The dye condensations are summarized in Table III. Unless otherwise stated, the components were refluxed together in the specified medium for the period indicated, and dye (D1-25) separated on cooling. The yield of crude, but washed, dye is given followed by the yield after one and two recrystallizations from the solvent indicated. All the dyes melted with decomposition.

Summary

1. The absorption maxima of vinylene homologous symmetrical cyanines show roughly constant differences of wave length of about 1000 Å. and such series may be termed non-convergent.

2. Many unsymmetrical cyanine series in which the two nuclei do not differ too greatly in basicity are similarly non-convergent, and the individual dyes do not show considerable deviations (between $\lambda_{max.}$ obsd. and the harmonic or the arithmetic mean of the values of $\lambda_{max.}$ of the parent dyes).

3. Beyond a certain limit, however, progressively increasing the imbalance of basicity between the nuclei of an unsymmetrical cyanine tends progressively to increase the deviation for a given chain length, and this deviation is the greater, the longer the polymethine chain joining the nuclei. A vinylene homologous series of this type shows progressively shorter vinylene shifts as the series is ascended and may be termed convergent. The degree of convergence is the greater for the first few members the greater the imbalance of basicity between the nuclei.

4. Introduction of the nitro group into the benzothiazole nucleus of a dye of the thia-4′-cyanine series (I → IV) gives rise to marked deviations, but the same substitution effected in a dye of the styryl series (XIV → XVI) results in a marked reduction of deviation, dyes of this type having previously been shown to give lower deviations the lower the basicity of the heterocyclic nitrogen.[4]

5. The deviation of a polymethine dye, and the degree of convergence of the vinylene homologous series of which it is a member, are determined by the degeneracy of the limiting resonance configurations. It is suggested that a classification of dyes may be based upon this latter property. In such a classification non-deviating dyes, members of non-converging series, appear to represent one limiting type in which degeneracy is complete. The polyene hydrocarbons may represent another limit in which non-degeneracy reaches a maximum. Between these extremes all gradations are possible.

ROCHESTER, N. Y. RECEIVED NOVEMBER 5, 1941

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

Sterols. CXXVII. 17-Bromopregnan-3(β)-ol-20-one*

BY RUSSELL E. MARKER, HARRY M. CROOKS, JR., AND R. B. WAGNER

While there has been rather extensive study of the bromination of steroids having a ketone group in the first or second ring,[1] there has been practically no work done on the halogenation of the 20-keto steroids. There has been a patent[2] on the haloform degradation of pregnan-20-one compounds to *etio*-cholanic acids. Reichstein[3] has prepared 21-halopregnan-20-one compounds but not by means of direct halogenation.

Ruzicka and Meldahl[4] reported the preparation of 17-bromo-5-pregnen-3(β)-ol-20-one acetate by phosphorus tribromide treatment of the corresponding 17-hydroxy compound, but since their starting material came from the boron fluoride-mercuric oxide hydration of 17-ethynyl-5-androstene-3,17-diol they were undoubtedly dealing with a compound of the so-called "D-homo" series[5] and not with a true pregnane type of compound. In a report of Butenandt[6] on 16-*allo*-pregnene compounds reference is made to a thesis of Masch at Danzig, 1938, describing the prepara-

* Original manuscript received March 26, 1941. Paper CXXVI, THIS JOURNAL, **64**, 180 (1942).

(1) Fieser, "Natural Products Related to Phenanthrene," 1937, p. 247–250, 402–404. Butenandt and co-workers, *Ber.*, **68**, 1850, 1854, 2091 (1935); **69**, 1158, 2289, 2779 (1936); **71**, 1681 (1938); **72**, 1614, 1617 (1939); **73**, 206 (1940). Heilbron and co-workers, *J. Chem. Soc.*, 801 (1937). Inhoffen and co-workers, *Ber.*, **69**, 1134, 1702, 2141 (1936); *Naturwiss.*, **25**, 125 (1937); *Ber.*, **70**, 1695 (1937); **71**, 1720 (1938); **72**, 1686 (1939); **73**, 451 (1940). Ruzicka and co-workers, *Helv. Chim. Acta*, **19**, 1147 (1936); **20**, 244 (1937).

(2) British Patent 493,055 to I. G. Farbenindustrie.

(3) Reichstein and co-workers, *Helv. Chim. Acta*, **20**, 1165 (1937); **22**, 1124 (1939); **23**, 658 (1940).

(4) Ruzicka and Meldahl, *Helv. Chim. Acta*, **22**, 421 (1939).

(5) Ruzicka, Gätzi and Reichstein, *ibid.*, **22**, 626 (1939).

(6) Butenandt, Mamoli and Heusser, *Ber.*, **72**, 1614 (1939).

tion of 16-pregnene-3,20-dione by means of 17-bromopregnan-3-ol-20-one, implying direct bromination of the hydroxy ketone but giving no experimental data or characteristics of the compounds.

It has been observed earlier by us[7] that the mono-bromination of pregnane-3,20-dione to obtain 4-bromopregnane-3,20-dione led, under virtually any conditions tried, to the formation as a by-product, in substantial and essentially constant quantity, of a bromo compound in which the halogen was of a tertiary nature. The most likely position for such a tertiary halogen is, of course, the 17. Faworskii's[8] thorough and extensive work on the halogenation of ketones in which a tertiary hydrogen was opposed by either primary or secondary hydrogens indicated that on the direct monobromination of 20-ketopregnane compounds the bromine should substitute almost exclusively at the ring α-carbon. With the present availability of the pregnane compounds[9] this project became feasible and mono-bromination has been found to occur at the 17-position in the pregnan-3(β)-ol-20-one series.

The mono-bromination of pregnan-3(β)-ol-20-one or its acetate in acetic acid solution led to formation of the 17-bromide in yields of 60–70%. The monobromide was stable under ordinary conditions but quite highly reactive, the bromine being replaced by hydrogen to reform the original configuration at C-17 of pregnanolone when treated with zinc or iron and acetic acid or upon reduction with hydrogen bromide readily to form 16-pregnen-3(β)-ol-20-one upon refluxing with pyridine. The 16-pregnen-3(β)-ol-20-one thus formed was reconvertible to pregnan-3(β)-ol-20-one by palladium–hydrogen reduction.

17-Bromopregnan-3(β)-ol-20-one was stable in acetic acid–chromic acid mixture and could be oxidized by such a mixture to obtain 17-bromopregnane-3,20-dione, in turn convertible either to pregnane-3,20-dione by reduction with hydrogen–palladium in the presence of pyridine or to 16-pregnene-3,20-dione by refluxing with pyridine. The 16-pregnene-3,20-dione thus formed could be reduced to pregnane-3,20-dione by zinc–acetic acid reduction.

It was surprising that 16-pregnene-3,20-dione could be reduced to pregnane-3,20-dione in good yields by the action of zinc and acetic acid. Windaus[10] showed that 4-cholestene-3,6-dione was reduced to the saturated dione by zinc–acetic acid where two keto groups were conjugated to the double bond. Butenandt[11] in the preparation of progesterone from pregnenolone noted that prolonged heating of 5,6-dibromopregnane-3,20-dione with zinc–acetic acid led to lower yields and isolated from the reaction 4-pregnen-20-one. In general, heating of a Δ^4-3-keto steroid with zinc and acetic acid has little effect on the system, *e. g.*, the preparation of cholestenone,[12] progesterone,[12] and testosterone.[12] The Δ^{16}-20-keto system is apparently more easily reduced to a saturated ketone than is the Δ^4-3-keto system.

The reactions have been summarized in the accompanying chart.

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

Experimental Part

Bromination of Pregnan-3(β)-ol-20-one Acetate.—A solution of 5 g. of pregnan-3(β)-ol-20-one acetate in 150 cc. of glacial acetic acid was warmed to 30°. Two drops of 48% hydrobromic acid was added and then 14.0 cc. of a 1 *M* solution of bromine in acetic acid in a dropwise manner. After standing for fifteen minutes the mixture was poured into water. The precipitated solid was extracted with ether and the ethereal extract was washed with water, 5% sodium bicarbonate solution and water. The ether was evaporated on the steam-bath and the residue was crystallized from methanol to give compact white crystals, m. p. 152–154°, yield 5.0 g.

Anal. Calcd. for $C_{23}H_{35}O_3Br$: C, 62.9; H, 8.0. Found: C, 63.0; H, 7.8.

Bromination of Pregnan-3(β)-ol-20-one.—To a solution of 1.0 g. of pregnan-3(β)-ol-20-one in 50 cc. of glacial acetic acid at 25° was added two drops of 48% hydrobromic acid and 3.13 cc. of a 1 *M* bromine solution in acetic acid was added slowly. The mixture was poured into water and the precipitated solid collected and washed with water. The material was crystallized from ether to give compact white crystals, m. p. 169–171°, yield 1.0 g.

Anal. Calcd. for $C_{21}H_{33}O_2Br$: C, 63.5; H, 8.4. Found: C, 63.1; H, 8.3.

Reduction of 17-Bromopregnan-3(β)-ol-20-one Acetate.—(a) With zinc and acetic acid. To a solution of 2 g. of 17-bromopregnan-3(β)-ol-20-one acetate in 50 cc. of glacial acetic acid was added 4 g. of zinc dust. The mixture was heated on a steam-bath for thirty minutes. The mixture was poured into water and extracted with ether. The ethereal extract was washed with water, 5% sodium bicar-

(7) Unpublished work in this Laboratory.

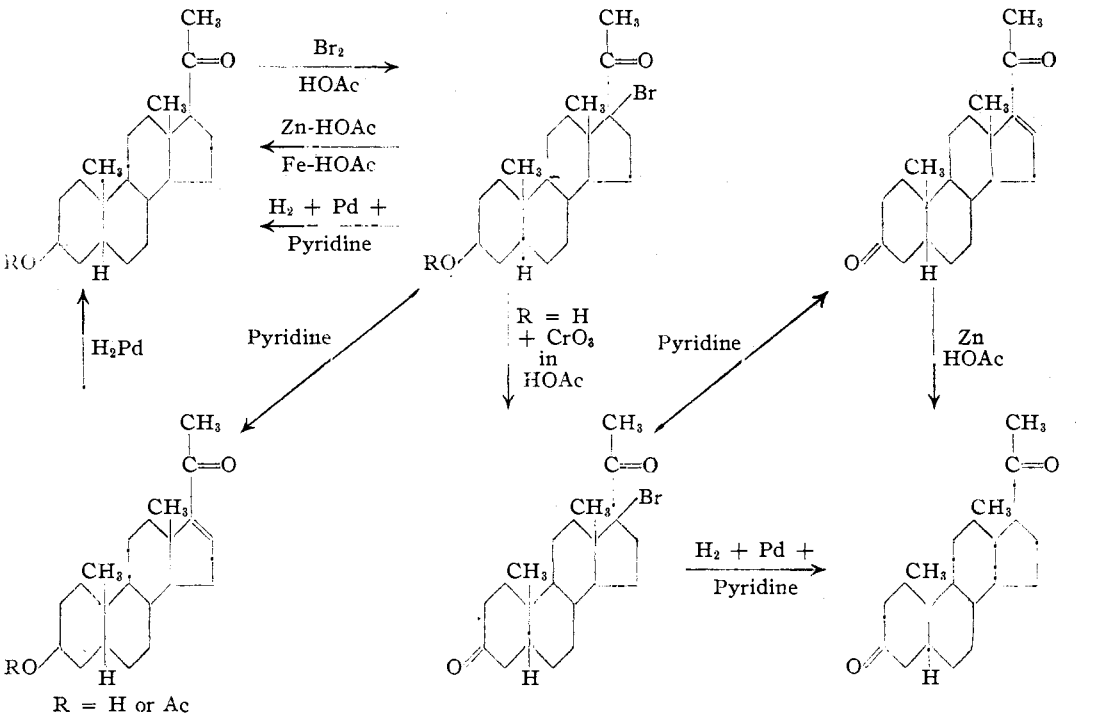
(8) Faworskii and co-workers, *J. Russ. Phys.-Chem. Soc.*, **44**, 1358 (1913); *J. prakt. Chem.*, **88**, 658 (1913).

(9) Marker and co-workers, THIS JOURNAL, **61**, 3592 (1939); **62**, 518, 648, 898, 2525, 2621, 3003, 3351 (1940).

(10) Windaus and co-workers, *Ber.*, **39**, 2249 (1906).

(11) Butenandt and co-workers, *ibid.*, **67**, 2085 (1934).

(12) Windaus, *Ber.*, **39**, 518 (1906); Schoenheimer, *J. Biol. Chem.*, **110**, 46 (1935); Butenandt and Hanisch, *Ber.*, **68**, 1859 (1935); Ruzicka and Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).



bonate solution and again with water. The ether was evaporated and the residue was crystallized from methanol to give white platelets, m. p. 119°, yield 1.3 g. This gave no depression in melting point with pregnan-3(β)-ol-20-one acetate, m. p. 118–120°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.7; H, 9.7.

(b) With iron and acetic acid. To a solution of 1 g. of 17-bromopregnan-3(β)-ol-20-one acetate in 50 cc. of glacial acetic acid heated on the steam-bath was added 2 g. of powdered iron (100 mesh). Heating was continued for two hours. The reaction mixture was filtered, poured into water and extracted with ether. The ethereal extract was washed free of acetic acid with dilute sodium carbonate solution and then treated with norite. The ether was evaporated and the residue was crystallized from methanol to give white plates, m. p. 119–120°, yield 0.6 g. This gave no depression with pregnan-3(β)-ol-20-one acetate, m. p. 118–120°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.4; H, 9.8.

(c) With palladium and pyridine. A mixture of 1 g. of 17-bromopregnan-3(β)-ol-20-one acetate, 3 cc. of dry distilled pyridine, 2 g. of 3% palladium–barium sulfate catalyst, 150 cc. of methanol and 50 cc. of ether was shaken with hydrogen at 4 atm. and room temperature for two hours. The reaction mixture was filtered and the filtrate was poured into water. The precipitated solid was extracted with ether and the ethereal solution was washed free of pyridine with 10% hydrochloric acid solution and with water. The ether was evaporated and the residue was crystallized from methanol to give white plates, m. p. 119°, yield 0.5 g. This gave no depression with pregnan-3(β)-ol-20-one acetate, m. p. 118–120°.

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

Reduction with palladium and hydrogen with no pyridine present resulted in recovery of the starting material.

Reduction of 17-Bromopregnan-3(β)-ol-20-one.—(a) With zinc and acetic acid. A mixture of 1.25 g. of 17-bromopregnan-3(β)-ol-20-one, 2.5 g. of zinc dust and 50 cc. of glacial acetic acid was heated on the steam-bath for thirty minutes. The reaction mixture was worked up in the usual manner to give compact white crystals from ethanol, m. p. 143–144°, yield 0.8 g., which gave no depression with pregnan-3(β)-ol-20-one, m. p. 144–145°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.5; H, 10.5.

(b) With palladium and pyridine. A mixture of 1 g. of 17-bromopregnan-3(β)-ol-20-one, 3 cc. of dry distilled pyridine, 2 g. of 3% palladium–barium sulfate catalyst, and 100 cc. of methanol was shaken with hydrogen at 3 atm. and room temperature for two hours. The reaction mixture was worked up in the usual manner to give compact white crystals from methanol, m. p. 144–146°, yield 0.6 g. This gave no depression with pregnan-3(β)-ol-20-one.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.4; H, 10.6.

Pyridine on 17-Bromopregnan-3(β)-ol-20-one Acetate.—A solution of 1 g. of 17-bromopregnan-3(β)-ol-20-one acetate in 25 cc. of dry distilled pyridine was refluxed for six hours. The reaction mixture was poured into water and the precipitated solid extracted with ether. The ethereal solution was washed free of pyridine with water and 10% hydrochloric acid solution and then washed with 5% sodium bicarbonate solution and water. The ether was evaporated on the steam-bath and the residue, after treat-

ment with Norit, was crystallized from methanol to give thick white needles, m. p. 141–142°, yield 0.6 g. This gave no depression with the acetate of 16-pregnen-3(β)-ol-20-one, m. p. 142–144°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.2; H, 9.7.

Pyridine on 17-Bromopregnan-3(β)-ol-20-one.—A solution of 1 g. of 17-bromopregnan-3(β)-ol-20-one in 50 cc. of dry distilled pyridine was refluxed for four hours. A white solid had separated at the end of this time. The reaction mixture was worked up in the usual manner to give compact white crystals from acetone, m. p. 169–172°, yield 0.6 g. This gave no depression when mixed with 16-pregnen-3(β)-ol-20-one, m. p. 170–171°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.4.

Treatment with boiling acetic anhydride gave the acetate, m. p. 143–145°, which gave no depression with the acetate of 16-pregnen-3(β)-ol-20-one.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.4; H, 9.3.

16-Pregnene-3,20-dione from 17-Bromopregnan-3(β)-ol-20-one.—To a solution of 2 g. of 17-bromopregnan-3(β)-ol-20-one in 80 cc. of acetic acid at room temperature was added a solution of 1 g. of chromic anhydride in 20 cc. of 90% acetic acid. After standing for forty-five minutes at room temperature, water was added and the product was extracted with ether, and washed free from acid with 5% sodium bicarbonate solution and water. No definite crystalline product was isolated. The entire product was dissolved in 15 cc. of dry distilled pyridine and refluxed for six hours. At the end of this time a solid had precipitated. The reaction mixture was poured into water and extracted with ether. The ethereal extract was washed free of pyridine with 10% hydrochloric acid and then washed with 5% sodium bicarbonate and water. After treatment with Norit, the ether was evaporated. The residue was crystallized from acetone to give white plates, m. p. 198–200°, yield 0.3 g. This did not depress the melting point of an authentic sample of 16-pregnene-3,20-dione.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.1; H, 9.6. Found: C, 80.0; H, 9.3.

Pregnane-3,20-dione from 17-Bromopregnan-3(β)-ol-20-one.—The non-crystalline product from the oxidation of 1 g. of 17-bromopregnan-3(β)-ol-20-one as described above was dissolved in 75 cc. of methanol. The solution was shaken with 2 g. of palladium–barium sulfate catalyst, 3 cc. of pyridine and hydrogen at 3 atm. and room temperature for three hours. The reaction mixture was filtered and the filtrate was poured into water. The precipitated solid was extracted with ether and the ether extract was washed with 10 per cent. hydrochloric acid and water. The ether was evaporated and the residue was crystallized from ethanol to give white crystals, m. p. 117–119°, yield 0.5 g. This gave no depression with an authentic sample of pregnane-3,20-dione, m. p. 118–120°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 9.9.

Zinc–Acetic Acid Reduction of 16-Pregnene-3,20-dione.—A mixture of 500 mg. of 16-pregnene-3,20-dione, 20 cc. of acetic acid and 1 g. of zinc dust was heated on a steam-bath for one hour. The reaction mixture was worked up in the usual manner and the product was crystallized from aqueous methanol, m. p. 118–120°. This did not depress the melting point of an authentic sample of pregnane-3,20-dione.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 80.0; H, 10.3.

Summary

17-Bromopregnan-3(β)-ol-20-one and its acetate have been prepared and some of their debromination reactions studied.

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

Sterols. CXXVIII. 17,21-Dibromopregnan-2(β)-ol-20-one and its Conversion to Pregnanol-3(β),21-diol-20-one*

BY RUSSELL E. MARKER, HARRY M. CROOKS, JR., AND R. B. WAGNER

The ease of mono-bromination[1] of pregnan-3(β)-ol-20-one opened up the possibility that if a dibromide could be as easily obtained it would offer a likely method of obtaining 21-hydroxy-20-ketosterols closely related to desoxycorticosterone. We have now prepared 17,21-dibromopregnan-3(β)-ol-20-one and studied some of its conversion products.

Pregnan-3(β)-ol-20-one or the acetate on direct dibromination in acetic acid solution gave a yield of 60% or more of 17,21-dibromide with or without the intermediate separation of the monobromide. That the formation of the dibromide was not attended by any rearrangement was shown by its ready reduction to the starting material by zinc or iron and acetic acid.

The position of the second bromine atom was proved as follows. Treatment of the dibromide with potassium acetate in acetic acid under mild conditions removed the less stable 17-bromine as hydrogen bromide to form 21-bromo-16-pregnen-3(β)-ol-20-one. The conjugation of the carbonyl

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(1) Marker, Crooks and Wagner, THIS JOURNAL, **64**, 210 (1942).