**N-Alkylation and N-Acylation of 1,3,5(10)-Estratrieno[17,16-c]pyrazoles. (a) [17,16-c]N-Methylpyrazoles. 3-Methoxy-1,3,5(10)-estratrieno[17,16-c]N-methylpyrazole (IId) from 3-Hydroxy-1,3,5(10)-estratrieno[17,16-c]pyrazole (IIa).**—To a stirred refluxing solution of 3-hydroxy-1,3,5(10)-estratrieno[17,-16-c]pyrazole (IIa, 1 g.) and potassium hydroxide (6 g.) in methanol (50 ml.) and water (10 ml.), was added dimethyl sulfate (1.0 ml.). After 30 min. another 1.0-ml. portion of dimethyl sulfate was added, and this operation was repeated twice more at 30 min. intervals (total volume of dimethyl sulfate used was 4 ml., total reaction time was 2 hr. under reflux). The reaction mixture was then concentrated to low volume, diluted with water, and left at room temperature overnight. The mixture was then extracted with methylene chloride, and the extract was washed with water and evaporated *in vacuo*. The solid residue was crystallized from aqueous methanol to give IId (740 mg.), identical in all respects with the compound obtained by the action of methylhydrazine on 16-hydroxymethylene estrone 3-methyl ether.

Similarly, 3-methoxy-1,3,5(10)-estratrieno[17,16-c]pyrazole (IIc) was N-methylated to IId, usingt he same procedure (dimethyl sulfate–potassium hydroxide).

**(b) 1,3,5(10)-Estratrieno[17,16-c]N-acetylpyrazoles.**—A solution of the steroidal [17,16-c]pyrazole (1.0 g.) in acetic anhydride (6 ml.) was heated at 95° for 3 hr. On cooling, the [17,16-c]-N-acetylpyrazole crystallized out, and was filtered off, dried, and recrystallized from acetone–hexane.

**3β-Hydroxy-5-androsteno[17,16-c]pyrazole (IVa).**—This compound was prepared from 16-hydroxymethylene-3β-hydroxy-5-androsten-17-one (10 g.) and hydrazine (10 g; 95%) in refluxing ethanol (300 ml.) for 3 hr. by the procedure outlined in b. The pure product (6.8 g.) had m.p. 256–259° dec.[9]; $[\alpha]_D$ −58, $\lambda_{max}^{MeOH}$ 222 mμ (6,300); $\lambda_{max}^{Nujol}$ 3.15, 6.00, 6.14, and 6.32 μ.

*Anal.* Calcd. for $C_{20}H_{28}N_2O$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.98; H, 9.17; N, 8.48.

**3β-Acetoxy-5-androsteno[17,16-c]N-acetylpyrazole (IVb).**—A solution of the foregoing pyrazole (IVa, 1 g.) in acetic anhydride (3.0 ml.) was heated at 95° for 1.5 hr. Evaporation to dryness gave a solid residue which was crystallized from aqueous methanol to furnish the pure N-acetylpyrazole (IVb, 880 mg.), m.p. 198–200°, $[\alpha]_D$ −60°, $\lambda_{max}^{MeOH}$ 255 mμ (ε 20,500); $\lambda_{max}^{Nujol}$ 5.75, 6.24, 6.62, and 8.00 μ.

*Anal.* Calcd. for $C_{24}H_{32}N_2O_3$: C, 72.69; H, 8.13; N, 7.07. Found: C, 72.93; H, 8.38; N, 7.35.

**3β-Hydroxy-5-androsteno[17,16-c]pyrazolium Chloride (IVa·HCl). (a).**—To a solution of 3β-hydroxy-5-androsteno[17,16-c]-pyrazole (IVa, 100 mg.) in methanol (15 ml.) was added concentrated hydrochloric acid (1.0 ml.), and the solution was left at room temperature overnight. Dilution with water and filtration gave the hydrochloride salt of IVa which was crystallized from aqueous methanol, to give material of m.p. 190–200° dec., $\lambda_{max}^{Nujol}$ 3.05, 3.85, 5.3, 6.38, and 6.55 μ.

*Anal.* Calcd. for $C_{20}H_{29}ClH_2O$: C, 68.84; H, 8.38; N, 8.03; Cl, 10.16. Found: C, 68.37; H, 8.00; N, 7.81; Cl, 10.17.

**(b)** A solution of the [17,16-c]pyrazole (IVa, 200 mg.) in ether (15 ml.) and dioxane (30 ml.) was stirred while a brisk stream of hydrogen chloride gas was bubbled through the solution. The precipitated hydrochloride salt was filtered, washed with ether, and dried to give material identical (m.p., m.m.p., infrared), with the compound prepared in a.

**3-Methoxy 1,3,5(10)-Estratrieno[17,16-c]pyrazolium Chloride.**—Dry HCl gas was bubbled through an ethereal solution (150 ml.) of 3-methoxy 1,3,5(10)-estratrieno[17,16-c]pyrazole (IIc, 1 g.) until a white precipitate formed. The mixture was filtered, and the solid was washed with ether and then crystallized twice from methanol to give the pyrazolium chloride (IIc·HCl, 200 mg.), m.p. 232–235°, $\lambda_{max}^{Nujol}$ 3.88, 6.22, 6.38, and 6.7 μ.

*Anal.* Calcd. for $C_{20}H_{33}ClN_2O$: C, 69.65; H, 7.31; N, 8.12; Cl, 10.28. Found: C, 69.43; H, 7.34; N, 8.38; Cl, 10.48.

**3-Hydroxy 1,3,5(10)-Estratrieno[17,16-c]pyrazolium Chloride.**—A solution of 3-hydroxy 1,3,5(10)-estratrieno[17,16-c]-pyrazole (IIa, 600 mg.) in methanol (90 ml.) containing concentrated HCl (6 ml.) was left at room temperature for 48 hr. Dilution with water gave a precipitate which was filtered, washed with water, and dried. Crystallization from methanol–water gave the pyrazolium chloride (IIa·HCl, 400 mg.), m.p. 303–309° dec.; $\lambda_{max}^{Nujol}$ 2.95, 3.18, 3.7, 5.3, 6.2, 6.35, 6.45, and 6.7 μ.

*Anal.* Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.97; H, 7.01; N, 8.47; Cl, 10.72. Found: C, 68.64; H, 7.38; N, 8.31; Cl, 10.99.

## Anesthetic Steroid Derivatives

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In connection with a study of water soluble derivatives of the anesthetic steroids, pregnan-3α-ol-20-one and pregnan-3α-ol-3,20-dione,[1] a number of functional derivatives were prepared which could revert to the parent compound *in vivo*. Two of the more interesting compounds in this series are described. The 3-phosphate ester of pregnan-3α-ol-20-one could conceivably be hydrolyzed to the parent sterol *in vivo*, since phosphate esters of 21-oxy steroids are known to possess the antiinflammatory activity of the parent steroid.[2] Likewise, 21-carboxypregnan-3α-ol-3,20-dione was prepared in the hope that the solubilizing carboxy group would be removed *in vivo* following intravenous administration of the sodium salt.

The phosphate ester of pregnanolone was prepared by addition of pregnanolone to phosphorus oxychloride to produce the dichlorophosphate. This in turn was hydrolyzed in dilute acid to the dihydrogen phosphate ester which fortunately could be separated by extraction from phosphoric acid.

The 21-carboxy derivative of 11-ketopregnanolone was obtained *via* the oxalyl derivative, isolated as the enolate following condensation of dimethyl oxalate with the steroid in the presence of dry sodium methoxide. Hydrogen peroxide cleavage of the keto ester gave the desired 21-carboxylic acid. The acid slowly lost carbon dioxide at room temperature and at the melting point was completely converted into 11-ketopregnanolone.

Intravenous administration of the 3-phosphate ester of pregnanolone to dogs at a dose of 10 mg./kg. produced no anesthesia. Similarly, administration of the freshly prepared sodium salt of 21-carboxy-11-keto pregnanolone at a dose of 10 mg./kg. (11-ketopregnanolone equivalent) resulted only in a transient sedation with no measurable anesthesia.[3]

### Experimental[4]

**21-Oxalylpregnan-3α-ol-11,20-dione.**—Sodium methoxide (2 *N*, 11 ml.) in methanol was added to 25 ml. of dry benzene and the solvent was removed *in vacuo*. Additional solvent was added followed by a second concentration and, finally, baking on a steam bath under vacuum. To the dry fluffy powder, 2.36 g. (0.02 mole) of freshly distilled dimethyl oxalate was added at room temperature. The mixture was heated with stirring to reflux and cooled, and then 3.32 g. (0.01 mole) of 11-ketopregnanolone in about 25 ml. of benzene was added portionwise at room temperature. Almost immediately a yellow gum precipitated. The reaction mixture was stirred for 2 hr. and then decanted, and the gum was washed with ether by decantation. Following drying *in vacuo*,

(1) For selected references on steroid anesthetics see: (a) H. Selye, *Proc. Soc. Exptl. Biol. Med.*, **46**, 116 (1941); (b) S. K. Figdor, M. J. Kodet, B. M. Bloom, E. G. Agnello, S. K. P'an, and G. D. Laubach, *J. Pharmacol. Exptl. Therap.*, **119**, 229 (1957).

(2) (a) G. I. Poos, R. Hirschmann, G. A. Bailey, F. Cutler, Jr., L. H. Sarett, and J. M. Chemerda, *Chem. Ind.* (London), 1260 (1958); (b) J. C. Melby and R. H. Silber, *Am. Practitioner Dig. Treat.*, **12**, 156 (1961).

(3) The authors are indebted to Dr. L. S. Watson of our Biological Research Laboratories for these results.

(4) Melting points were taken on a Kofler micro hot stage. The authors are indebted to Dr. N. R. Trenner and Mr. R. Walker for the infrared spectra and to Mr. R. Boos for the microanalyses.

the yellow granular solid (the sodium salt of the 21-oxalyl enolate) weighed 3.85 g. The ester enolate salt (3.5 g.) was saponified with 5 g. of KOH in 100 ml. of methanol at room temperature for 3 hr. The reaction mixture was then diluted with 2 ml. of ether to give a light yellow precipitate (1 g.). This salt was dissolved in a small amount of water and acidified with $N$ acetic acid to give 312 mg. of material, m.p. 222–228°. The product gave a red-brown ferric chloride test and its infrared spectrum (Nujol) showed broad bonded hydroxyl absorption at 3.8–4.6, carbonyl bands at 5.79, 5.92 and additional bands (enol?) at 6.12 with a shoulder at 6.25 μ.

**21-Carboxypregnan-3α-ol-11,20-dione.**—The oxalyl derivative (2 g.) was added to a solution of 800 mg. of potassium bicarbonate in 20 ml. of water. On cooling in ice a thick gel formed. To this gel was added with stirring 3 ml. of 30% hydrogen peroxide in three portions over a 10-min. period. After an additional 10 min. of stirring in the ice bath, when gas evolution had ceased, the reaction mixture was extracted well with several portions of ether to remove any neutral material. Then the aqueous layer from the extraction was made acid with 2 $N$ sulfuric acid and again extracted with ether to separate the acidic fraction. This was reextracted into 800 mg. of potassium bicarbonate, dissolved in 10 ml. of cold water, acidified with 2 $N$ sulfuric acid, and reextracted into ether. The ether extract was dried with magnesium sulfate, filtered, and concentrated in a dry stream of nitrogen at 20°. A first group of crystals (285 mg.) was obtained from a small residual volume of ether, m.p. 140–145° ($CO_2$ evolution). The Kofler block was slowly heated above the melting point, and crystallization occurred on the microscope slide with a second m.p. of 176–178°. This second melting point was not depressed on admixture with authentic 11-ketopregnanolone. Although good analytical data were difficult to obtain because of facile decarboxylation, analysis of the material agreed reasonably well with a hemihydrate.

*Anal.* Calcd. for $C_{22}H_{32}O_5 \cdot 0.5H_2O$: C, 68.6; H, 8.7. Found: C, 68.93; H, 8.53.

The infrared spectrum (Nujol) showed bands at 2.98 (hydroxyl), 3.8 (broad bonded hydroxyl), 5.77 (moderate), 5.92 (strong), and 6.1 (very strong) μ; ($[\alpha]^{25}D$ +103 (acetone)).

**Pregnan-3α-ol-20-one-3-phosphate Ester.**—Pregnanolone (0.5 g.) in 5 ml. of pyridine was added dropwise to a cool stirred solution of 1 ml. of phosphorus oxychloride in 10 ml. of pyridine. The ice in the bath was allowed to melt, and the reaction mixture was stirred overnight at room temperature. Then the reaction mixture was slowly poured with stirring into an acidified medium of cracked ice (approximately $N$ HCl). This reaction mixture was heated on a steam bath for approximately 1 hr. to complete hydrolysis of the residual chlorophosphate ester. The hydrolysate was then cooled in ice and extracted into ethyl acetate. The extract was washed with $N$ HCl, and dried over magnesium sulfate. Following concentration of the solution, 325 mg. of crystalline material was obtained, melting at 198–203°. Recrystallization from ethyl acetate sharpened the melting point to 196–198°. The infrared spectrum (Nujol) showed a broad band at 3.5–4.5 and a carbonyl band at 5.84 μ.

*Anal.* Calcd. for $C_{21}H_{35}O_5P$: P, 7.77. Found: P, 7.40.

Potentiometric titration in 20% methanol–water showed $pH_{1/2}$ 3.6 and pH 7.8 (equiv. for the former, 4.69, and the latter 4.32; theory 3.98). For comparison the $pH_{1/2}$ values for cortisone-21-phosphate are 3.0 and 7.1.

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## π-Complexes with Biologically Significant Materials. II.[1] Acetylergosterol Iron Tricarbonyl

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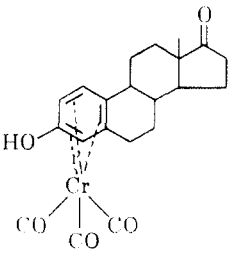
It is generally accepted that a trace amount of transition metals is essential in many biological systems. Many important enzymes contain certain transition metals. The problem of bonding of these metals to the enzymes or other biologically significant materials has attracted much interest. Recently, the possible significance of organometallic π-complexes in biological media has been pointed out by one of us.[2]

π-Complexes with transition metals sometimes are very stable and quite effective in certain reactions as catalysts. Therefore, the trace amount of transition metals in biological systems might be in the form of π-complexes. As the first step in the elucidation of the nature of bonding of transition metals in biological systems, we have prepared several organometallic π-complexes with biologically significant materials, for example, vitamins and hormones.[1]

We have reported the synthesis of a π-complex of the aromatic steroid hormone,[1] estrone, with a chromium tricarbonyl group 1. The three double bonds in the A ring of estrone are thought to be coordinated to the chromium forming a stable bond. On the other hand,

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conjugated diene systems have been found to form stable π-complexes with the iron tricarbonyl group. Therefore, the conjugated diene part of ergosterol can likewise form a stable π-complex with the iron tricarbonyl group. This paper describes a detailed account of the preparation of acetylergosterol iron tricarbonyl (II).

The reaction of acetylergosterol with triiron dodecacarbonyl in refluxing benzene gave a mixture of products, which was then separated by chromatography on alumina into two major fractions. The one fraction eluted with hexane gave colorless crystals of III in small yield. The crystals III were identified as 3,5-cyclo-$\Delta^{6,8(14),22}$-ergostatriene by a comparison of the infrared and ultraviolet spectra with those of an authentic sample.[3] The other fraction eluted with benzene gave a yellow solid. The solid was dissolved partly in methanol forming a yellow solution. A methanol-insoluble portion was almost colorless and found to be unchanged acetylergosterol by its infrared spectrum. The yellow methanol solution was evaporated to give yellow crystals II in 16% yield. Compound II was identified as acetylergosterol iron tricarbonyl by elemental analysis and by spectral evidence explained later.

The infrared spectrum of II has strong absorption peaks at 1950 and 2030 cm.$^{-1}$ due to the iron carbonyl group and a peak at 1730 cm.$^{-1}$ due to the acetyl group. The peaks due to the iron carbonyl group fall into regions generally known to be due to diene iron tricarbonyl complexes, near 1950 and 2030 cm.$^{-1}$.

(1) Part I: A. Nakamura and M. Tsutsui, *Z. Naturforsch.*, **18b**, in press.

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