hydroxypropyl)-piperidine, 0.1 ml. of acetic acid and 200 ml. of benzene was refluxed for three hours using a water-trap (3.4 ml. of water collected). Distillation gave 42.0 g. (91%) of product, b. p. 93° at 0.04 mm., $n^{25}D$ 1.5433.

Anal. Calcd for $C_{15}H_{21}NO$: N, 6.06. Found: N, 6.11.

2-(3-Hydroxypropyl)-1-(1,2-diphenylethyl)-piperidine Hydrochloride.—To a solution of benzylmagnesium chloride (1 mole) was added 57.8 g. of 2-phenyl-3,4-tetramethylenehexahydro-1,3-oxazepine dissolved in dry ether. After stirring and refluxing for four hours it was poured into ice and 250 ml. of concentrated hydrochloric acid. The ether layer was separated and discarded. The water layer was treated with enough sodium hydroxide solution to liberate the amine. The amine was extracted with ether and the extracts were dried over potassium carbonate. The hydrochloride was precipitated with gaseous hydrogen chloride as a hygroscopic, gummy material. After boiling with methyl ethyl ketone and cooling, it gave 29 g. of white crystals, m. p. 185–188°. Recrystallization gave 25 g. of pure product, m. p. 188–191°.

Anal. Calcd. for $C_{22}H_{29}NO\cdot HCl$: Cl, 9.85. Found: Cl, 9.82.

N-(1,2-Diphenylethyl)-piperidine Hydrochloride.—The preferred method of preparation of this compound was by the treatment of α-piperidylphenylacetonitrile with benzylmagnesium chloride (Tables I and II). Two alternatives are described below:

(a) **Alkylation.**—1,2-Diphenylethyl bromide (44 g. prepared by treating 1,2-diphenylethanol with phosphorus tribromide at 0 to 10°) was allowed to react with 30 g. of piperidine in 50 ml. of alcohol for one month at room temperature. The stilbene was removed (approx. 24 g.) and the product obtained weighed 3.8 g., m. p. 207–208.5°. This product appeared to be identical with that of Christiaen (*loc. cit.*), m. p. 120°. When Christiaen's procedure was followed, the product obtained melted low until it was vacuum-dried at 76°, after which it melted at the higher temperature and gave no mixed melting point depression (probably polymorphic forms). As noted in Table II this compound also melts at 158°.

(b) **From Benzaldipiperidine.**[7]—To a solution of benzylmagnesium chloride (1 mole) in ether was added 64.5 g. of benzaldipiperidine. The mixture was stirred and refluxed four hours and then poured into ice and 250 ml. of concentrated hydrochloric acid. After standing overnight at +5° the mixture was filtered to give 14 g. of white crystals of N-(1,2-diphenylethyl)-piperidine hydrochloride, m. p. 207–209°, which gave no mixed melting point depression with the material prepared by the other methods.

N-(1,2-Diphenylethyl)-4-methylpiperidine Hydrochloride. (a) **From Benzaldi-γ-pipecoline.**—A mixture of 26.5 g. of benzaldehyde, 50 g. of γ-pipecoline and 250 ml. of benzene was refluxed using a water-trap for four hours (8.5 ml. of water was collected). Since this product could not be made to crystallize and since these compounds cannot be distilled by conventional means without decomposition, this impure intermediate, benzaldi-γ-pipecoline, was added directly to benzylmagnesium chloride (1 mole) in ether. The ether was replaced with benzene and the mixture was heated to 80° for two hours. It was then poured into ice and concentrated hydrochloric acid. The amine was separated from the aqueous layer and precipitated from ether solution as its hydrochloride; yield, 17.5 g. Crystallization from methyl ethyl ketone containing a few drops of water gave 10.5 g., m. p. 230.5–231.5.

Anal. Calcd. for $C_{20}H_{25}N\cdot HCl$: Cl, 11.23. Found: Cl, 11.27.

(b) **From α-(4-Methylpiperidyl)-phenylacetonitrile.**—To a solution of benzylmagnesium chloride (0.5 mole) in ether was added 53.6 g. of α-(4-methylpiperidyl)-phenylacetonitrile. The mixture was refluxed for three hours, then poured onto ice and 100 ml. of concd. hydrochloric acid; yield of crystalline product 56.5 g. Recrystallization from methyl ethyl ketone containing a little alcohol, yielded 34 g. of amine hydrochloride, m. p. 228–230°, identical with the preparation described above.

(7) Laun, *Ber.*, **17**, 678 (1884).

Summary

Diphenylethylamines having a tertiary nitrogen atom have been prepared by the addition of benzylmagnesium chloride to: (a) α-aminophenylacetonitriles, (b) 3-substituted 2-aryloxazolidines and (c) benzaldipiperidines.

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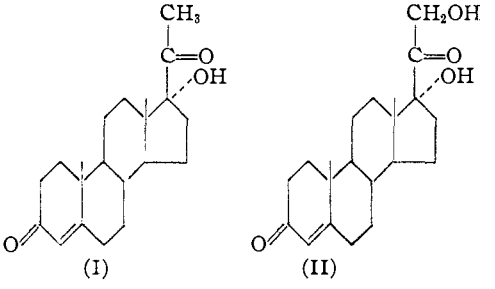
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. IX. The Selective Halogenation and Dehalogenation of Certain Steroids (Part 1)

BY PERCY L. JULIAN* AND WILLIAM J. KARPEL

The broad program, planned in this Laboratory several years ago, on the large-scale preparation of 17-hydroxysteroids, included as first objectives the preparation of what have now come to be designated 17α-hydroxyprogesterone (I) and 17-α-hydroxy-11-desoxycorticosterone (II). It appeared to us that, if the hurdles involved in the large-scale preparations of these 17α-hydroxysteroids could be successfully overcome, a significant part of the groundwork for the commercial preparation of substances like Kendall's Compound E and related cortical hormones would have been laid.

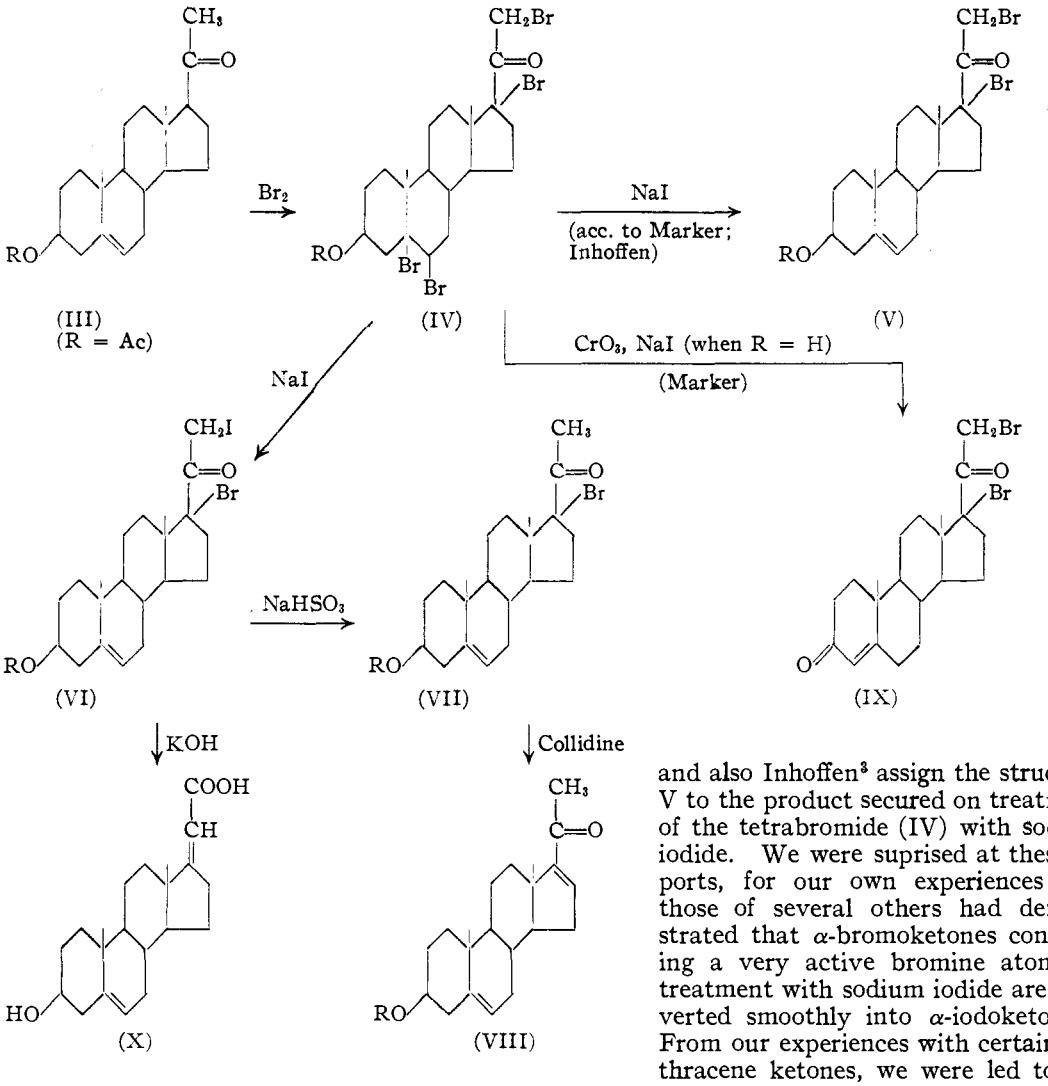
For our proposed preparation of 17α-hydroxyprogesterone (I) and related substances, we desired a clean-cut route to 17-bromopregnenolones (VII) or pregnanolones, as precursors for the corresponding 16-dehydro-derivatives (VIII).[1] No such clean-cut route is discernible in the



(I) (II)

* Harvard University A.M. 1923.

(1) Julian, Meyer and Ryden, THIS JOURNAL, **71**, 756 (1949).



literature up to the present, despite the numerous investigations. The yields of pure 17-bromopregnenolones and pregnanolones are for the most part too poor if these substances are to be used as starting material for economical synthesis of adrenal cortical hormones.[2]

Our studies began with the bromination of 5-pregnen-3β-ol-20-one or the acetate (III) as reported by Marker and his co-workers. If the pregnenolone is pure, a yield of over 80% of crystalline tetrabromide (IV) can be separated. Most of the remainder can be recovered as pregnenolone acetate by debromination of the mother liquors with zinc dust. Thus, in our hands, this reaction has been made almost quantitative.

The story is not quite so simple with respect to the selective dehalogenation of the tetrabromide (IV). Marker and his co-workers[2] and also Inhoffen[3] assign the structure V to the product secured on treatment of the tetrabromide (IV) with sodium iodide. We were suprised at these reports, for our own experiences and those of several others had demonstrated that α-bromoketones containing a very active bromine atom on treatment with sodium iodide are converted smoothly into α-iodoketones.[4] From our experiences with certain anthracene ketones, we were led to believe that such replacement does not take place rapidly when the bromine atom is tertiary and attached to a ring carbon atom. We were, therefore, of the opinion that both Marker and Inhoffen were in error and that certainly Inhoffen's product, reputed to have the structure V, is actually 17-bromo-21-iodo-5-pregnen-3β-ol-20-one acetate (VI). Indeed, this view was further strengthened by the fact that even brominated allyl derivatives like 7-bromocholesteryl acetate are converted into the corresponding 7-iodo-derivatives by treatment with sodium iodide at room temperature.[5] Moreover, ethyl ω-bromo-*o*-toluate in acetone solution, on treatment with

(2) Marker (with Crooks, Jones, Shabica, Wagner, and Wittbecker), THIS JOURNAL, **64**, 210, 1276, 2090 (1942); Plattner, Heusser and Boyce, *Helv. Chim. Acta*, **31**, 603 (1948); Koechlin and Reichstein, *ibid.*, **27**, 562 (1944); *cf.* Djerassi and Scholz. *J. Org. Chem.*, **14**, 661 (1949).

(3) Inhoffen, U. S. Patent 2,409,043 (1946).

(4) See several examples in experimental portion; also *cf.* Conant and Kirner, THIS JOURNAL, **46**, 232 (1924); Conant, Kirner and Hussey, *ibid.*, **47**, 488 (1925); Blicke, Faust, Gearien and Warzynski, *ibid.*, **65**, 2465 (1943); Hurd and Perletz, *ibid.*, **68**, 38 (1946); Ercoli and D'Alò, *Farmaco sci. e teç.*, **1**, 313 (1946); Rheinboldt and Perrier, THIS JOURNAL, **69**, 3148 (1947).

(5) Unpublished results from this laboratory; also *cf.* Bide, Henbest, Jones and Wilkinson, *J. Chem. Soc.*, 1792 (1948).

sodium iodide, gives ethyl ω-iodo-*o*-toluate.[6]

Repetition of the work of Inhoffen[3] confirmed our views and showed that his 149° melting compound is actually impure VI and not V, the purity of the compound having been impaired by the high temperature reaction with sodium iodide, for VI, though considerably more stable than 21-iodopregnenolone acetate, is, nevertheless, destroyed to a great extent by refluxing for any extended period with sodium iodide in benzene–ethanol. When pure, it melts at 157–158° (dec.). By the same token the structure of the compound IX reported by Marker and Crooks is also in error.[7] Moreover, even when the theoretically required amount of sodium iodide to restore the 5,6-double bond is employed, as Marker did, replacement of bromine by iodine at C–21 competes with replacement at the 5,6-position so that the resulting product is quite a mixture. Under proper conditions an excellent yield of the 17-bromo-21-iodo-compound is obtained, and this product gives practically a quantitative yield of acid (X) in the Favorskii rearrangement.

For our own first objective, namely, that of securing pure 17-bromo-pregnenolone acetate (VII), the discovery of the replacement of the bromine atom at C–21 by iodine was most fortunate, since we were soon able to demonstrate that this iodine atom in its turn was quantitatively replaced by hydrogen on shaking an ethereal solution of the 17-bromo-21-iodo-product (VI) with an aqueous solution of sodium bisulfite. This reaction makes possible the preparation of pure 17-bromo-pregnenolone acetate (VII) from the tetrabromo-compound (IV) and enables one to test the accuracy of Plattner's assumption[2] that his 17-bromo-product contained approximately 10% of the 17,21-dibromo-compound, since treatment with sodium iodide, followed by bisulfite, should give pure 17-bromo-allopregnanolone.

This reductive replacement of iodine in α-iodoketones by hydrogen, using sodium bisulfite, is a most intriguing reaction. When an ethereal solution of the α-iodoketone is brought into contact with an aqueous solution of the bisulfite, the color of iodine appears in the ether layer. On shaking or stirring for a short time this color is discharged, only to reappear when shaking ceases. The reaction is over when the color of iodine no longer appears in the ether phase. We hope to report later on a study of the kinetics and mechanism of this reaction.

The reaction involving replacement of bromine by iodine serves also as an interesting tool for knowledge as to the relative reactivity of bromine atoms in α-bromoketones. While our study is by no means complete, we are able at this time to report some interesting similarities and differences. Thus 5,6,23-tribromo-3β-acetoxycholanophenone is converted smoothly into the corresponding α-iodocholenophenone on treatment with sodium iodide in ethanol–benzene. Likewise 23-bromo-desoxycholophenone and α-bromo-α-benzylacetophenone are converted into the corresponding α-iodoketones. Each of these iodoketones is quantitatively reduced to the parent ketone on treatment with sodium bisulfite as described above. On the other hand, 4-bromopregnandione is inert toward sodium iodide in benzene–ethanol solution.[8]

Finally more light has been thrown on the bromination of pregnenolones and pregnanolones by isolation of what we believe to be 17,21,21-tribromo-derivatives. In attempts to secure 17,21-dihalogenated compounds, whether in the 5,6-unsaturated series or in the corresponding saturated derivatives, one always secures some of the 17,21,21-tribromo-compounds. The tendency toward the formation of such a derivative is reduced in the case of the 5,6-unsaturated compounds because of the relative insolubility of the tetrabromo-compound and its ready separation from the reaction mixture. This probably explains why one secures much more of the 17,21,-21-tribromopregnanolone in the saturated series than in the Δ^5 series. Elevated temperatures seem to favor formation of the tribromo compounds. Their separation and identification are based upon the fact that they are high melting and rather difficultly soluble.

The chemistry of these 17,21,21-dibromopregnanolones is reserved for later treatment. Their formation undoubtedly explains why the reaction between 3.2 moles of bromine and one mole of 3α,12α-diacetoxypregnanone-20 afforded Koechlin and Reichstein[2] such poor specimens of their desired 17,21-dibromo-derivative, the majority of their material consisting of the 17,21,21-tribromo-compound.

The clarification of the chemistry of the selective halogenation of pregnenolones and pregnanolones and the subsequent selective dehalogenation of their derivatives, recorded in this paper, has made it possible for us to secure the 17-bromo-derivatives in good yield and a high degree of purity. While the bromination of the pregnanolones saturated at the 5,6-position deserves separate treatment and will be discussed more fully in a later communication, it can now be stated that in most instances the 17-bromo-pregnanolone is always contaminated by both the 17,21-dibromo- and the 17,21-tribromo-derivatives, and precautions must be taken to remove these if reasonably pure 17-bromopregnanolone is to be secured.

With a procedure for preparing pure 17-bromo-5-pregnen-3β-ol-20-one acetate (VII) in good yield, we have been able to secure therefrom the desired 5,16-pregnadien-3β-ol-20-one acetate (VIII) in yields of 75% of theory by dehydro-

(6) Davies and Perkin, *J. Chem. Soc.*, 2202 (1922).

(7) Marker and Crooks, U. S. Patent 2,369,065 (1945) (Claim 18).

(8) *Cf.* Conant, *et al.*, ref. 4.

halogenation with collidine at elevated temperatures.

Experimental

17-Bromo-21-iodo-5-pregnen-3β-ol-20-one Acetate (VI).—A solution of 96.4 g. of pregnenolone acetate in 1900 cc. of glacial acetic acid was treated with one molar equivalent of bromine in acetic acid at 20°, followed by 1 cc. of 32% hydrobromic acid in acetic acid and then slowly with two molar equivalents of bromine in acetic acid at room temperature. After the addition of bromine was completed, the mixture was held at 35° for fifteen minutes to complete the reaction, and then cooled to room temperature, filtered and washed with ether. The yield of 5,6,17,21-tetrabromopregnan-3β-ol-20-one acetate was 151.3 g., m. p. 176–177°, dec.

Anal. Calcd. for $C_{23}H_{32}O_3Br_4$: C, 40.85; H, 4.77. Found: C, 40.43; H, 4.85.

A solution of 17.0 g. of 5,6,17,21-tetrabromopregnan-3-β-ol-20-one acetate (IV) in 205 cc. of benzene was treated with a solution of 45 g. of sodium iodide in 205 cc. of absolute ethanol at room temperature for twenty-four hours. The reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with 1% sodium hydroxide solution to remove free iodine, then with water to neutrality and dried over sodium sulfate. Upon concentration of the solution *in vacuo* to a volume of 40 cc. and dilution with 80 cc. of warm methanol, there was obtained 10.3 g. of 17-bromo-21-iodo-5-pregnen-3β-ol-20-one acetate (VI), m. p. 158°, dec.

Anal. Calcd. for $C_{23}H_{33}O_3BrI$: C, 49.03; H, 5.74. Found: C, 48.83; H, 5.72.

Reduction of 17-Bromo-21-iodo-5-pregnen-3β-ol-20-one Acetate (VI) with Sodium Bisulfite.—A solution of 5.9 g. of 17-bromo-21-iodo-5-pregnen-3β-ol-20-one acetate in 50 cc. of benzene and 50 cc. of ether was shaken with 30 cc. of 10% sodium bisulfite solution. Free iodine was liberated in the ether–benzene layer, whereupon the mixture was shaken to remove the iodine. As iodine was again liberated the mixture was again shaken. This procedure was repeated until no more iodine was liberated. From fifteen to thirty minutes was required to complete the reduction. The ethereal solution was washed with 1% sodium carbonate solution, with water to neutrality and then dried over sodium sulfate. The solution was concentrated *in vacuo* to 10 cc. and diluted with 25 cc. of warm methanol. There was obtained 3.8 g. of 17-bromo-5-pregnen-3β-ol-20-one acetate (VII), m. p. 134–140°. Crystallization from methanol raised the melting point to 146–148°.

Anal. Calcd. for $C_{23}H_{33}O_3Br$: C, 63.15; H, 7.6. Found: C, 62.77; H, 7.48.

Direct Preparation of 17-bromo-5-pregnen-3β-ol-20-one Acetate (VII) from Tetrabromo Compound (IV).—A solution of 151.3 g. of 5,6,17,21-tetrabromopregnan-3β-ol-20-one acetate in 1800 cc. of benzene was treated with a solution of 400 g. of sodium iodide in 1800 cc. of absolute ethanol at room temperature for twenty-four hours. The reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with 1% sodium hydroxide solution to remove free iodine and then washed with water to neutrality. The ethereal solution was shaken with 300 cc. of 10% sodium bisulfite solution. Free iodine was liberated in the ether–benzene layer, whereupon the mixture was again shaken. This procedure was repeated until no more iodine was liberated. The ethereal solution was washed with 1% aqueous sodium carbonate solution, with water to neutrality and then dried over sodium sulfate. The solution was concentrated *in vacuo* to 150 cc. and diluted with 265 cc. of warm methanol. There was obtained 84 g. of crude 17-bromo-5-pregnen-3β-ol-20-one acetate, m. p. 133–139°.

5,6,17-Tribromopregnan-3β-ol-20-one Acetate.—A solution of 0.16 g. of bromine in 1 cc. of chloroform was added dropwise to a solution of 0.437 g. of 17-bromo-5-pregnen-3 β-ol-20-one acetate chilled in an ice-bath. The chloroform was removed *in vacuo* and the residue was crystallized from acetone–ligroin (b. p. 88–98°). There was obtained 0.37 g., m. p. 164–166°, dec.; and from the liquor upon further concentration an additional 0.12 g. was obtained, m. p. 160–164°, dec.

Repetition of Marker's Experiment on the Debromination of 5,6,17,21-Tetrabromopregnan-3β-ol-20-one Acetate with Two Molar Equivalents of Sodium Iodide.—A solution of 0.872 g. of sodium iodide (2.0 molar equivalents) in 20 cc. of ethanol was added to a boiling suspension of 2.9 g. of the tetrabromopregnanolone acetate in 300 cc. of ethanol and refluxed for one hour. The solution was cooled, diluted with water and extracted with ether. The ethereal solution was washed with 5% sodium thiosulfate solution to remove free iodine and then washed with water. The colorless, ethereal solution was divided into two equal parts. Part I was dried and concentrated *in vacuo* to 0.7 g. of solid residue which when crystallized from ether–methanol yielded 0.47 g., m. p. 100–110°. A portion of this material after fusion with sodium gave a qualitative test for iodine via the sodium nitrite technique. A portion was recrystallized three times from ether–methanol; it then melted at 148° and did not show a depression in melting point when admixed with 17-bromo-21-iodo-5-pregnen-3β-ol-20-one acetate.

Part II of the original ethereal solution was shaken with 10% sodium bisulfite solution. Free iodine was liberated in the ethereal layer. This was repeated three times until no more iodine was liberated. The solution was washed with 1% sodium carbonate solution, with water to neutrality, and then dried and concentrated to a solid residue which, upon crystallization from ether–methanol, yielded 0.33 g., m. p. 106–115°.

Repetition of Inhoffen's Experiment.—A solution of 1.0 g. of the tetrabromopregnanolone acetate in 30 cc. of benzene was treated with a solution of 0.8 g. of sodium iodide in 14 cc. of ethanol (3.6 mol.) and refluxed for two hours. The solution was cooled, diluted with water and extracted with ether, washed with sodium thiosulfate solution and then with water. Upon concentration *in vacuo* and crystallization from benzene–methanol, there was obtained 0.6 g. of material, m. p. 130–132°, dec. This, after three crystallizations from benzene–methanol, melted at 146° dec., and did not show a depression in melting point when admixed with 17-bromo-21-iodo-5-pregnen-3β-ol-20-one acetate. The optical rotation of this material is $[\alpha]^{28}D$ −53° (chloroform) and that of 17-bromo-21-iodo-5-pregnen-3β-ol-20-one acetate is $[\alpha]^{28}D$ −54° (chloroform).

Anal. Calcd. for $C_{23}H_{32}O_3BrI$: C, 49.03; H, 5.74. Found: C, 49.25; H, 5.69.

16-Allopregnen-3β-ol-20-one Acetate.—A solution of 2.5 g. of allopregnan-3β-ol-20-one acetate in 75 cc. of glacial acetic acid containing two drops of 32% hydrobromic acid was treated slowly at 25–30° with 15.4 cc. of a 1 *M* solution of bromine (2.2 molar equivalents) in acetic acid. After the solution had stood at 30° for fifteen minutes, water was added slowly until precipitation was complete. The crystalline mass was filtered, washed with water and dried. The crude bromination product was crystallized from acetone–methanol yielding 2.9 g., m. p. 165–170°.

To a solution of 3.0 g. of the thus formed 17,21-dibromoallopregnanolone acetate in 36 cc. of benzene was added a solution of 5.1 g. of sodium iodide in 36 cc. of ethanol and the mixture was allowed to stand at room temperature for twenty-four hours. The reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with 1% sodium hydroxide solution to remove free iodine, then washed with water to neutrality. The 17-bromo-21-iodo-allopregnan-3β-ol-20-one acetate, m. p. 136–138° dec., need not be isolated and can be reduced directly. The ethereal benzene solution was shaken with 20 cc. of 10% sodium bisulfite solution. Free iodine was liberated in the ether–benzene layer, whereupon the mixture was again shaken. The procedure was repeated until no more iodine was liberated. The solution was then

washed with 1% sodium carbonate solution, with water to neutrality and then dried and concentrated. The residue, upon recrystallization from ether, gave 0.9 g. of a tribromo-derivative, m. p. 197–199° dec., as a by-product.

Anal. Calcd. for $C_{23}H_{33}O_3Br_3$: C, 46.25; H, 5.57. Found: C, 46.51; H, 5.55.

From the liquor there was obtained 1.2 g., m. p. 112–115°, of 17-bromo-allopregnan-3β-ol-20-one acetate. Crystallization from methanol raised the melting point to 128°.

A solution of 0.4 g. of 17-bromo-allopregnan-3β-ol-20-one acetate in 4 cc. of collidine is refluxed for three hours. The cooled mixture was diluted with ether and extracted with 15% hydrochloric acid to remove collidine and then washed with water to neutrality. The ethereal solution was dried, concentrated and petroleum ether added. There was readily obtained 0.2 g. of 16-allopregnen-3β-ol-20-one acetate, m. p. 158°. After recrystallization from acetone, it melted at 162°.[9]

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.90; H, 9.55.

Removal of High-melting 17,21,21-Tribromo-5-pregnen-3β-ol-20-one Acetate.—One gram of crude 17-bromopregnenolone acetate was taken up in 5 cc. of hexane and allowed to crystallize at room temperature, whereupon 0.1 g. of hard prisms, m. p. 190°, separated.

Anal. Calcd. for $C_{23}H_{31}O_3Br_3$: C, 46.41; H, 5.25. Found: C, 46.64; H, 5.39.

The hexane liquor was concentrated and the residue, upon crystallization from methanol, yielded 0.8 g. of 17-bromo-5-pregnen-3β-ol-20-one acetate, m. p. 143°, and on recrystallization from benzene–methanol, it melted at 146–148°.

5,16-Pregnediene-3β-ol-20-one Acetate from 17-Bromo-5-pregnen-3β-ol-20-one Acetate (VIII).—A solution of 25 g. of 17-bromo-5-pregnen-3β-ol-20-one acetate in 100 cc. of collidine was refluxed for six hours. The cooled mixture was diluted with ether and extracted with 15% hydrochloric acid to remove the collidine and then washed with water to neutrality. The ethereal solution was dried over sodium sulfate and concentrated to the point of crystallization and then chilled and filtered. There was obtained 15.2 g. of 5,16-pregnadiene-3β-ol-20-one acetate, m. p. 172–174°.[10] Recrystallization from acetone raised the melting point to 175–177°.

23-Iodo-3α,12α-diacetoxy-*nor*-cholanyl Phenyl Ketone.—To a solution of 1 g. of 23-bromo-3α,12α-diacetoxy-*nor*cholanyl phenyl ketone[11] in 13 cc. of benzene, a solution of 0.9 g. of sodium iodide in 6 cc. of ethanol was added. The mixture was allowed to stand at room temperature for twenty-four hours. The solution was then diluted with water, extracted with ether, and the ether freed from iodine by washing with 5% sodium thiosulfate solution. The dried ether solution was concentrated *in vacuo* and the residue, upon crystallization from ether–petroleum ether, yielded 0.75 g. of the 23-iodoketone, m. p. 168–173°. Further recrystallization raised its melting point to 183–185°.

Anal. Calcd. for $C_{34}H_{47}O_5I$: C, 61.62; H, 7.15. Found: C, 61.74; H, 7.24.

An ethereal solution of the iodoketone was reduced in 85% yield to the parent ketone, 3α,12α-diacetoxycholanyl phenyl ketone,[11] m. p. 130° with sodium bisulfite solution essentially as described for other iodoketones already recorded.

23-Iodo-3β-acetoxy-5-*nor*-cholenyl Phenyl Ketone.—A solution of 1 g. of 3β-acetoxy-5-*nor*-cholenyl phenyl ketone in 3 cc. of chloroform was treated with 1 molar equivalent of bromine in chloroform at approximately 5°, followed by one drop of 48% hydrobromic acid and the addition of a second molar equivalent of bromine. The solvent was removed *in vacuo* and the residue triturated with methanol and filtered. Crystallization from methanol gave 1.5 g. of 3 β-acetoxy-5,6,23-tribromo*nor*cholanyl phenyl ketone, m. p. 169–170°.

Anal. Calcd. for $C_{32}H_{43}O_3Br_3$: C, 53.72; H, 6.06. Found: C, 53.30; H, 5.74.

The tribromo ketone was converted into 23-iodo-3β-acetoxy-5-*nor*-cholenyl phenyl ketone, m. p. 199° (from chloroform–methanol) in a manner similar to that described for the 5,6,17,21-tribromopregnanolone (IV).

Anal. Calcd. for $C_{32}H_{43}O_3I$: C, 63.77; H, 7.19. Found: C, 63.40; H, 7.16.

This iodoketone was reduced with sodium bisulfite to the parent ketone m. p. 156–158° in the manner described.

α-Iodobenzylacetophenone.—α-Bromobenzylacetophenone was converted into α-iodobenzylacetophenone with sodium iodide, essentially as described above, in 90% yield. The melting point upon recrystallization from alcohol was 78°.

Anal. Calcd. for $C_{15}H_{13}OI$: C, 53.59; H, 3.89. Found: C, 53.46; H, 3.91.

The iodoketone was converted into the parent ketone, benzylacetophenone, m. p. 73°, in the usual manner with sodium bisulfite.

Summary

1. The selective dehalogenation of 5,6,17,-21-tetrabromopregnan-3β-20-one acetate with sodium iodide leads to 17-bromo-21-iodo-5-pregnen-3β-ol-20-one acetate and not to 17,21-dibromo-5-pregnen-3β-ol-20-one acetate as claimed by Marker and Inhoffen.

2. 17-Bromo-21-iodo-5-pregnen-3β-ol-20-one acetate is cleanly reduced by sodium bisulfite to 17-bromo-5-pregnen-3β-ol-20-one acetate.

3. The replacement of bromine by iodine and subsequent replacement of the latter by hydrogen with sodium bisulfite is described for several α-bromoketones.

4. Bromination of pregnanolones leads not only to 17-bromo- and 17,21-dibromo-pregnanolones but also to 17,21,21-tribromopregnanolones, which latter can usually be separated by careful recrystallization.

5. The preparation in good yield of pure 17-bromo-pregnenolones and pregnanolones becomes feasible if judicious use is made of the above outlined facts. These 17-bromo-pregnanolones and pregnenolones thus prepared are suitable raw material for dehydrohalogenation to the corresponding Δ^{16}-derivatives.

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(9) Plattner, Ruzicka, Heusser and Angliker, *Helv. Chim. Acta*, **30**, 385 (1947).

(10) Goldberg and Aeschbacker, *ibid.*, **22**, 1185 (1939); Butenandt, Schmidt and Thomé, *Ber.*, **72**, 182 (1939); Marker, Wagner, Ulshafer, Wittbacker, Goldsmith and Ruof, THIS JOURNAL, **65**, 1199 (1943); Marker and Lopez, *ibid.*, **69**, 2380 (1947).

(11) Julian, Cole, Magnani and Meyer, *ibid.*, **67**, 1728 (1945).