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CONJUGATE ADDITION OF REFORMATSKY REAGENTS TO Δ^{16}-20-KETOSTEROIDS

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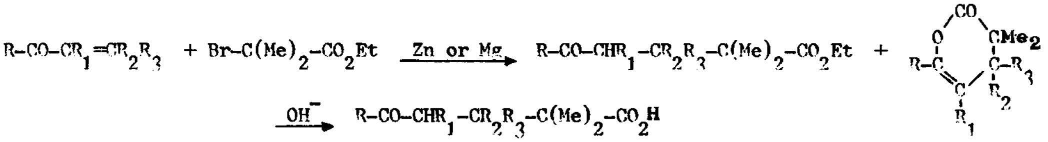
It was recently found (1) that α,β-ethylene ketones undergo conjugate addition of the Reformatsky reagent derived from ethyl-α-bromo-isobutyrate, contrary to widespread previous opinion (2 a,b).

The reaction produces a mixture of δ-ketoesters and enolic-δ-lactones, from which by hydrolysis substituted δ-ketoacids are obtained, as shown in the sequence herewith:



$$R\text{-}CO\text{-}CR_1\text{=}CR_2R_3 + Br\text{-}C(Me)_2\text{-}CO_2Et \xrightarrow{\text{Zn or Mg}} R\text{-}CO\text{-}CHR_1\text{-}CR_2R_3\text{-}C(Me)_2\text{-}CO_2Et +$$

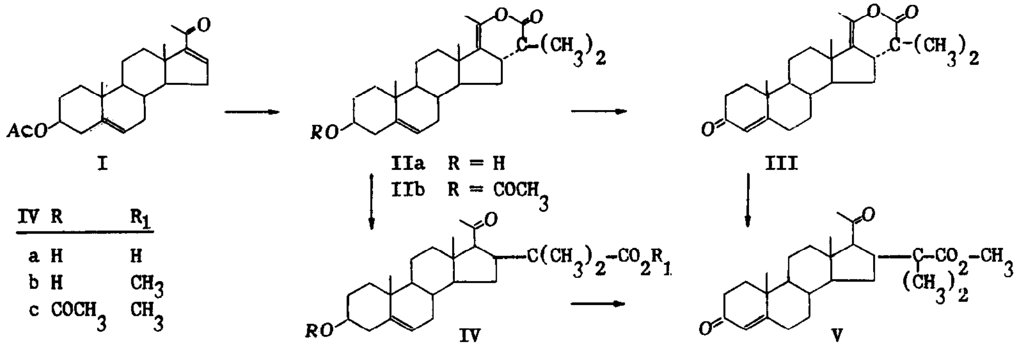
$$\xrightarrow{OH^-} R\text{-}CO\text{-}CHR_1\text{-}CR_2R_3\text{-}C(Me)_2\text{-}CO_2H$$

Of the large number of aliphatic, alicyclic and aromatic ketones tested, only the α,β-ethylene methyl-ketones fail to undergo conjugate addition: thus 1-acetyl-cyclohex-1-ene, methylstyrylketone and pent-2-en-4-one (1).

We have ourselves investigated the behaviour of 16-dehydropregnenolone acetate (I), which may be regarded as an α,β-ethylene methylketone system, against the Reformatsky reagents obtained from the ethyl-α-bromo-esters of isobutyric, malonic and butyric acids; and we have found that conjugate additions are easily achieved with this compound, although the results depend largely upon the type of α-bromo-ester used. The same peculiarity had previously been pointed out by Kohler (3 a-c, 4), who investigated the 1,4-conjugate addition of the same Reformatsky reagents to benzalacetophenone.

All our reactions were effected in anhydrous tetrahydrofuran, in which organo-metallic complexes are easily soluble; and our reagents were prepared with Zn or Mg (the latter giving less reproducible results). The highest reaction yields were obtained with a 1:6 molar ratio of steroid to Reformatsky reagent.

(a) Reaction of I with Zn or Mg and ethyl-α-bromo-isobutyrate:



I

IIa R = H
IIb R = $COCH_3$

III

IV

V

IV	R	R_1
a	H	H
b	H	CH_3
c	$COCH_3$	CH_3

From the reaction mixture we isolated a single product with a 75% yield: this was the γ,δ-enol-lactone IIa,with m.p. 155-157 C,$[\alpha]_D$=-118° (5),IR Δ 17(20) 1665 cm^{-1},C=O 1730 cm^{-1}.

Acetylation of this compound gave 16a-dimethyl-pregna-5,17(20)-dien-3β,20-diol-16α-acetic acid (16b→20)δ-lactone (IIb),with m.p. 191-192 C,$[\alpha]_D$=-119°,$[\alpha]_{365°}$= -482° ($\phi_{370°}$=-1706, $\phi_{280°}$= -8960,$\phi_{265°}$= -15785,$\phi_{258°}$= -17917,$\phi_{252°}$= -15367,$\phi_{245°}$= -1706);NMR at δ 0.96 (s,3H,18-Me) 0.98 (s,3H,gem-Me), 1.04 (s,3H,19-Me), 1.23 (s,3H,gem-Me), 1.89 (d,3H,J=1.8 cps homoallylic coupling with 16β-H), 2.00 (s,3H,$\underline{CH_3}CO_2$-).

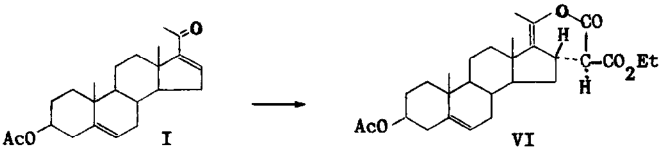
By Oppenauer reaction, IIa afforded the Δ^4-3-keto-derivative (III),with m.p. 216-218 C, $[\alpha]_D$= -13°,λ_{max} 242 mμ (ε= 16,800);NMR at δ 0.94 (s,6H,18-Me and gem-Me), 1.18 (s,3H,19-Me) 1.85 (d,3H, J=1.8cps homoallylic coupling with 16β-H),2.75 (m,1H,16β-H), 5.66 (broad s,1H,4-H).

The cycloaddition reaction creates a new center of asymmetry; we anticipated addition to take place on the rear side at C-16 in accordance with typical steroid reactions (6), and therefore attributed the 16α-configuration to the new substituent.Confirmation of this assignment was obtained from further transformation of the adduct (7) and on the basis of 18-Me frequencies of IIb and III in the NMR spectrum (8).

Structural confirmation of IIa was provided by the fact that saponification with potassium hydroxide in ethanol produced the δ-ketoacid IVa, with m.p. 265-268 C,$[\alpha]_D$= +18°; this was first treated with diazomethane to give the δ-ketoester IVb with m.p. 162-163 C,$[\alpha]_D$ =+22°, IR CO (keto) 1695 cm^{-1}, CO (ester) 1710 c m^{-1},and then converted to 16a-dimethyl-pregn-5-en-3β-ol-20-one-16α-acetic acid methyl ester acetate (IVc),with m.p. 149-150° C,$[\alpha]_D$= +10° ($\phi_{315°}$ =7711,$\phi_{311°}$ =8140,$\phi_{300°}$=4586,$\phi_{265°}$= -13070, $\phi_{250°}$= -11465, a =+212,1);NMR at δ 0.64 (s, 3H,18-Me), 1.01 (s,3H,19-Me), 1.06 and 1.07 (s,6H,16a gem-dimethyl),2.11 (s,3H,21-Me), 2.01 (s,3H, CH_3CO_2-), 2.69 (d,17α-H,J=8.4 cps).

16α-configuration of IVc is well supported by the C-18 chemical shift in the NMR spectrum (9) Hydrolysis of both IIa and IIb with 0.9% potassium hydrogen carbonate in aqueous methanol readily gave IVb ; this, by Oppenauer oxidation, gave 16a-dimethyl-pregn-4-en-3,20-dione-16α-acetic acid methyl ester (V), with m.p. 120–122 C, $/\alpha/_D$ = -70°, λ_{max} 242 mμ (ε=16,200). The product obtained with this reaction sequence was in every respect identical to that obtained by transesterification of III with 0.9% potassium hydrogen carbonate in methanol.

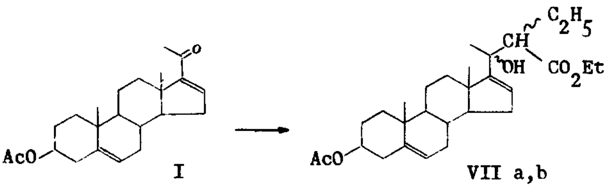
(b) Reaction of I with Zn or Mg and ethyl-α-bromo-malonate:



This reaction yielded a mixture of 3β-ol and 3β-acetoxy compounds; acetylation of the mixture with acetic anhydride in pyridine solution gave a 60 to 65% yield of 16aβ-carboethoxy-pregna 5,17(20)-dien-3β,20-diol-16α-acetic acid-(16b→20)δ-lactone (VI), with m.p. 204,5–206 C, $/\alpha/_D$= -172° ($\emptyset_{300°}$= -7060, $\emptyset_{265°}$= -20236, $\emptyset_{257°}$= -17883, $\emptyset_{245°}$= -9412); IR(CCl_4) $\Delta^{17(20)}$ 1665 cm^{-1}, CO (ester) 1725 cm^{-1}, CO (lactone) 1760 cm^{-1}; NMR at δ 0.97 (s,3H,18-Me), 1.04 (s,3H,19-Me), 1.31 (t,3H,J = 6.8 cps,$-CO_2CH_2-\underline{CH_3}$),2.01 (s,3H,$\underline{CH_3}$-CO-O-), 1.93 (d,3H,J = 1.9 cps homoallylic coupling,21-Me), 3.19 (B part of an AB quartet,J = 14.5 cps,16aα-H).

The cycloaddition reaction now introduces two new asymmetric carbons, namely C-16 and C-16a In the case of C-16 we attributed the α-configuration by analogy with IIa,b (6).In the case of C-16a,instead,confirmation of the configuration is wanting; however, certain indications emerge from the study of molecular models and NMR spectra. Molecular models showed less hindrance and higher degree of symmetry in the 16aβ-carboethoxy isomer; and as NMR spectra indicated a trans diaxial orientation of the two hydrogen atoms at C-16 and C-16a, this was the configuration attributed to VI.

(c) Reaction of I with Zn or Mg and ethyl-α-bromo-butyrate:



Even by operating in the presence of cupreous chloride, we obtained only products corresponding to 1,2-addition to α,β-ethylene ketones. Acetylation of the crude reaction mixture, followed by silica gel chromatography, afforded separation of two compounds, namely 24-nor-22ξ-ethyl cola-5,16-dien-3β,20ξ-diol-23-oic acid ethyl ester (VIIa), with m.p. 140–141 C, IR(CCl_4) OH 3515 cm^{-1}, CO (3-ester) 1728 cm^{-1}, CO_2Et 1706 cm^{-1}; NMR at δ 0.857 (t,3H, J = 1.0 cps, 22- $CH_2-\underline{CH_3}$), 0.97 (s,3H,18-Me), 1.049 (s,3H,19-Me), 1.301 (s,6H,21-Me overlapped with CH_3-CH_2-O-CO-),2.015

(s,3H,$\underline{CH}_3$-CO_2-), and VIIb with m.p. 106-108 C, IR(CCl_4) OH 3503 cm^{-1},CO (3 ester) 1730 cm^{-1}, CO_2Et 1706 cm^{-1}; NMR at δ 0.92 (t,3H,J = 7.05 cps,22 CH_2-$\underline{CH}_3$), 0.93 (s,3H,18-Me), 1.05 (s, 3H,19-Me), 1.24 (t,J = 7.03 cps,$\underline{CH}_3$-CH_2-O-CO-), 1.28 (s,3H,21-Me), 2.01 (s,3H,CH_3-CO_2-).

Infrared and NMR spectra studies suggested an erythro configuration for VIIa and a threo configuration for VIIb (10). Stereochemical attribution of 20-ol groups is uncertain; however, reduction of Δ^{16}-20-ketosteroids with $LiAlH_4$ (11 a,b) appears to suggest a 20α-configuration.

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