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MODIFIED STEROID HORMONES—LI[1]

APPLICATION OF THE VILSMEIER REACTION TO 11β-HYDROXY STEROIDS

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Abstract—The preparation of 6-methylated 11β-hydroxy steroids by means of a Vilsmeier reaction is described.

EARLIER papers in this series have described the application of the Vilsmeier reaction, and subsequent transformations, to the preparation of 6-methylated steroids.[2] The importance of 6-methylated corticoids such as Medrol (6α-methylprednisolone) prompted a careful study of the application of the Vilsmeier reaction to steroids containing an 11β-hydroxyl group.

Treatment of hydrocortisone acetate enol methyl ether (Ia) with the Vilsmeier reagent prepared from dimethylformamide and phosphoryl chloride for 2 hr at 0° gave 21-acetoxy-11β-formyloxy-6-formyl-3-methoxy-3,5-pregnadien-17α-ol-20-one (Ib) in about 60–70% yield. If, however, the dimethylformamide-phosgene reagent was used under the same experimental conditions, the major product, obtained in 35–45% yield, proved to be the 9(11)-ene (II). The formation of two different products was unexpected, and so the reactions were investigated by a sampling technique involving analysis by TLC (Experimental). The results, assessed qualitatively, are summarised in Table 1.

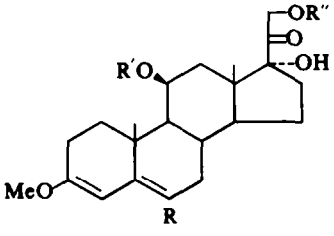
TABLE 1. TLC INVESTIGATION OF THE REACTION OF COMPOUND (Ia) WITH THE VILSMEIER REAGENTS

Sampling time	Products (see Fig. 1)					
	[DMF – $POCl_3$]			[DMF – $COCl_2$]		
	Id	Ib	II	Id	Ib	II
5 min	++++*	+	–	++++	+	–
15 min	+++	+++	–	+++	+++	+
30 min	++	++++	–	++	+++	++
1 hr	+	++++	–	+	+++	+++
1·5 hr	–	++++	–	–	++	++++
2 hr	–	++++	+	–	+	++++
3 hr	–	++++	++	–	–	++++
5 hr	–	+++	+++	–	–	++++

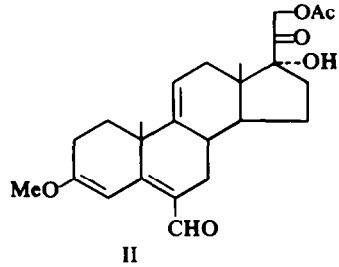
* Intensity of spot increases from + (very faint) to ++++; – indicates not detectable.

From these results, it can be seen that the Vilsmeier reaction with steroidal 3-alkoxy-3,5-dienes, using either reagent, is very much faster than was hitherto supposed, being essentially complete within 5–10 min at 0°. Participation of the 11β-OH group under these conditions is also very rapid, and attempts to prepare the 6-formyl-11β-hydroxy compound (Id) by employing brief reaction times gave rather poor yields (ca. 30%). On the other hand acceptable yields of the 11β-formate (Ib) could be obtained provided that the Vilsmeier reagent prepared with phosphoryl chloride was used. Compound Ib could readily be detected (TLC) in reactions using the phosgene reagent, but it was not possible to isolate it since dehydration to the 9(11)-ene (II) was the major reaction.

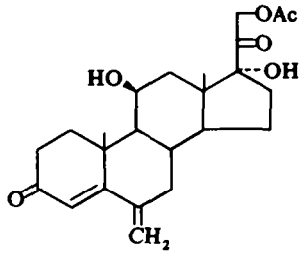
The structures of compounds Ib, Id and II were established by elemental analysis, UV and NMR spectra. The more rapid dehydration observed with the phosgene reagent may be attributed to an E2 elimination of the initially formed, strongly



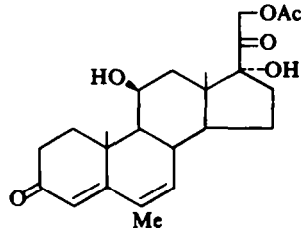
I a: R = R' = H, R'' = Ac
b: R = R' = CHO, R'' = Ac
c: R = CHO, R' = R'' = H
d: R = CHO, R' = H, R'' = Ac
e: R = CH_2OH, R' = H, R'' = Ac



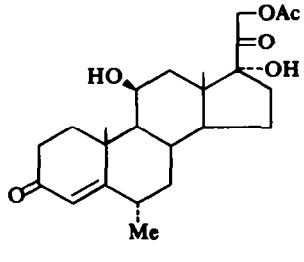
II



III



IV



V

election-attracting 11β-O·CH=$\overset{\oplus}{N}$ME$_2$ group, which will be favoured by the greater concentration of chloride ion in this reagent.

The preferred preparation of the 11β-OH compound (Id) consisted in hydrolysis of the 21-acetate-11β-formate (Ib) with aqueous methanolic sodium hydroxide to the triol (Ic), followed by re-acetylation of the 21-OH group. Selective hydrogenation of the resulting 21-acetate (Id) over a platinum–charcoal catalyst[2c] gave the 6-hydroxymethyl analogue (Ie) which was converted, without purification, into 6-methylenehydrocortisone acetate (III)[3] by brief treatment with acid. Isomerization of the foregoing compound (III) to the corresponding 6-methyl-4,6-diene-3-one[4] (IV) was effected in excellent yield by refluxing in ethanol in the presence of 5% palladium on charcoal.[2c]

Transfer hydrogenation of the 6-methyl-4,6-dien-3-one over palladium-charcoal, using cyclohexene as hydrogen donor,[2c] gave 6α-methyl hydrocortisone acetate[5,6] (V) in about 60% yield. The conversion of this compound (in a suitably protected form) into biologically important corticoids such as Medrol has been described.[5]

EXPERIMENTAL

Optical rotations were determined at a concentration of ca 1% in A.R. $CHCl_3$ at room temp unless otherwise stated. UV spectra refer to solns in Spectro-grade EtOH. IR spectra were determined with a Hilger H800 Spectrophotometer fitted with CaF_2 and NaCl prisms for the frequency ranges 4000–1300 and 1350–650 cm^{-1} respectively. NMR spectra were determined on a Perkin–Elmer 60MC/S instrument, usually in $CDCl_3$ with TMS as an internal standard. M.ps are uncorrected.

21-*Acetoxy*-3-*methoxy*-3,5-*pregnadiene*-11β,17α-*diol*-20-*one*[7] (Ia). This compound was prepared by the general procedure given earlier.[2a] It crystallized from aqueous MeOH (containing a few drops of pyridine) as plates, m.p. 170–180°, $[\alpha]_D$ −15° (dioxan), λ_{max} 239·5 mμ (ε 19,680), ν_{max}^{Nujol} 3390 (OH), 1735 (OAc), 1718 (20-ketone), 1654 and 1628 cm^{-1} (3,5-diene). (Found: C, 68·8; H, 8·0. $C_{24}H_{34}O_6$ requires: C, 68·85; H, 8·2%).

21-*Acetoxy*-11β-*formyloxy*-6-*formyl*-3-*methoxy*-3,5-*pregnadien*-17α-*ol*-20-*one* (Ib). A soln of the foregoing Ia (40 g, 0·095 mol) in CH_2Cl_2 (400 ml) containing pyridine (1 ml) was added all at once to a stirred soln of the Vilsmeier reagent prepared at 0° from phosphoryl chloride (28 ml, 0·3 mol) and dimethylformamide (82·5 ml) in CH_2Cl_2 (250 ml). After 2 hr at 0°, 20% NaOAcaq (400 ml) was added and stirring was continued for 15 min. at room temp. Ether (2 l.) was added, the organic layer was separated, washed with 10% $NaHCO_3$ aq then with water and dried (Na_2SO_4). Concentration of the solution to ca. 250–300 ml gave the 6-*formyl* compound Ib (30 g) as pale yellow crystals, m.p. 195–200°. Recrystallization from $CHCl_3$–MeOH gave yellow prisms, m.p. 207–208°, $[\alpha]_D$ +2·3°, λ_{max} 218 (ε 11,250) and 322 mμ (ε 16,700), NMR 9·18 (C19-H), 8·83 (C18-H), 7·87 (OAc), 6·8 (C17-OH), 6·3 (C3-OMe), 1·90 (C11-OCHO), −0·24 τ (C6-CHO). (Found: C, 65·8; H, 7·2. $C_{26}H_{34}O_8$ requires: C, 65·75; H, 7·15%).

21-*Acetoxy*-6-*formyl*-3-*methoxy*-3,5,9(11)-*pregnatrien*-17α-*ol*-20-*one* (II). This compound was prepared as described above, except that the molar equivalent amount of phosgene was used in place of phosphoryl chloride. Evaporation of the ether extract gave a gummy solid which crystallized on trituration with ether. Recrystallization from $CHCl_3$–MeOH gave the 6-*formyl compound* II as pale yellow prisms, m.p. 194–195°, $[\alpha]_D$ −98°, λ_{max} 219 (ε 12,210) and 321 mμ (ε 15,510), NMR 9·37 (C19-H), 8·79 (C18-H), 7·86 (OAc), 6·97 (C17-OH), 6·3 (C3-OMe), −0·25 τ (C6-CHO). (Found: C, 69·65; H, 7·7. $C_{25}H_{32}O_6$ requires: C, 70·05; H, 7·55%).

To follow the course of these reactions, a 2-3 ml aliquot portion was withdrawn at an appropriate time, worked up as described above, and a ca. 2 μl. sample of the total extract was placed on a Silica Gel G plate (7·5 × 2·5 × 0·025 cm). The plates were developed in CH_2Cl_2–MeOH (5:1) and sprayed with dodecamolybdophosphoric acid/95% EtOH.

6-*Formyl*-3-*methoxy*-3,5-*pregnadiene*-11β,17α,21-*triol*-20-*one* (Ic). A soln of Ib (8·5 g) and NaOH (1·45 g) in MeOH (250 ml) and water (50 ml) was kept overnight at room temp under N_2. AcOH (6 ml) was added, the solution was concentrated to ca. 80 ml at reduced press and diluted with water. Crystallization of the ppt from aqueous acetone gave the *triol* (5·9 g) as solvated needles, m.p. 152–153°, $[\alpha]_D$ −6·4° (EtOH),

λ_{max} 218·5 (ε 11,030) and 323 mμ (ε 15,630). (Found: C, 65·05; H, 8·0. $C_{23}H_{32}O_6 \cdot H_2O$ requires: C, 65·4; H, 8·1%).

21-*Acetoxy*-6-*formyl*-3-*methoxy*-3,5-*pregnadiene*-11β,17α-*diol*-20-*one* (1d). The foregoing triol (4·15 g) was acetylated with Ac_2O (10 ml) and pyridine (25 ml) at room temp for 3 hr. The 21-*acetate* (3·7 g) crystallized from aqueous MeOH as solvated rods, m.p. 207–208°, $[\alpha]_D$ −10°, λ_{max} 218 (ε 11,480) and 324 mμ (ε 16,700), $\nu_{max}^{CH_2Cl_2}$ 3600 (OH), 1749 (OAc), 1730 (20 ketone), 1647, 1615 and 1583 cm^{-1} (6-formyl-3-methoxy-3,5-diene), NMR 9·06 (C19-H), 8·71 (C18-H), 7·84 (OAc), 7·1 (C11- and C17-OH), 6·3 (C3-OMe), −0·22 τ (C6-CHO). (Found: C, 64·7; H, 7·7. $C_{25}H_{34}O_7 \cdot H_2O$ requires: C, 64·65; H, 7·8%).

21-*Acetoxy*-6-*methylene*-4-*pregnene*-11β,17α-*diol*-3,20-*dione* (III). A soln of the foregoing 21-acetate (3·6 g) and NaOAc (3·6 g) in MeOH (100 ml) was added to pre-reduced 5% Pt–C (1·25 g) in MeOH (25 ml), and the mixture was hydrogenated until ca 180 ml (1 mol equiv.) of H_2 had been absorbed. The catalyst was removed by filtration, the solvent was evaporated at reduced press and the residue was partitioned between $CHCl_3$ and water. The organic phase was separated and toluene-*p*-sulphonic acid (0·2 g) and MeOH (ca. 10 ml) were added. After 15 min. at room temperature, the solution was washed with Na_2CO_3 aq and then with water, dried (Na_2SO_4) and evaporated under reduced pressure. Crystallization of the residue from $CHCl_3$–di-isopropyl ether gave the 6-*methylene* derivative (1·8 g) as prisms, m.p. 206–207°, $[\alpha]_D$ +301°, λ_{max} 260 mμ (ε 11,800), $\nu_{max}^{CH_2Cl_2}$ 3600 (OH), 1747 (OAc), 1725 (20 ketone), 1662, 1627 and 1601 cm^{-1} (6-methylen-4-en-3-one). (Found: C, 68·9; H, 7·75. $C_{24}H_{32}O_6$ requires: C, 69·2; H, 7·75%). (Lit.[3] m.p. 199–204°, $[\alpha]_D$ +293°).

21-*Acetoxy*-6-*methyl*-4,6-*pregnadiene*-11β,17α-*diol*-3,20-*dione* (IV). A soln of the foregoing 6-methylene derivative (1·75 g) in EtOH (35 ml) was stirred and refluxed with 5% Pd–C (0·5 g) whilst a 5% soln of benzyl alcohol in EtOH (10 ml) was slowly added. The UV spectra of ca. 1 ml aliquots were determined at appropriate times and after 1 hr the change from λ_{max} 260 mμ to λ_{max} 289 mμ was complete. The catalyst was removed by filtration, the solvent was evaporated at reduced pressure and the residue was crystallized from $CHCl_3$–acetone. The 6-*methyldienone* (1·75 g) formed solvated prisms, double m.p. 147° (effervescence) and 198°, $[\alpha]_D$ +179·1°, λ_{max} 289 mμ (ε 23,800), $\nu_{max}^{CH_2Cl_2}$ 3610 (OH), 1750 (OAc), 1729 (20 ketone), 1713 (Me_2CO), 1658, 1626 and 1583 cm^{-1} (4,6-dien-3-one) [lit.[4] m.p. 133–137°, 141–143, $[\alpha]_D$ +171° (EtOH), +168·2° ($CHCl_3$)]. (Found: C, 67·35; H, 7·9. $C_{24}H_{32}O_6 \cdot C_3H_6O$ requires: C, 67·5; H, 8·25%).

21-*Acetoxy*-6α-*methyl*-4-*pregnene*-11β,17α-*diol*-3,20-*diqne* (V). A soln of the foregoing 4,6-dien-3-one (3·4 g) and cyclohexene (7 ml) in EtOH (60 ml) was refluxed and stirred with 5% Pd-C (1·3 g) for 16 hr with periodic additions of cyclohexene (3 × 10 ml). The UV spectra of ca. 1 ml aliquots were periodically determined, and reaction was complete when the peak at 289 mμ had been completely replaced by one at 240 mμ. The catalyst was removed by filtration, the solvent was evaporated at reduced press and the residue was crystallized, first from acetone and then from aqueous MeOH. The *product* formed prisms, m.p. 208°, $[\alpha]_D$ +128°, λ_{max} 241·5 mμ (ε 13,300) [Lit.[5,6] m.p. 208–211°, $[\alpha]_D$ +136°, λ_{max} 242 mμ (ε 14,800). M.p. 213–214°, $[\alpha]_D$ +115°, λ_{max} 243 mμ (ε 14,525)], $\nu_{max}^{CH_2Cl_2}$ 3600 (OH), 1746 (OAc), 1725 (20 ketone), 1665 and 1609 cm^{-1} (4-en-3-one). (Found: C, 68·3; H, 8·25. $C_{24}H_{34}O_6$ requires: C, 68·85; H, 8·2%).

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[3] Since this work was completed, this compound has been described in U.S. Pat. 3,074,935.

[4] This compound has also been prepared since the completion of this work *cf* U.S. Pat. 3,031,476 (*Chem. Abstr.* **57**, 9927 d) and Huang-Minlon, Kuang-Tien Ham and Wei-shan Chou, *Hua Hsueh Hsueh Pao* **29**, 99 (1963); *Chem. Abstr.* **59**, 12868f.

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