derivative of VIII (free steroid) was obtained as an amorphous solid in the manner described above. Treatment with methyl iodide and potassium carbonate in acetone followed by reaction with sodium methoxide in methanol and finally hydrolysis in dilute methanolic sulfuric acid yielded after partition chromatography[4] 16$\alpha$,17$\alpha$,21-trihydroxy-2$\alpha$-methyl-4,9(11)-pregnadiene-3-20-dione, (Xa), m.p. 203–207, $[\alpha]^{25}D$ + 103° ($CHCl_3$); (*Anal.* Found: C, 70.75; H, 8.29). Acetylation afforded the 16$\alpha$,21-diacetate (Xb), m.p. 221.5–224°, $[\alpha]^{25}D$ + 104° ($CHCl_3$); (*Anal.* Found: C, 68.10; H, 7.53).

Addition of N-bromoacetamide and 10% perchloric acid to a solution of Xb in dioxane gave the bromohydrin XI as an amorphous solid, m.p. 131–134° which could not be purified. Treatment of XI with potassium acetate in acetone furnished the 9$\beta$,11$\beta$-epoxide XII, m.p. 222–223°, $[\alpha]^{25}D$ − 34° ($CHCl_3$); (*Anal.* Found: C, 65.57; H, 7.49). Hydrofluoric acid converted XII to 16$\alpha$,21-diacetoxy- 9$\alpha$ -fluoro -11$\beta$,17$\alpha$- dihydroxy- 2$\alpha$ -methyl-4-pregnene-3,20-dione (XIIIb), m.p. 140–200°[8], $\lambda_{max}$ 237–238 m$\mu$ ($\epsilon$ 16,300), $\upsilon_{max}^{KBr}$ 3420, 1740, 1732, 1725, 1660, 1627 (shoulder) and 1235 $cm^{-1}$; (*Anal.* F, 3.87. Found: F, 4.29). The corresponding 16$\alpha$,21-diol XIIIa formed from XIIIb by potassium hydroxide hydrolysis melted at 231–234° d., $\lambda_{max}$ 237–238 m$\mu$ ($\epsilon$ 15,100), $\upsilon_{max}^{KBr}$ 3450, 1720, 1660, and 1635 $cm.^{-1}$, $[\alpha]^{25}D$ + 115° (pyridine); (*Anal.* Found: C, 64.30; H, 7.66; F, 4.57).

**Bio-assays.**[9]—Preliminary assay (rat liver glycogen procedure) of 11$\beta$,16$\alpha$,17$\alpha$,21-tetrahydroxy-2$\alpha$-methyl-4-pregnene-3,20-dione (IVa) indicated definite activity (less than that of hydrocortisone); the 16$\alpha$,21-diacetate IVb and the 16$\alpha$,21-diacetoxy-11-one V were inactive. In the same assay, 9$\alpha$-fluoro - 11$\beta$,16$\alpha$,17$\alpha$,21 - tetrahydroxy - 2$\alpha$ - methyl-4-pregnene-3,20-dione (XIIIa), and its diacetate XIIIb were found to be at least two times as active as hydrocortisone.

In the rate electrolyte (sodium retention) assay, IVa, IVb and V were inactive. The 9$\alpha$-fluoro-compounds XIIIa and XIIIb exhibited minor activity (much less than that of desoxycorticosterone).

(9) The assays were done by L. Bortle, E. Heyder, J. Perrine, E. Ross, and I. Ringler (Experimental Therapeutics Research Section of these Laboratories).

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RECEIVED JULY 2, 1957

## STEROIDS. LXXXIX.[1] 19-NORDIHYDROTESTOSTERONE DERIVATIVES. A POTENT CLASS OF ANTI-ESTROGENIC COMPOUNDS.

*Sir:*

Following Birch's[2] synthesis of 19-nortestosterone (Ia) in 1949 a number of 19-nor analogs of the steroid hormones and metabolites have been prepared[3a–h] and many of these substances exhibited unusual biological activity.

We now wish to describe the synthesis of a new series of biologically active 19-nor compounds, namely, the 4,5-dihydroallo derivatives of nortestosterone and 17$\alpha$-alkyl substituted nortestosterones as well as the corresponding 3$\beta$,17$\beta$-diols.

While catalytic hydrogenation of Ia, Ib and Ic led to mixtures of the rings A/B *cis* and *trans* compounds, it was found that reduction of the unsaturated ketones in ether–dioxane solution with lithium in liquid ammonia[4] followed by ammonium chloride decomposition, furnished in excellent yield the dihydroallo derivatives: 19-norandrostan-17$\beta$-ol-3-one (IIa) (m.p. 130–132°, $[\alpha]D$ + 60°.[5] Found for $C_{18}H_{28}O_2$: C, 78.34; H, 9.94); 17$\alpha$-methyl-19-norandrostan-17$\beta$-ol-3-one (IIb) (m.p. 145–146°, $[\alpha]D$ +35°. Found for $C_{19}H_{30}O_2$: C, 78.49; H, 10.40); and 17$\alpha$-ethyl-19-norandrostan-17$\beta$-ol-3-one (IIc) (m.p. 212–213°, $[\alpha]D$ +33°. Found for $C_{20}H_{32}O_2$: C, 78.47; H, 10.49). Reduction of the 17-vinyl (Id) and the 17-ethynyl (Ie) compounds by this technique resulted in saturation of the 4,5-double bonds only, furnishing, respectively, 17$\alpha$-vinyl-19-norandrostan-17$\beta$-ol-3-one (IId) (m.p. 192–193°, $[\alpha]D$ +47°. Found for $C_{20}H_{30}O_2$: C, 79.18; H, 10.05) and 17$\alpha$-ethynyl-19-norandrostan-17$\beta$-ol-3-one (IIe) (m.p. 222–223°, $[\alpha]D$ +6°. Found for $C_{20}H_{28}O_2$: C, 80.30; H, 9.52). That the unsaturated side-chains had withstood the reduction conditions was demonstrated conclusively by the conversion of IIe to IId by partial hydrogenation (palladium on calcium carbonate–pyridine) and the derivation of IIc from either IId or IIe by reduction over palladium–carbon in methanol solution. The A/B allo configuration for compounds II which could be predicted on thermodynamic grounds,[6] is firmly established by the rotatory dispersion curves[7] of these dihydro compounds, the curves being virtually identical with that of androstan-17$\beta$-ol-3-one.

Treatment of IIa through IIe with sodium borohydride in aqueous dioxane gave the corresponding 19-norandrostan-3$\beta$,17$\beta$-diols: IIIa (m.p. 168–170°, $[\alpha]D$ +37°. Found for $C_{18}H_{30}O_2 \cdot 2C_3H_6O$: C, 72.88; H, 10.94); IIIb (m.p. 174–176°, $[\alpha]D$ ±0°. Found for $C_{19}H_{32}O_2.2C_3H_6O$: C, 73.76; H, 11.12); IIIc (m.p. 181–183°, $[\alpha]D$ +2°. Found for $C_{20}H_{34}O_2$: C, 78.20; H, 11.03[8]); IIId (m.p. 167–169°, $[\alpha]D$ +9°. Found for $C_{20}H_{32}O_2$: C,

(1) Paper LXXXVIII, J. Romo, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **79**, in press. (1957).

(2) A. J. Birch, *J. Chem. Soc.*, 367 (1950).

(3) (a) L. Miramontes, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3540 (1951); **75**, 4440 (1953); (b) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 4117 (1953); (c) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953); (d) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954); (e) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *ibid.*, **76**, 6210 (1954); (f) B. J. Magerlein and J. A. Hogg, *ibid.*, **79**, 1508 (1957); (g) F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *ibid.*, **79**, 1123 (1957); (h) F. B. Colton, U. S Patent 2,725,389 (1955).

(4) *Cf.* F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2695 (1952).

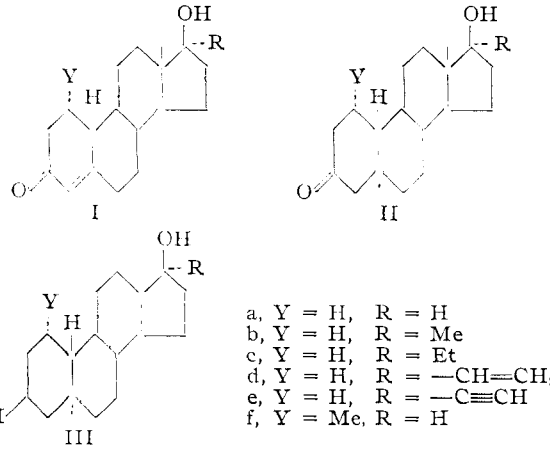
(5) All melting points are uncorrected and rotations were determined at 20° in chloroform. Thanks are due Mr. E. Denot for his able technical assistance and to Mr. E. Avila for rotations and spectra.

(6) See D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954), and references cited therein.

(7) We are grateful to Professor C. Djerassi, Wayne State University, for determination and comparison of rotatory dispersions.

(8) Analytical sample sublimed in high vacuum.

78.63; H, 10.71[8]); IIIe (m.p. 192–193°, $[\alpha]_D$ −15°. Found for $C_{20}H_{30}O_2$: C, 79.63; H, 9.84[8]).




a, Y = H, R = H
b, Y = H, R = Me
c, Y = H, R = Et
d, Y = H, R = —CH=CH$_2$
e, Y = H, R = —C≡CH
f, Y = Me, R = H

Similarly, 1α-methyl-19-nortestosterone (If)[9] was converted to the allo[7] compound, 1α-methyl-19-norandrostan-17β-ol-3-one (IIf) (m.p. 186–188°, $[\alpha]_D$ +46°. Found for $C_{19}H_{30}O_2$: C, 78.78; H, 9.94) and to the 3β,17β-diol (IIIf) (m.p. 204–206°, $[\alpha]_D$ +51°. Found for $C_{19}H_{32}O_2$: C, 77.55; H, 10.84).

This series of nordihydrotestosterone derivatives (II) and the diols (III) are potent anti-estrogens as measured by inhibition of the uterotrophic activity of estrone in the immature mouse.[10] Nordihydrotestosterone (IIa) exhibits about 8× the activity of 19-nortestosterone (Ia) in this assay (subcutaneous route) while the 17-alkyl compounds (*e.g.* IIb) are highly active by the oral as well as subcutaneous route. Clinical evaluation of some of these compounds in certain types of hormone dependent tumors has been initiated.

(9) H. J. Ringold, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 2477 (1956). For assignment of the 1α-configuration, see C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6377 (1956).

(10) Bioassays carried out at the Worcester Foundation for Experimental Biology under the direction of one of the authors (R. I. D.).

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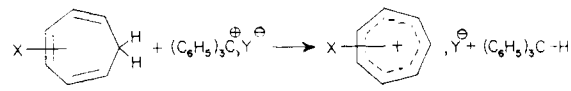
## SYNTHESIS OF TROPENIUM (CYCLOHEPTATRIENYLIUM) SALTS BY HYDRIDE EXCHANGE[1]

*Sir:*

The previously reported[2] novel method of synthesis of tropenium[3] perchlorate by hydride abstraction from cycloheptatriene by trityl perchlorate in acetonitrile has been found to be versatile and adaptable to the preparation of a number of tropenium salts containing various anions and/or nuclear substituents, some previously unknown or unavailable by other methods.




Hydride exchange reactions between cycloheptatrienes and trityl salts occur rapidly and quantitatively only in solvents which effect dissociation of these salts. In consonance with conductivity studies, trityl halides function satisfactorily as hydride abstractors in liquid sulfur dioxide but trityl perchlorate or fluoborate gives equally good results in acetonitrile or sulfur dioxide. Most tropenium salts may be prepared by the following general procedure (all reactants and conditions anhydrous): equivalent quantities of trityl salt and the cycloheptatriene[4] in acetonitrile (minimum amount) at room temperature or sulfur dioxide (30–50 ml./g. triene) at −20° or lower are allowed to react for a few minutes, all solvent then evaporated (acetonitrile *in vacuo;* sulfur dioxide by warming, finally *in vacuo*), triphenylmethane removed by trituration and extraction with ether from the tropenium salt product; pure perchlorate and fluoborate salts obtained by recrystallization from acetonitrile–ethyl acetate, halide salts by sublimation at 80–100° (1 mm.); yields of crude salts almost quantitative, of pure salts 60–90%. Tropenium salts prepared ($\lambda_{max}$ and $\epsilon_{max}$ in concd. sulfuric acid): (i) X = H, Y = $ClO_4$,[2] white, m.p. >300°, 217 mμ (41,000) and 273.5 mμ (4350)(ii, iii, iv, v show same spectrum), 44.03% C, 3.71% H; (ii) X = H, Y = $BF_4$,[5c] white, m.p. dec. slowly above 210°, 47.17% C, 3.59% H; (iii) X = H, Y = Cl,[5] white, 66.61% C, 5.56% H; (iv) X = H, Y = Br,[2,5] yellow, m.p. 203°; (v) X = H, Y = I,[5] red, m.p. 127°, readily transformed into tropenium triiodide, deep red-black, m.p. 127°, 292 mμ (39,800) and 361 mμ (22,100) in acetonitrile, 18.06% C, 1.51% H; (vi) X = Cl, Y = $ClO_4$, white, m.p. 164°, 237 mμ (29,800) and 310 mμ (8220), 37.37%, C 2.77% H, converted to tropone by water or ethanol[5b] (analogous preparation of bromide or iodide salts gives mixed halotropenium halides due to halogen interchange); (vii) X = Br, Y = $ClO_4$, white, m.p. 149.5°, 247 mμ (22,750) and 323 mμ (8900), 31.27% C, 1.89% H, converted to tropone by water or ethanol[5b]; (viii) X = MeO, Y = $ClO_4$, white, m.p. 107°, 234 mμ (32,100) and 315 mμ (10,050), 43.38% C, 4.34% H (similarly prepared bromide or iodide salts yield tropone and methyl bromide or iodide on warming); (ix) X = Me, Y = $ClO_4$,[5c] white, m.p. 109°, 226 mμ (37,100) and 288 mμ (3500), 46.89% C, 4.73% H (yellow bromide salt preparable in sulfur dioxide at −70° but decomposes on warming). Perchlorate and fluoborate salts, due to greater stability and non-hygroscopicity, are easier to handle than chloride (very hy-

(1) Supported in part by the Office of Ordnance Research, U. S. Army, Contracts DA-04-200-ORD-235 and 601.

(2) H. J. Dauben, Jr., and D. L. Pearson, Abstracts, 126th Meeting, American Chemical Society, New York, N. Y., Sept. 13, 1954, p. 18-O.

(3) Tropenium seems preferable to tropylium as the name for the $C_7H_7^{\oplus}$ ion because of its representation of all structural features of the ion and its consistency with benzenium, azulenium, etc., names for related carbonium ions.

(4) Substituted cycloheptatrienes prepared by the method of W. v. E. Doering and L. H. Knox, THIS JOURNAL, **75**, 297 (1953).

(5) Previously reported by: (a) Doering and Knox, *ibid.*, **76**, 3203 (1954); (b) W. v. E. Doering and H. Krauch, *Angew. Chem.*, **68**, 661 (1956); (c) M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 2021, 2026 (1956); the color, stability and spectrum reported for their methyltropenium bromide monohydrate are inconsistent with this structural assignment.