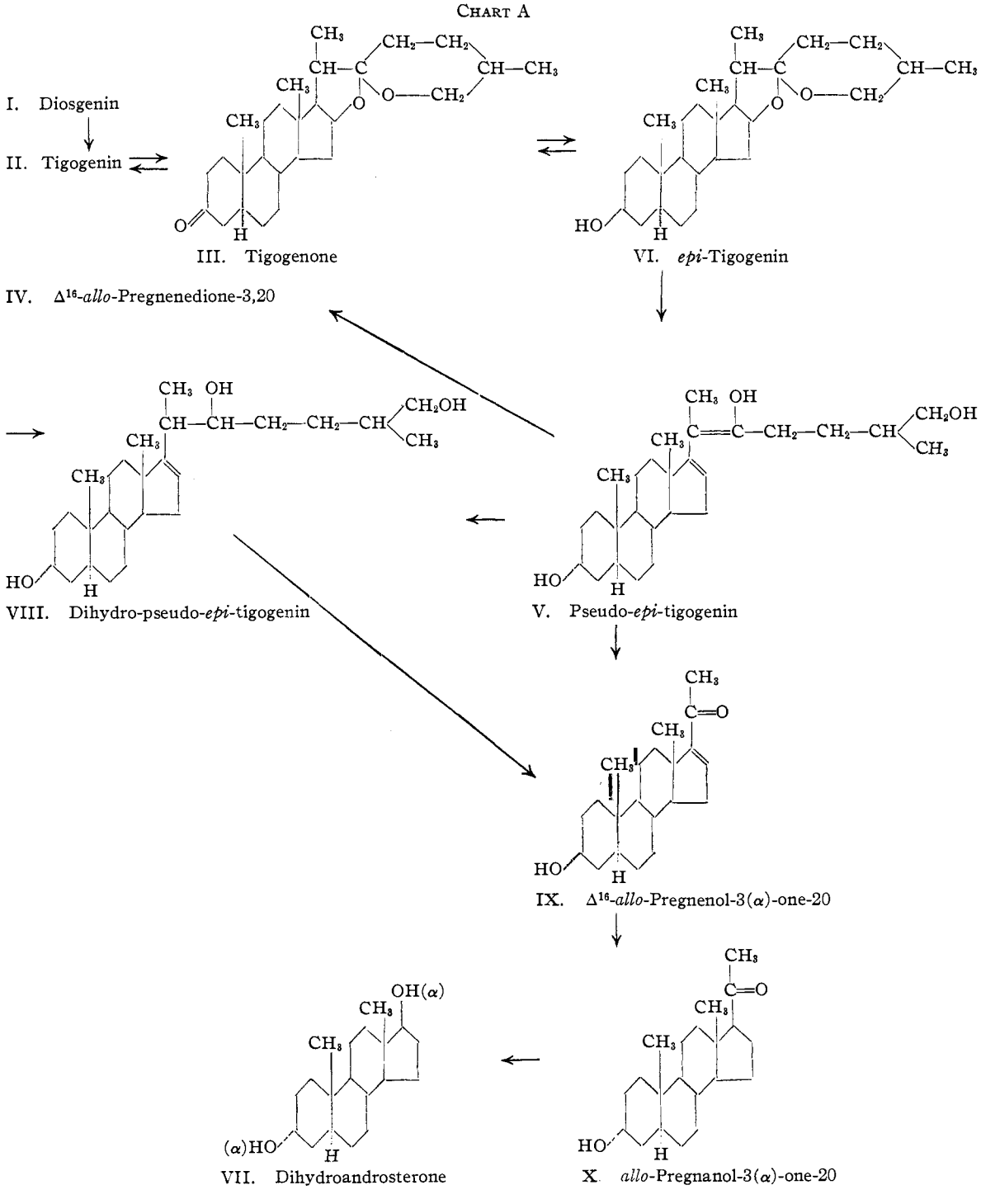
(3) Marker, *ibid.*, **62**, 2543 (1940).

(4) Marker and Rohrmann, *ibid.*, **62**, 518 (1940).

Pseudo-*epi*-tigogenin undergoes the reactions characteristic of pseudosapogenins. Thus treatment with acid gave *epi*-tigogenin. Catalytic reduction with hydrogen and Adams catalyst gave dihydropseudo-*epi*-tigogenin. This gave a crystalline diacetate which was also made by the reduction of the acetate of pseudo-*epi*-tigogenin, although the latter was not obtained in crystalline form.

Oxidation of pseudo-*epi*-tigogenin with chromic acid at 25–30° gave Δ^{16}-*allo*-pregnenedione-3,20. When the hydroxyl group of pseudo-*epi*-tigogenin was first protected by acetylation, a similar

CHART A



oxidation gave Δ^{16}-*allo*-pregnenol-3(α)-one-20. Marker and Rohrmann[5] found that oxidation of the diacetates of dihydropseudosapogenins gave the same pregnene compounds that were obtained from the acetates of the corresponding pseudosapogenins. This is also true of the diacetate of dihydropseudo-*epi*-tigogenin. The oxidation of this compound gave Δ^{16}-*allo*-pregnenol-3(α)-one-20. The latter compound was characterized by oxidation to the well-known Δ^{16}-*allo*-pregnenedione-3,20. When Δ^{16}-*allo*-pregnenol-3(α)-one-20 was reduced with hydrogen using palladium–barium sulfate as a catalyst, *allo*-pregnanol-3(α)-one-20 was obtained.

allo-Pregnanol-3(α)-one-20 acetate was then oxidized with Caro's acid. After hydrolysis of the reaction product androstanediol-3(α),17(α) was obtained. The excellent yields obtained in the series of reactions reported make diosgenin a desirable source for the preparation of dihydroandrosterone.

We wish to thank Parke, Davis and Company for their generous assistance.

Experimental Part

The tigogenin used in these experiments was prepared by the catalytic reduction of diosgenin.

***epi*-Tigogenin (VI).**—A mixture of 20 g. of tigogenone (III) (prepared by the chromic anhydride oxidation of tigogenin (II) at room temperature), 20 g. of aluminum isopropylate and 500 cc. of dry isopropyl alcohol was refluxed on a steam-bath for eight hours. The solvent was then slowly distilled off over a period of four hours. The residue was refluxed for fifteen minutes with 20 g. of potassium hydroxide in 500 cc. of methanol. The mixture was poured into water and acidified with hydrochloric acid. The precipitated solid was extracted with ether and the extract was washed well with water. The ether was evaporated on a steam-bath and the residue dissolved in 1 liter of 95% alcohol. To this was added a boiling solution of 40 g. of digitonin in 3 liters of 95% alcohol. After standing for three hours at room temperature the digitonide was filtered and washed with alcohol. The digitonide upon decomposition gave tigogenin. The filtrate was concentrated to 500 cc. and 4 liters of ether was added. A small amount of precipitate was filtered off and the filtrate was washed well with water. The solvent was removed and the residue crystallized from acetone, methanol and ethyl acetate; m. p. 242–245°. When mixed with tigogenin, m. p. 205–207°, it melted at 215–230°; yield 7.2 g.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6. Found: C, 77.7; H, 10.6.

A solution of 100 mg. of *epi*-tigogenin (VI) was refluxed with 5 cc. of acetic anhydride for thirty minutes. On cooling the product crystallized in needles. It was recrystallized from methanol–acetone, in which it was very insoluble; m. p. 199–202°. When mixed with tigogenin acetate, m. p. 199–202°, it melted at 170–182°.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 75.7; H, 10.1.

Oxidation of *epi*-Tigogenin to Tigogenone.—This was done in the usual way. The product was crystallized from ethanol and acetone, m. p. 205–207°. Mixed with tigogenone, m. p. 204–206°, it melted at 205–207°.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.2; H, 10.3. Found: C, 78.0; H, 10.2.

Pseudo-*epi*-tigogenin (V).—This was prepared in the usual way. It was crystallized from ether–pentane, dilute acetone, and acetone as needles, m. p. 148–150°; yield, 75%.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6. Found: C, 77.9; H, 10.8.

Conversion of Pseudo-*epi*-tigogenin to *epi*-Tigogenin.—To a solution of 100 mg. of pseudo-*epi*-tigogenin in 10 cc. of ethanol was added 2 cc. of concentrated hydrochloric acid. Almost immediately a precipitate appeared. After standing for one hour this was filtered, washed with ethanol and recrystallized from ethyl acetate; m. p. 241–244°; yield, 80 mg. When mixed with *epi*-tigogenin, m. p. 242–245°, it melted at 242–245°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.8; H, 10.6. Found: C, 77.6; H, 10.7.

The acetate had m. p. 198–200° and when mixed with an authentic sample of *epi*-tigogenin acetate, m. p. 199–202°, it gave no depression in melting point.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75.9; H, 10.1. Found: C, 76.0; H, 9.9.

Oxidation of Pseudo-*epi*-tigogenin to Δ^{16}-*allo*-Pregnenedione-3,20 (IV).—To a solution of 500 mg. of pseudo-*epi*-tigogenin in 20 cc. of glacial acetic acid at 25° was added a solution of 500 mg. of chromic anhydride in 5 cc. of 80% acetic acid, and allowed to stand at 25° for one hour. Water was added and the product dissolved in ether. The ethereal extract was washed with water and 2% sodium hydroxide solution. The neutral fraction was crystallized from ether–pentane and finally from ether; m. p. 208–210°. When mixed with Δ^{16}-*allo*-pregnenedione-3,20, m. p. 209–211°, it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.0; H, 9.6.

Oxidation of Acetylated Pseudo-*epi*-tigogenin to Δ^{16}-*allo*-Pregnenol-3(α)-one-20 (IX).—A solution of 1.5 g. of pseudo-*epi*-tigogenin in 10 cc. of acetic anhydride was refluxed for thirty minutes. The acetic anhydride was distilled *in vacuo* and the residue was dissolved in 50 cc. of acetic acid. To this solution was added 1.5 g. of chromic anhydride in 15 cc. of 80% acetic acid and the mixture was allowed to stand at 25° for ninety minutes. Water was added and the precipitated material was extracted with ether. The ethereal solution was washed with water and 2% sodium hydroxide solution. The ether was removed and the residue was hydrolyzed by refluxing for ten minutes with a 2% alcoholic potassium hydroxide solution. The product was extracted with ether and after removal of the solvent was crystallized from ether–

(5) Marker and Rohrmann, THIS JOURNAL, **62**, 521 (1940).

pentane and from dilute methanol; m. p. 219–222°; yield, 410 mg.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.8; H, 10.2. Found: C, 79.5; H, 10.1.

When refluxed with acetic anhydride it gave an acetate which was crystallized from dilute methanol; m. p. 156–158°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.0; H, 9.7.

Reduction of Δ^{16}-*allo*-Pregnenol-3(α)-one-20 (IX) to *allo*-Pregnanol-3(α)-one-20 (X).—A mixture of 2 g. of Δ^{16}-*allo*-pregnenol-3(α)-one-20, 50 cc. of ethanol, 50 cc. of ether and 1 g. of palladium–barium sulfate catalyst was shaken at room temperature for three hours under a pressure of hydrogen of 1.5 atm. The catalyst was filtered and the filtrate evaporated. The residue was crystallized from dilute ethanol and dilute acetone, m. p. 172–174°; yield, 1.4 g. When mixed with an authentic sample of *allo*-pregnanol-3(α)-one-20, m. p. 171–174°, there was no depression in m. p.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.2; H, 10.7.

It gave an acetate when refluxed for thirty minutes with acetic anhydride which was crystallized from dilute methanol, m. p. 138–140°. It gave no depression in melting point when mixed with an authentic sample of the acetate of *allo*-pregnanol-3(α)-one-20.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.4; H, 10.0.

Dihydroandrosterone (VII) from *allo*-Pregnanol-3(α)-one-20 (X).—To a solution of 1.2 g. of *allo*-pregnanol-3(α)-one-20 acetate in 200 cc. of glacial acetic acid was added 40 g. of von Bayer's dry persulfate mixture. It was let stand for seven days at 25°. At the end of this time 20 g. additional persulfate mixture was added and let stand for three more days with occasional shaking. At the end of this time an excess of 50% potassium hydroxide solution was added to neutralize the inorganic acids. The salts were filtered and the filtrate was concentrated *in vacuo*. The residue was extracted well with ether and washed with water. The solvent was removed and the residue was treated with Girard reagent to remove ketones. The non-ketonic fraction (410 mg.) was hydrolyzed with alcoholic potassium hydroxide and extracted with ether. The solvent was removed and the residue was sublimed in a high vacuum. The sublimate was crystallized from dilute ethanol and ethyl acetate, m. p. 219–222°. When mixed with an authentic sample of androstanediol-3(α), 17(α) (VII) prepared by the reduction of androsterone by sodium in propyl alcohol, m. p. 220°, it gave no depression in melting point.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.0; H, 11.1. Found: C, 78.2; H, 11.0.

A solution of 50 mg. of androstanediol-3(α),17(α) in 10 cc. of acetic anhydride was refluxed for thirty minutes. The acetic anhydride was vacuum distilled and the residue was crystallized from methanol; m. p. 160–162°. It gave no depression in melting point when mixed with an authentic sample.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.4; H, 9.7. Found: C, 73.2; H, 9.6.

Oxidation of Δ^{16}-*allo*-Pregnenol-3(α)-one-20 (IX) to Δ^{16}-*allo*-Pregnenedione-3,20 (IV).—This was performed in the usual way. The product was crystallized from ether–pentane and from ether, m. p. 209–211°. With Δ^{16}-*allo*-pregnenedione-3,20, m. p. 209–211° it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.3; H, 9.6.

Dihydro-pseudo-*epi*-tigogenin (VIII).—A mixture of 1 g. of pseudo-*epi*-tigogenin, 500 mg. of Adams platinum oxide catalyst and 100 cc. of glacial acetic acid was shaken with hydrogen at 3 atm. at room temperature for twelve hours. The catalyst was filtered and the filtrate was evaporated *in vacuo*. The product was crystallized from ether, from which it is quite insoluble, acetone, and methanol. From the latter solvent it crystallized in long needles, m. p. 193–196°, yield, 800 mg.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.4; H, 11.2. Found: C, 77.7; H, 11.1.

Diacetate.—M. p., 118–121°.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.0; H, 10.0. Found: C, 74.0; H, 10.1.

Similarly pseudo-*epi*-tigogenin was converted to the diacetate and hydrogenated. The product was crystallized from methanol as small needles, m. p. 118–120°. It gave no depression in melting point with the above diacetate. Hydrolysis of the diacetate of dihydro-pseudo-*epi*-tigogenin with alcoholic potassium hydroxide gave the original product which was crystallized from methanol, m. p. 194–196°.

Oxidation of Dihydro-pseudo-*epi*-tigogenin to Δ^{16}-*allo*-Pregnenedione-3,20 (IV).—This was achieved in the usual way. The product was crystallized from ether–pentane and ether, m. p. 208–211°. It was identical with an authentic sample of Δ^{16}-*allo*-pregnenedione-3,20.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found C, 80.3; H, 9.4.

Oxidation of the Diacetate of Dihydro-pseudo-*epi*-tigogenin.—To a solution of 1 g. of the diacetate of dihydro-pseudo-*epi*-tigogenin in 30 cc. of glacial acetic acid at 25–28° was added a solution of 1.2 g. of chromic anhydride in 20 cc. of 90% acetic acid. The oxidation mixture was allowed to stand for ninety minutes, water was added and the product was extracted with ether. The ethereal extract was washed well with water and 3% sodium hydroxide solution. After evaporation of the solvent, the residue crystallized from dilute methanol; yield 220 mg., m. p. 157–159°. It gave no depression in melting point when mixed with an authentic sample of the acetate of Δ^{16}-*allo*-pregnenol-3(α)-one-20 (IX).

A solution of 200 mg. of the acetate of Δ^{16}-*allo*-pregnenol-3(α)-one-20 in 50 cc. of alcohol was shaken with 100 mg. of platinum oxide catalyst under a pressure of 3 atm. of hydrogen for four hours. The catalyst was filtered and the solvent removed. The residue was dissolved in 20 cc. of acetic acid and to this was added a solution of 100 mg. of chromic oxide in 10 cc. of 90% acetic acid. It was allowed to stand at room temperature for thirty minutes. Water was added and the product was extracted with ether. The ethereal solution was washed with water and sodium

hydroxide solution and evaporated. The residue was crystallized from dilute methanol, m. p. 138–140°. Mixed with the **acetate** of *allo*-pregnanol-3(α)-one-20 (X), m. p. 140–141°, it gave no depression in melting point. When mixed with the acetate of Δ^{16}-*allo*-pregnenol-3(α)-one-20 it melted at 120–132°.

Summary

Dihydroandrosterone was obtained from diosgenin. The intermediates in this preparation are described.

STATE COLLEGE, PENNA. RECEIVED MAY 16, 1940

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Polyalkylbenzenes. XXVII.[1] Preparation of Pure Ethylbenzenes

BY LEE IRVIN SMITH AND CYRUS O. GUSS[2]

Ethylation of benzene to polyethylbenzene has generally been effected by means of the Friedel–Crafts reaction in which ethyl bromide or ethyl chloride and aluminum bromide or aluminum chloride were the reagents used,[3,4,5,6,7] although ethylene[8,9,10] as well as ethanol,[11] ethyl carbonate or diethyl ether[12] have been used in place of the organic halides, and phosphoric acid[13] or phosphorus pentoxide[14] as well as various metallic halides[15,16] have replaced the aluminum halides. Most of the recent work on alkylation to polyethylbenzenes[7,10,11] has indicated that there is a preferential formation of triethylbenzenes. Although tetra-, penta- and hexa-ethylbenzenes were noted, except for the last, the amounts of these substances were small and no study of them was made.

The present work was undertaken in order to devise preparative methods for as many of the pure polyethylbenzenes as possible. It has been found that the ethylation of benzene by ethyl chloride and aluminum chloride occurs quite as readily as does the corresponding methylation, and that it is easily possible to control the alkylation so that the major portion of the product will consist of any desired polyethylbenzenes from tri- to hexa-ethylbenzenes. Moreover, the generalizations with regard to the isomers formed, established in the case of methylations, also hold for the ethylations, namely, that all of the isomers result except the vicinal ones. Thus the triethylbenzene fraction contains no 1,2,3-triethylbenzene, but does contain the other two isomers; the tetraethylbenzene fraction contains no 1,2,3,4-tetraethylbenzene, but the other two isomers are present. Norris and Rubinstein[7] reported that their triethylbenzene fraction consisted only of the 1,3,5-isomer. They used ethyl bromide, while ethyl chloride was used in this work. However, it does not seem likely that the difference in the halide used could account for the complete absence of the 1,2,4-isomer in one case and not in the other. In view of the known orientation effects of alkyl groups, and the peculiar orientations which result when alkylbenzenes are rearranged by aluminum chloride,[17] it is more likely that the absence of the 1,2,4-isomer in the experiments of Norris and Rubinstein was due, not so much to its non-formation as to its rearrangement to the 1,3,5-isomer when in prolonged contact with aluminum chloride.

Good yields of polyethylbenzenes were obtained by passing ethyl chloride into a suspension of aluminum chloride (1.5 moles) in benzene (11.27 moles, 1000 cc.) at 70–75° and at a rate of 2.17 to 2.4 moles per hour. Practically all of the ethyl chloride reacted under these conditions, and the amounts of the different ethylation stages depended upon the amount of ethyl chloride introduced. Using 25–28 moles of the halide, the yield of the polyethylbenzenes was 80–85%, of which 70–75% was triethylbenzenes. When the amount of ethyl chloride was increased to 35

(1) XXVI, THIS JOURNAL, **62**, 1349 (1940). The series, started as "Polymethylbenzenes," will be continued henceforth under the more general term "Polyalkylbenzenes."

(2) Abstracted from a thesis by Cyrus O. Guss, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, January, 1940.

(3) Klages, *J. prakt. Chem.*, [2] **65**, 394 (1902).

(4) Gustavson, *ibid.*, [2] **68**, 209 (1903).

(5) Sollscher, *Ber.*, **15**, 1680 (1882).

(6) Wertyporoch and Firla, *Ann.*, **500**, 287 (1933).

(7) Norris and Rubinstein, THIS JOURNAL, **61**, 1163 (1939).

(8) Gattermann, Fritz and Beck, *Ber.*, **32**, 1122 (1899).

(9) Balsohn, *Bull. soc. chim.*, **31**, 540, 635 (1879).

(10) (a) Milligan and Reid, THIS JOURNAL, **44**, 206 (1922); (b) Berry and Reid, *ibid.*, **49**, 3142 (1927); (c) Cline and Reid, *ibid.*, **49**, 3150 (1927); (d) Copenhaver and Reid, *ibid.*, **49**, 3157 (1927).

(11) Norris and Ingraham, *ibid.*, **60**, 1422 (1938).

(12) Norris and Sturgis, *ibid.*, **61**, 1414 (1939).

(13) Ipatieff, Pines and Komarewsky, *Ind. Eng. Chem.*, **28**, 222 (1936).

(14) Malishev, THIS JOURNAL, **57**, 883 (1935).

(15) Wertyporoch, Kowaski and Roeske, *Ber.*, **66**, 1232 (1933).

(16) Grosse and Ipatieff, *J. Org. Chem.*, **1**, 559 (1937).

(17) Nightingale, *Chem. Rev.*, **25**, 329 (1939).