Tetrahedron, 1967, Vol. 23, pp. 335 to 340. Pergamon Press Ltd. Printed in Northern Ireland

ACETYLATION AND TRIFLUOROACETYLATION OF STEROIDS AT CARBON 16

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(*Received* 28 *April* 1966)

Abstract—3,3-Ethylenedioxy-5-androstene-17-one and estrone 3-methyl ether were subjected to Claisen condensations with ethyl acetate and trifluoroacetate. The enol acetates of 16-trifluoroacetyl derivatives underwent hydrogenolysis with the formation of trifluoroethyl compounds. UV and IR spectral data and other evidence are cited in support of the proposed structures.

ACYLATIONS of the steroid nucleus at position 16 by means of a Claisen reaction are described. In the course of this work, results were encountered which motivated further investigations by one of us (M.H.), the results of which have been incorporated in a number of patents.[1,2]

In preliminary studies, the 3-ethylene glycol ketal (Ia) of 4-androstene-3,17-dione (Chart I) was treated with ethyl acetate and gave the 16-acetyl derivative (Ib) which is soluble in dilute sodium hydroxide. The UV max at 279 mμ shifted to 305·5 mμ upon addition of alkali, in accordance with the proposed β-diketone structure. Acetylation with acetic anhydride and pyridine produced a mixture of the acetoxy compounds (Ic and VI), as evidenced by examination of the NMR spectrum, despite the established preference to locate double bonds in an exocyclic rather than endocyclic position relative to a five membered ring. Similarly, estrone methyl ether reacted with ethyl acetate in the presence of sodium methoxide to give the β-diketone (IIIa).

When the ketal Ia was trifluoroacetylated, a sparingly soluble sodium salt of the β-diketone (Id) was obtained. The UV absorption of the free trifluoroacetyl compound exhibited peaks at 238·5 and 306 mμ which indicate that it exists largely, if not completely, in the enol form (Id″) rather than the keto form (Id′). In the trifluoroacetyl derivative IIIb and others obtained later,[1] a very high enol content has also been observed, which must be due to the electronegative character of the trifluoromethyl group. On the other hand, the ketonic quality of these compounds is not completely absent, since they react with hydrazine to form pyrazole derivatives.[2]

Treatment of the sodium salt of Id with hot acetic anhydride gave an enol acetate formulated as Ie, in which (as in the other trifluoro enol acetate IIId described below) the double bond is exocyclic. Similar treatment of the potassium salt of the 2-trifluoroacetyl derivative of testosterone gave the dienol acetate (IV), while treatment of

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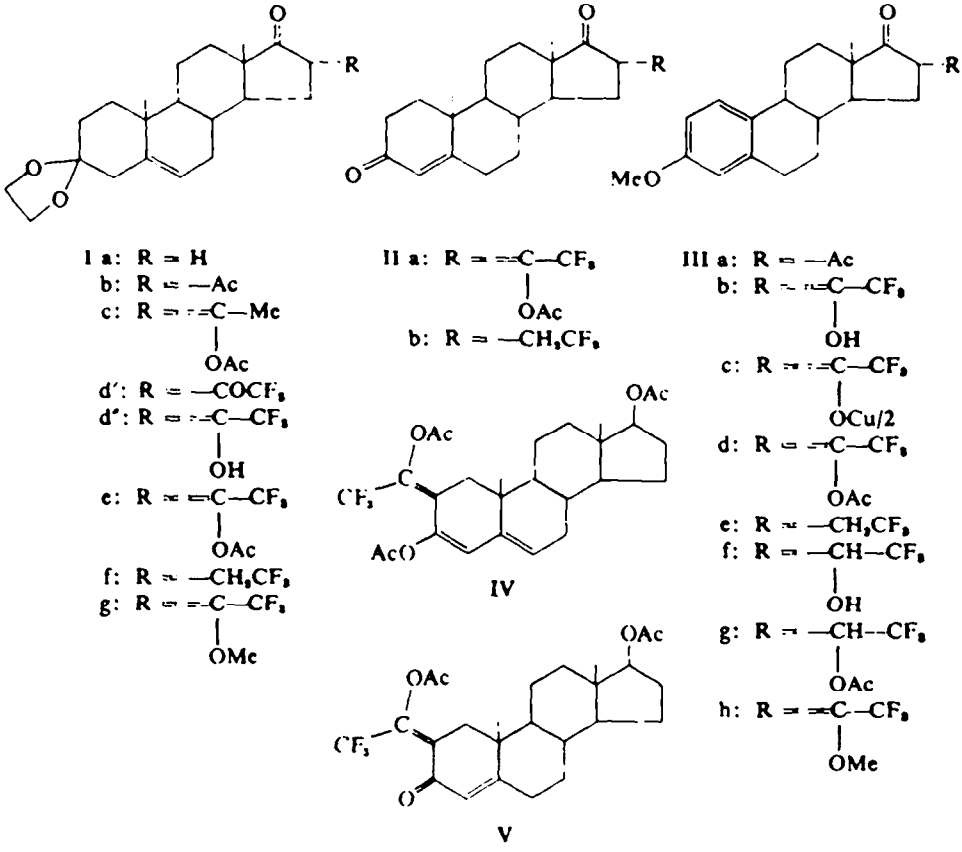
[1a] M. Harnik, U.S. Patent 3,051,732; *Chem. Abstr.* **57**, 16,701 (1962); [1b] M. Harnik, U.S. Patent 3,076,824; *Chem. Abstr.* **59**, 6488 (1963); [1c] M. Harnik, U.S. Patent 3,096,352; *Chem. Abstr.* **60**, 606 (1964); [1d] M. Harnik, U.S. Patent 3,096,354: *Chem. Abstr.* **60**, 605 (1964); [1e] M. Harnik, U.S. Patent 3,107,256; *Chem. Abstr.* **60**, 1824 (1964).

[2] M. Harnik, U.S. Patent 3,096,327; *Chem. Abstr.* **59**, 14,063 (1963).

the free 2-trifluoroacetyl derivative of testosterone with isopropenyl acetate and *p*-toluenesulfonic acid afforded the monoenol acetate (V).[1d] Mild acid hydrolysis of the ketal Ie gave the enol acetate IIa. Catalytic reduction of Ie with Pd–C caused absorption of 2 moles of hydrogen with formation of a product exhibiting a carbonyl peak at 5·76 μ. Mild acid hydrolysis of the overall crude hydrogenation product If furnished material with a spectrum showing absorption at 5·76 and 5·86 μ. The

CHART I



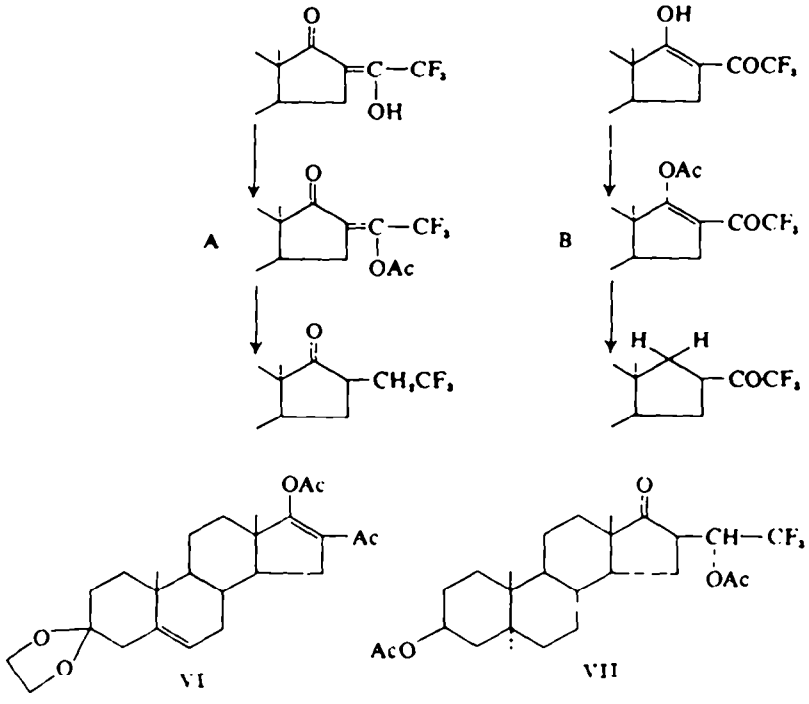
carbonyl absorption at 5·76 μ is due to a five-membered cyclic ketone, or much less probably, to the trifluoroacetyl group (usual value 5·64 μ). The hydrolysed product has been assigned the formula IIb derived via the hydrogenolysis pathway A and not B (Chart II).

Since hydrogenolyses of enol acetates normally take place with Pt[3] and not Pd as catalyst, it was decided to reinvestigate the reaction in steroids without interference from the Δ4-3-ketone system. Isopropenyl acetate was hydrogenated overnight in the presence of Pd–C and also with Pt over a 5 hr period, the degree of hydrogenolysis being measured by titration of the acetic acid produced. In the former case there was practically no hydrogenolysis, while in the latter it was nearly complete, in accordance with the results of Inhoffen.[3] It follows, then, that the hydrogenolysis of the steroid

[3] H. H. Inhoffen, G. Stoeck and G. Kölling. *Liebigs Ann.* **568**, 52 (1950).

enol acetate in alcohol in the presence of Pd was due to the presence of the adjacent fluorine atoms. Similarly, estrone methyl ether was converted into the trifluoroacetylated derivative (IIIb), isolated through the copper chelate (IIIc). As in the case of the ketal Id, its UV spectrum indicated a high degree of enolization. Treatment with hot acetic anhydride afforded the enol acetate (IIId), the IR spectrum of which exhibited maxima at 5·58 μ (—C=C(CF_3)-OAc), 5·75 μ (conjugated carbonyl in a five-membered ring) and 6·00 μ[4]. Hydrogenolysis of this enol acetate in the presence of Pd,

CHART II



afforded a mixture of the two possible isomers (IIIe) from which one, of unknown configuration of C_{16}, could be isolated. As in the case of compound If in the hydroaromatic series, it absorbed at 5·76 μ. When the free β-diketone (IIIb) or its copper salt (IIIc) instead of the enol acetate was hydrogenated in the presence of Pd, only saturation of the double bond took place and one of the 4 possible isomers of IIIf could be isolated in fair yield. Heating of this ketol with acetic anhydride caused no dehydration to the unsaturated ketone; instead, conversion to the acetate IIIg took place. Further hydrogenation of the acetate IIIf had no effect.

Similar reductions to 2,2,2-trifluoro-1-hydroxyethyl derivatives were later observed with other 16-trifluoroacetylated 17-keto steroids[1a,1e] and with 21-trifluoroacetylated pregnanes[1b]. It is of interest that dehydration was possible when 2-(2,2,2-trifluoro-1-hydroxyethyl)-5α-dihydrotestosterone was heated with anhydrous formic acid.[1c] Later experience has also shown that only enol acetates of steroids trifluoroacetylated in the 16-position undergo hydrogenolysis with Pd, while enol acetates of steroids trifluoroacetylated in the 2 or 21-positions are reduced, like the trifluoroacetyl

[4] R. Filler and S. M. Naqvi, *Tetrahedron* **19**, 879 (1963).

derivatives themselves, to the corresponding 2,2,2-trifluoro-1-hydroxyethyl derivatives.[1a–e]

In addition to the position of the IR bands of the enol acetates and their hydrogenolysed products, two additional facts support the formulation of the trifluoroacetyl derivatives as Id[e] and IIIb respectively, (but not as the alternative enolic formulae), consequently also supporting the formulation of reactions taking place according to route A (and not B). The trifluoroacetyl derivatives (Id and IIIb) can be transformed readily with diazomethane or methyl sulfate into the methoxy compounds (Ig and IIIh). This points to the presence of a fairly acidic hydroxyl group, as would be expected in IIIb.[5] Furthermore, 3β-acetoxy-16-(2,2,2-trifluoro-1-acetoxyethyl)-5α-androstane-17-one (VII), synthesized like IIIg, was subsequently found[6] to undergo facile methanolysis, even in the presence of potassium bicarbonate at room temperature, to the corresponding 1-methoxyethyl compound. Such a displacement by the methoxy ion can occur only at a carbon atom which has a partial positive charge caused by the adjacent trifluoromethyl group.

EXPERIMENTAL

10% Pd–C (American Platinum Works) was used throughout this investigation. All optical rotations were measured in chf. All m.ps are uncorrected. IR spectra were taken in KBr pellets.

16-Acetyl-3,3-ethylenedioxy-5-androstene-17-one (Ib). A soln of Ia (1·6 g) in dry benzene (50 ml) was treated under N with NaH (2 g) and then with AcOEt (1·5 ml). The mixture was refluxed for 3 hr after stirring for 30 min at room temp, then cooled and treated with EtOH to destroy excess NaH. The ether layer was extracted several times with cold 5% aqueous NaOH after addition of cold water and ether. The combined aqueous extracts were acidified with HCl, the ppt collected and washed with water. The crude (Ib), m.p. 128–131°, was recrystallized from EtOH to give a total of 649 mg, m.p. 140–148°. The analytical sample melted at 146–147°. λ_{max}^{EtOH} 279 mμ (ε 6,390); $\lambda_{max}^{5\%KOH/EtOH}$ 305·5 mμ (ε 24,520). (Found: C, 74·12; H, 8·65; Calc. for $C_{23}H_{34}O_4$: C, 74·16: H, 8·66%.)

Acetylation of the β-diketone (Ib). A soln of Ib (239 mg) in Ac_2O (20 ml) containing 1 ml of pyridine, was kept overnight at room temp, then heated for 1 hr at 60°. Evaporation *in vacuo* gave a solid which was washed with water, dried in desiccator (253 mg, m.p. 132–137°) and recrystallized from aqueous EtOH to afford 185 mg, m.p. 140–142. The analytical sample melted at 146–147°. λ_{max}^{EtOH} 241 mμ (ε 12,140); λ_{max}^{KBr} 5·69 μ (carbonyl of enol acetate), 5·80 μ and 6·07 μ (C=C). (Found: C, 72·68; H, 8·39. Calc. for $C_{25}H_{36}O_6$: C, 72·43; H, 8·27%.)

The methyl signals showed that the product must be a mixture of 16-(1-*acetoxyethylidene*) 3,3-*ethylenedioxy*-5-*androstene*-17-*one* (Ic) and 16-*acetyl*-17-*acetoxy*-3,3-*ethylenedioxy*-5,16-*androstadiene* (VI).

Sodium salt of 3,3-*ethylenedioxy*-16-*trifluoroacetyl*-5-*androstene*-17-*one* (Id). A soln of 3,3-ethylenedioxy-5-androstene-17-one (2 g) in dry benzene (100 ml) was treated under N with NaH (2·5 g) and after 10 min with 10 ml of ethyl trifluoroacetate. The stirred mixture was refluxed for 3 hr and then cooled. Excess NaH was decomposed with alcohol, followed by the addition of 200 ml 5% Na_2CO_3aq. The precipitation of the Na-salt of the β-diketone was complete after stirring for 30 min. The solid was filtered off, washed with water and ether and recrystallized from EtOH to give a total of 2·22 g of the Na salt of Id[e], m.p. 223–226°. The purest sample obtained melted at 226–230°. λ_{max}^{EtOH} 309 mμ (ε 15,000); λ_{max}^{KBr} 6·09 and 6·21 μ. (Found: C, 59·29; H, 6·80; F, 10·17; ash 9·0. Calc. for $C_{23}H_{34}F_3O_4Na$: C, 61·60; H, 6·29; F, 12·72; Na, 5·12%.)

A suspension of 100 mg of the Na salt in 70 ml ether was shaken with 5 ml of 10% AcOH. The crystals dissolved rapidly, the ether layer was washed with water and then with bicarbonate soln. Evaporation gave leaflets of (Id), m.p. 93° which were difficult to recrystallize. λ_{max}^{EtOH} 238·5 and 306 mμ (ε 12,080 and 10,130).

3,3-*Ethylenedioxy*-16-(2,2,2-*trifluoro*-1-*acetoxyethylidene*) 5-*androstene*-17-*one* (Ie). A mixture of the above Na-salt (2·4 g) and Ac_2O (50 ml) was boiled for 30 min. The solvent was removed

[5] A. L. Henne, and R. L. Pelley *J. Amer. Chem. Soc.* 74, 1426 (1952).

[6] M. Harnik, U.S. Patent 3,189,621; *Chem. Abstr.* 63, 7089 (1965).

in vacuo and the residue twice recrystallized from EtOH to furnish 1·34 g, m.p. 171–174°. The analytical sample was obtained by sublimation and melted at 181–182°. (Found: C, 63·94; H, 6·63; F, 12·21. Calc. for $C_{28}H_{31}F_3O_4$: C, 64·09; H, 6·67; F, 12·17%.)

16-(2,2,2-*Trifluoro*-1-*acetoxyethylidene*) *5-androstene*-3,17-*dione* (IIa). A soln of Ie (530 mg) in hot MeOH (30ml) was treated with conc HCl (1 ml) and water (1 ml). The mixture was diluted with water and chilled after standing at room temp for 2 hr. The solid was collected, washed with water (m.p. 135–144°), recrystallized from EtOH (m.p. 153–157°) and then from heptane (m.p. 157–158·5°). For analysis the substance was sublimed (m.p. 158–161°). λ_{max}^{EtOH} 236·5 mμ (e 26,800). (Found: C, 65·39; H, 6·35; F, 13·17. Calc. for $C_{28}H_{31}F_3O_4$: C, 65·08; H, 6·44; F, 13·43%.)

3,3-*Ethylenedioxy*-16-(2,2,2-*trifluoro*-1-*methoxyethylidene*) *5-androstene*-17-*one* (Ig). A soln of the Na-salt of Id (200 mg) in dry benzene (20 ml) was treated with anhyd Na_2CO_3 (1 g) dimethyl sulfate (0·6 g) and refluxed overnight. The solvent was evaporated *in vacuo*, AcONa and water were added, the mixture warmed sightly and then extracted with ether. Evaporation furnished a solid which after 2 crystallizations from MeOH gave a sample m.p. 167–168·5°. λ_{max}^{EtOH} 248 and 300 mμ (e 34,000 and 12,600). (Found: C, 66·08; H, 7·05; F, 13·39. Calc. for $C_{24}H_{31}F_3O_4$; C, 65·43; H, 7·10; F, 12·94%.)

16-*Acetyl-estrone*-3-*methyl ether* (IIIa). Estrone 3-methyl ether (10·5 g) was added to a suspension of MeONa (from 6 g Na) in dry benzene (200 ml) followed by AcOEt (50 ml). The mixture was refluxed for 4 hr, cooled and poured into ice-water. Ten extractions with cold 5% NaOHaq (20 ml each) and acidification of the combined extracts with cold dil H_2SO_4 gave the oily β-diketone which was taken up in ether. Evaporation of the water-washed ether layer and crystallization (charcoal) from EtOH furnished 4·3 g, m.p. 112–118°. The analytical sample melted at 119–120°. $[\alpha]_D$ 142°; λ_{max}^{EtOH} 278·5 and 286 mμ (e 8,370 and 7,820); $\lambda_{max}^{2\%KOH/EtOH}$ 304 mμ (e 31,250). (Found: C, 77·52; H, 7·98. Calc. for $C_{21}H_{26}O_3$: C, 77·27; H, 8·03%.)

16-*Trifluoroacetyl-estrone*-3-*methyl-ether* (IIIb) *and the copper salt* (IIIc). *A.* A soln of estrone 3-methyl ether (1·95 g) in dry benzene (60 ml) was added to a suspension of MeONa (freshly prepared from 2 g Na) in benzene (40 ml) followed by ethyl trifluoroacetate (20 ml). The mixture was stirred at room temp for 1·5 hr and then at reflux for 1·5 hr. The cooled mixture was poured into 200 ml ice-cooled 5% HCl and then extracted with 100 ml ether. The organic-phase was washed with water and evaporated to a gum which eventually crystallized from EtOH giving 746 mg, m.p. 100–103°, and 1 g, m.p. 106–121°. The β-diketone (IIIb) was recrystallized several times but exhibited a variable m.p. ranging from 119° to 124°.

B. Estrone 3-methyl ether (1 g) was condensed with ethyl trifluoroacetate as described above. The reaction mixture was poured into water and just acidified with HCl. A concentrated soln of 1 g of cupric acetate in water was added and the mixture was stirred with heating for 30 minutes. Benzene was removed *in vacuo* and the crystals (1·5 g), m.p. above 250°, were recrystallized from aqueous acetone yielding 1·25 g of IIIc. (Found: C, 61·02; H, 6·02; Cu, 8·14. Calc. for $(C_{21}H_{25}F_3O_3)_2$ Cu: C, 61·32; H, 5·39; Cu, 7·73%.)

A stream of H_2S was passed through a soln of the Cu salt (3 g) in benzene (100 ml). CuS was filtered off and the soln was taken to dryness *in vacuo*. The product was crystallized from MeOH–ether and melted at 132–135°. The analytical sample of IIIb melted at 134–135°. $[\alpha]_D$ 75°; λ_{max}^{EtOH} 312 mμ (e 8,710); $\lambda_{max}^{2\%KOH/EtOH}$ 312 mμ (e 12,030); λ_{max}^{KBr} 5·89 and 6·12 μ. (Found: C, 63·89; H, 6·76; F, 13·82. Calc. for $C_{21}H_{25}F_3O_3 \cdot CH_3OH$: C, 64·06; H, 6·60; F, 13·82%.)

16-(2,2,2-*Trifluoro*-1-*acetoxyethylidene*) *estrone*-3-*methyl ether* (IIId). Compound IIIb (1 g) was refluxed for 30 min with Ac_2O (25 ml). Distillation of the solvent *in vacuo* and crystallization from EtOH furnished 470 mg of a IIId, m.p. 108–115° Three additional recrystallizations gave a sample m.p. 118·5–120°. $[\alpha]_D$ 73°; λ_{max}^{EtOH} 225, 277 and 286 mμ (e 14,950, 2,450 and 2,400). (Found: C, 65·14; H, 5·74; F, 13·52. Calc. for $C_{23}H_{25}F_3O_4$: C, 65·39; H, 5·96; F, 13·49%.)

16ξ-(2,2,2-*Trifluoroethyl*) *estrone*-3-*methyl ether* (IIIe). A soln of IIId (400 mg) in EtOH (25 ml) was hydrogenated for 4 hr in the presence of Pd catalyst (100 mg). The product was recrystallized from EtOH or, better, aqueous acetone, to give 150 mg, m.p. 161–169°. The pure sample melted at 170–171°. $[\alpha]_D$ 128°; λ_{max}^{EtOH} 286 mμ (e 4.035); λ_{max}^{KBr} 5·76 μ. (Found: C, 68·94; H, 6·94; F, 15·63. Calc. for $C_{21}H_{25}F_3O_3$: C, 68·89; F, 15·55%.)

Essentially the same results were obtained when $NaHCO_3$ or Et_3N were present in the hydrogenation mixture.

16ξ-(2,2,2-*Trifluoro*-1-*hydroxyethyl*) *estrone*-3-*methyl ether* (IIIf). *A.* A soln of IIIc (500 mg)

in benzene was treated with H_2S as described above. The resulting crude IIIb was dissolved in EtOH (50 ml) and hydrogenated for 3 hr with Pd–C (300 mg). The filtered soln was evaporated and the crude solid (m.p. 208–212°) recrystallized from AcOEt–hexane. The product melted at 210° (mixed m.p. with the compound obtained below was 213–215°).

B. A soln of IIIc (610 mg) in EtOH (25 ml) was hydrogenated for 16 hr in the presence of Pd–C (200 mg). The filtered (celite pad) soln was taken to dryness, the residue dissolved in ether and again filtered to remove a small amount of a Cu-containing material. Recrystallization of the product from AcOEt–methylcyclohexane gave IIIf (280 mg) m.p. 213–215°. The analytical sample melted at 216–217°. $[\alpha]_D$ 127°; λ_{max}^{EtOH} 277 and 286 mμ (e 1,260 and 1,230); λ_{max}^{KBr} 5·75 μ. (Found: C, 65·84; H, 6·70; F, 15·46. Calc. for $C_{21}H_{28}F_2O_2$: C, 65·95; H, 6·59; F, 14·93%.)

16ξ-(2,2,2-*Trifluoro*-1-*acetoxyethyl*) *estrone*-3-*methyl-ether* (IIIg). A soln of IIIf (100 mg) in Ac_2O (25 ml) was refluxed for 30 min. The mixture was distilled *in vacuo*, the residue well dried and then recrystallized from EtOH to furnish the acetate (62 mg) m.p. 161–168°. The pure sample melted at 176–177°. $[\alpha]_D$ 60°; λ_{max}^{EtOH} 225, 272 and 286 mμ (e 14,950, 2,450 and 2,400). (Found: C, 65·50; H, 6·61; F, 13·70. Calc. for $C_{23}H_{27}F_3O_4$: C, 65·70; H, 6·47; F, 13·56%.)

16-(2,2,2-*Trifluoro*-1-*methoxyethylidene*) *estrone*-3-*methyl ether* (IIIh). A soln of IIIb (200 mg) freshly obtained from the Cu salt, in 20 ml of ether was titrated with ethereal diazomethane to a permanent yellow color. Evaporation of solvent gave a solid which was recrystallized from MeOH to yield a sample (129 mg), m.p. 145–153°. Chromatography over alumina (elution with 20% benzene in pet. ether) gave a sample m.p. 156·5–157·5°. λ_{max}^{EtOH} 248 and 286 mμ (e 7,560 and 2,000); λ_{max}^{KBr} 5·74 mμ. (Found: C, 66·96; H, 6·69; Calc. for $C_{22}H_{28}F_3O_3$: C, 66·99; H, 6·39%.)