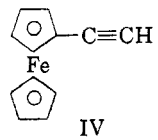
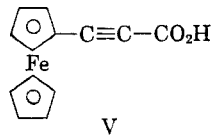
α,β-Dibromoethylferrocene (III) was prepared (74.5% yield) by adding bromine to vinylferrocene in pentane at −78°. The purified yellow solid melted to a yellow liquid at 63–64°. It was completely stable at −78°, but decomposed at room temperature. (*Anal.* Calcd. for $C_{12}H_{12}FeBr_2$: C, 38.78; H, 3.22; Fe, 15.00; Br, 43.00. Found: C, 39.23; H, 3.34; Fe, 15.03; Br, 42.50.)

When a pentane solution of this dibromide was added to potassium amide in liquid ammonia, an amber crystalline solid (29% conversion), melting at 54–55°, was obtained. The infrared spectrum of the amber solid showed a —C≡C—H band at 3.2 μ, a —C≡C— band at 4.8 μ, as well as bands at 9, 10 and 12.2 μ. The spectrum was devoid of olefinic absorption. (*Anal.* Calcd. for $C_{12}H_{10}Fe$: C, 68.56; H, 4.75; Fe, 26.60. Found: C, 68.84; H, 4.92; Fe, 26.41.)

Further evidence that this material was ferrocenylacetylene (IV) was obtained by treating it



IV



V

with methyllithium followed by carbonation with Dry Ice. A dark red crystalline solid was obtained (94% yield) melting with effervescence at 122°.

Its infrared spectrum showed a shifted —C≡C— band at 4.65 μ, a carboxyl peak at 6.05 μ, a broad shallow —OH region, and bands at 9, 10, and 12.2 μ, identifying the material as ferrocenylpropiolic acid (V). (*Anal.* Calcd. for $C_{13}H_{10}FeO_2$: C, 61.46; H, 3.97; Fe, 21.98. Found: C, 61.49; H, 4.20; Fe, 21.78.)

CHEMICAL LABORATORIES
PURDUE UNIVERSITY
LAFAYETTE, IND.

ROBERT A. BENKESER
WALTER P. FITZGERALD, JR.

Received May 26, 1961

Alkoxylation of Steroids with Cupric Bromide: Alcohol

Sir:

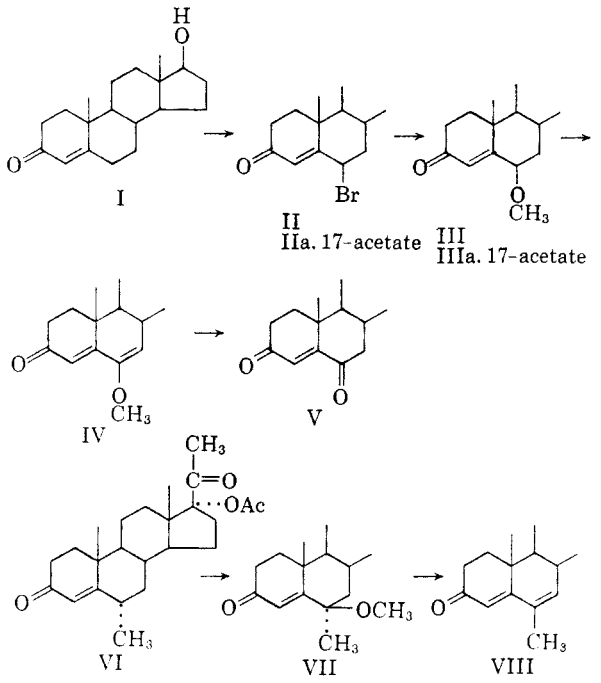
The halogenation of ketones with cupric halides has been reported by Kochi[1] and, very recently, by Fort.[2] While attempting to find more specific methods for the halogenation of steroids, we investigated the oxidation of steroids with cupric halides in alcohol in the presence and absence of pyridine. In most cases, 6-alkoxylation of the steroid resulted.

Treatment of 4-androstene-3,17-dione with two molar equivalents of cupric bromide and two molar equivalents of pyridine in methanol at reflux for thirty-five minutes yielded 6β-methoxy-4-androstene-3,17-dione, m.p. 164–166°; $\lambda_{max}^{Methanol}$ 233.5 mμ (ϵ 13,100); $[\alpha]_D$ +123° (chloroform); $\lambda_{max}^{CHCl_3}$ 5.72, 5.92, 6.18, 9.22 μ (found: C, 75.56; H, 8.95; OCH_3, 9.67). This material was identical in all respects with a sample of 6β-methoxy-4-androstene-3,17-dione prepared from 5α,6α-epoxy-3β-hydroxyandrostan-17-one *via* reaction with methanol, oxidation, and very mild dehydration.[3]

To provide evidence for the course of the reaction, a more thorough study was made on testosterone. Treatment of testosterone (I) with two molar equivalents of cupric bromide in methanol at 5° for seven days yielded 6β-methoxytestosterone (III) (35% yield), m.p. 210–214° [4]; $\lambda_{max}^{methanol}$ 235 mμ (ϵ 13,000); λ_{max}^{KBr} 2.87, 6.01, 9.18 μ $[\alpha]_D$ +45° (chloroform); (found: C, 75.60; H, 9.25). The use of four molar equivalents of cupric bromide with testosterone, under the above conditions yielded 6-methoxy-6-dehydrotestosterone (IV) (60% yield), m.p. 167–168°; $\lambda_{max}^{methanol}$ 248 mμ (ϵ 7580), 304 mμ (ϵ 14,900); (found: C, 75.57; H, 9.24; OCH_3, 9.83); 17-acetate, m.p. 161–162°; $\lambda_{max}^{methanol}$ 248.5 mμ (ϵ 7900), 303 mμ (ϵ 15,400); (found: C, 74.08: H, 8.27). Acid hydrolysis of IV acetate produced 6-oxotestosterone acetate (V), m.p. 209–211°, $\lambda_{max}^{CHCl_3}$ 5.75, 5.88, 7.94 μ, identical in all respects (mixed melting point and infrared spectra) with an authentic sample.[5] To investigate the possibility that bromination at C-6 could precede the introduction of the methoxy group, 6β-bromotestosterone acetate (IIa)[6] was heated under reflux in methanol with two molar equivalents of cupric bromide and five molar equivalents of pyridine. This reaction gave a 70% yield of 6β-methoxytestosterone acetate (IIIa). When the above reaction was run at room temperature in the absence of pyridine, 6-methoxy-6-dehydrotestosterone (IV) (70% yield) was obtained.

Oxidation of 6α - methyl - 17α - acetoxyprogesterone[7] (VI) with two molar equivalents of cupric bromide in methanol at 2°, produced 6β - methoxy - 6α - methyl - 17α - acetoxyprogesterone (VII) (50% yield), m.p. 207–212°; $\lambda_{max}^{methanol}$ 235.5 mμ (ϵ 13,500); (found: C, 72.06; H, 8.46). Compound VII was very easily demethoxylated with concentrated hydrochloric acid to the known

(1) J. K. Kochi, *J. Am. Chem. Soc.*, **77**, 5274 (1955).
(2) A. W. Fort, *J. Org. Chem.*, **26**, 765 (1961).
(3) We are indebted to Dr. Roy Bible of these laboratories for this sample.
(4) E. Kaspar, R. Weichert, and M. Schenck, Deutsches Patentamt Auslegeschrift **1,071,081**, June 20, 1958.
(5) A. Butenandt and B. Riegel, *Ber.*, **69**, 1163 (1936). See C. Amendolla, G. Rosenkranz, and F. Sondheimer [*J. Chem. Soc.*, 1226 (1954)] for the melting point of 6-oxotestosterone.
(6) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).
(7) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *J. Am. Chem. Soc.*, **80**, 2904 (1958).



6-dehydro-6-methyl-17α-acetoxyprogesterone.[8] In the Clauberg assay, when given orally, VII was approximately as active as Norlutin (17α-ethynyl-19-nortestosterone) as a progestational agent.[9]

In view of the above reactions, it seems probable that cupric bromide supplies bromine at low concentration[10] for the selective ionic bromination of the steroid at C-6, and that this bromide, in the presence of cupric bromide, is solvolyzed to the 6β-alkoxy compound.

G. D. SEARLE & Co. PAUL B. SOLLMAN
CHICAGO 80, ILL. R. M. DODSON

Received June 27, 1961

(8) H. J. Ringold, J. P. Ruelas, E. Batres and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959). R. M. Dodson and P. B. Sollman, U. S. Patent **2,891,079**, June 16, 1959.

(9) O. v. St. Whitelock, Editor-in-Chief, *New Steroid Compounds with Progestational Activity, Ann. N. Y. Acad. Sci.*, **71**, 479–806 (1958). C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954).

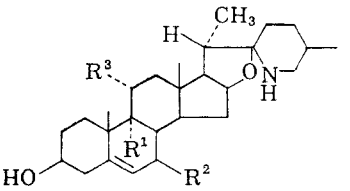
(10) J. W. Mellor, *Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. 3, p. 197. B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc.*, **80**, (1961).

Microbiological Hydroxylation of Steroidal Alkaloids

Sir:

The hydroxylation of steroids by microorganisms has been extensively applied to the C_{19} and C_{21} steroids of adrenal and sex hormonal origin.[1,2] More recently this technique has been extended to the cardiac lactones.[3,4] The steroidal sapogenins,[5] on the other hand, do not appear to hydroxylate readily.

The hydroxylation of the amino analogs of these sapogenins, the steroidal alkaloids solasodine and tomatidine, has not been reported so far. We wish now to report the microbiological hydroxylation of these alkaloids. The incubation of solasodine (I) (R^1, R^2, R^3 = H) with *Helicostylum piriforme* (A.T.C.C. 8992) resulted in the formation of 9α-hydroxysolasodine (II) (R^1 = OH; R^2, R^3 = H), m.p. 213–215°, $[\alpha]_D^{20}$ −138° (chloroform) (found: C, 75.38; H, 9.99) (yield *ca.* 27%); 11α-hydroxysolasodine (III) (R^3 = OH; R^1, R^2 = H) m.p. 200–203°, $[\alpha]_D^{20}$ −110° (chloroform) (found: C, 75.41; H, 10.41) (yield *ca.* 1%); 7ξ-hydroxysolasodine (IV) (R^2— = ~~OH; R^1, R^3 = H) m.p. 234–238° dec., $[\alpha]_D^{20}$ −82.4° (chloroform)



I. (R^1, R^2, R^3 = H)
II. (R^1 = OH; R^2, R^3 = H)
III. (R^3 = OH; R^1, R^2 = H)
IV. (R^2— = ~~OH; R^1, R^3 = H)
VI. (R^1, R^3 = H; R^2— = O=)

(found: C, 76.73; H, 10.58) (yield *ca.* 1%) and an unidentified dihydroxysolasodine (V), m.p. 256–259° dec., $[\alpha]_D^{20}$ −43.1° (ethanol) (found: C, 72.56; H, 10.02) (yield *ca.* 0.5%). The identity of II was established by its conversion to 9α-hydroxyprogesterone[6] by the degradative procedure previously reported from our laboratory.[7] Substance III was likewise identified as 11α-hydroxysolasodine by conversion into 11-oxo-16-dehydroprogesterone[8] and into 11α-hydroxyprogesterone[9] in an analogous manner. The structure of IV was deduced from the fact that it was very readily converted into the α,β-unsaturated carbonyl derivative, 7-oxosolasodine (VI) (R^1, R^3 = H; R^2— = O=) m.p. 188–191°, 238 mμ (log ϵ 3.95) by allylic oxidation with

(1) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progress in Hormone Research*, Vol. 11, Academic Press Inc., New York, 1955, p. 149.

(2) T. H. Stoudt, *Advances in Applied Microbiology*, Vol. 2, Academic Press Inc., New York, 1960, p. 183.

(3) A. Gubler and Ch. Tamm, *Helv. Chim. Acta*, **41**, 297, 301 (1958).

(4) Ch. Tamm and A. Gubler, *Helv. Chim. Acta*, **41**, 1762 (1958); **42**, 239, 473 (1959).

(5) R. F. Mininger, M. E. Wall, R. G. Dworshack, and R. W. Jackson, *Arch. Biochem. and Biophys.*, 60, 427 (1956).

(6) We thank Dr. J. Fried of the Squibb Institute, New Brunswick, N. J., for an authentic specimen of this compound.

(7) Y. Sato, N. Ikekawa, and E. Mosettig, *J. Org. Chem.*, **24**, 893 (1959).

(8) We wish to thank the Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda, Md., for providing us with an authentic specimen of this compound.

(9) D. H. Peterson and H. C. Murray, *J. Am. Chem. Soc.*, **74**, 1871 (1952).