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Scheme 1: synthetic transformations of compounds I-XI

Figure 1: Scheme 1: synthetic transformations of compounds I-XI

Abstract

Full Text

Chemistry

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Synthesis of trans-1-hydroxy-1-acetoxyacetyl-6-acetoxy-4,5-(4′-methoxybenzo)-hydrindane—an analogue of corticoid hormones

(Presented by Academician M. M. Shemyakin, February 20, 1960)

With the aim of obtaining tricyclic analogues of steroid hormones containing a dioxyacetone and glycerol side chain, as well as other functional groupings, we carried out the synthetic route shown in Scheme 1. The relative simplicity of obtaining the starting trans-acid (I, $R = H$) ([1]), containing two rings and a carboxymethylene chain for construction of the third ring, makes possible the synthesis, by a short route, of polycyclic systems with trans ring fusion. Replacement of the carbonyl group by a carbomethoxymethylene group permits cyclization of acid (II) in 75% yield and then the introduction of a dioxyacetone and glycerol chain, whereas cyclization of the trans-keto acid (I, $R = H$) and of its transformation products (ethylene ketal, acetoxy- and methoxy-substituted compounds) led to the formation of lactones ([2,3]).

Methyl ester of trans-2-carbomethyl-3-(p-anisyl)-cyclopentylidene-1-acetic acid (II) was obtained by us by the Reformatsky reaction, through condensation of the keto ester (I, $R = CH_3$) with methyl bromoacetate.

acid with subsequent dehydration in 35-37% yield. The exocyclic position of the double bond in acid (II) was confirmed by the UV spectrum, which contains maxima at 226 and 275 mμ. Acid (II) was isolated by us as a single geometrical isomer with m.p. 125-126°, evidently having the trans configuration,* since the cis isomer should experience substantial steric hindrance.

$C_{17}H_{20}O_5$.	Found, %:	C 67.19; H 6.78
	Calculated, %:	C 67.09; H 6.62

On cyclization of acid (II) by the Friedel-Crafts method, the methyl ester of trans-6-keto-4,5-(4′-methoxybenzo)-hydrindylidene-1-acetic acid (III) was ob-

tained, with m.p. 168–169°, λ_{max} 226 mμ, 254 mμ ($\lg \varepsilon$ 4.26; 3.7). Yield 75–78%.

$C_{17}H_{18}O_4$.	Found, %:	C 71.32; H 6.25
	Calculated, %:	C 71.31; H 6.34

The 2,4-dinitrophenylhydrazone has m.p. 285° with decomposition,

$C_{23}H_{22}O_7N_4$.	Found, %:	N 12.01
	Calculated, %:	N 12.18

For conversion of the carbomethoxymethylene chain into a dioxyacetone or glycerol chain, the method described by Hogg and co-workers ([5]) was used, comprising three stages: reduction with lithium aluminum hydride, acetylation of the resulting alcohol, and finally oxidation of $\Delta^{17,20}$-21-acyloxysteroids with N-methylmorpholine peroxide in the presence of a catalytic amount of osmium tetroxide.

On reduction of the keto ester (III) with lithium aluminum hydride, trans-6-hydroxy-4,5-(4′-methoxybenzo)-hydrindylidene-1-ethyl alcohol (IVa) is formed, with m.p. 141–141.5°. Yield 78%.

$C_{16}H_{20}O_3$.	Found, %:	C 73.81; H 7.84
	Calculated, %:	C 73.82; H 7.74

On acetylation of IVa, the diacetate (IVb) was obtained, with m.p. 67.5–68.5°, in 70–75% yield.

$C_{20}H_{24}O_5$.	Found, %:	C 69.90; H 7.19
	Calculated, %:	C 69.75; H 7.03

Reduction of the carbonyl group to an alcohol group in compound III, as in the compounds described by us earlier ([6]), proceeds stereodirectionally with formation of a hydroxyl occupying, apparently, the equatorial position (α), since, in contrast to steroids, the β-face is not shielded by angular methyl groups and therefore approach of the reagent from the β-face can lead to formation of the thermodynamically more stable hydroxyl group.

Oxidation of compound (IVb) with N-methylmorpholine peroxide leads to a mixture of substances, from which, by separation by chromatography on silica gel, trans-1-hydroxy-acetoxyacetyl-6-acetoxy-4,5-(4′-methoxybenzo)-hydrindane (Va, $R_1 = R_2 = COCH_3$) with m.p. 120–121° (yield 30%, $R_f = 0.3$) and trans-1-hydroxy-1-(α-hydroxy-β-acetoxyethyl)-6-acetoxy-4,5-(4′-methoxybenzo)-hydrindane (VIa, $R_1 = R_2 = COCH_3$, $R_3 = H$) in the form of an oil (yield 30%, $R_f = 0.03$)** were obtained. The structure of the substances obtained was established as follows. Substance (Va) gives an intense

* The stereoselectivity (formation of the trans isomer) of this type of reaction was shown by Linstead ([4]).

** Paper-chromatographic separation of the substances described in the present work was carried out in the benzene–formamide system. Chromatograms were developed with a saturated solution of antimony chloride in chloroform.

coloration with triphenyltetrazolium chloride and has absorption bands in the IR spectrum at 1730 cm^{-1} and 3500 cm^{-1}, characteristic of CO and OH groups.

$C_{20}H_{24}O_7$.	Found, %:	C 63.52; H 6.30
	Calculated, %:	C 63.82; H 6.43

After saponification, compound (Vb, $R_1 = R_2 = H$) was obtained, m.p. 194–196°, containing one carbonyl group (1708 cm^{-1}).

$C_{16}H_{20}O_5$.	Found, %:	C 65.96; H 6.90
	Calculated, %:	C 65.73; H 6.90

However, substance (Va) gives neither a semicarbazone nor a 2,4-dinitrophenylhydrazone. Upon its oxidation with periodic acid, acid (X) was obtained, m.p. 148–150°, which confirms the presence of a dioxyacetone chain. Acetylation of substance (Va) under the usual conditions with acetic anhydride in pyridine does not proceed. When acetylation was carried out under conditions in which the hydroxyl group in the 17α-position is capable of being acetylated (in the presence of *p*-toluenesulfonic acid as catalyst), the triacetate (XI) was obtained, m.p. 169–169.5°, $R_f = 0.93$.

$C_{22}H_{26}O_8$.	Found, %:	C 63.07; H 6.39
	Calculated, %:	C 63.14; H 6.27

By analogy with the oxidation of $\Delta^{17,20}$-21-acyloxysteroids with N-methylmorpholine peroxide, and also from the behavior of Va on acetylation of the tertiary hydroxyl, we assume that in our case the mutual arrangement of the groups at C_1 is analogous to the arrangement of such groups in corticosteroids at C_{17}.

On chromatography of the product of oxidation with N-methylmorpholine peroxide on alumina, instead of substance Va with m.p. 120° a substance with m.p. 177–178° was isolated. Yield 25%. Evidently, on alumina, rearrangement of (Va) into compound (VII) takes place (found, %: C 64.01; H 6.57. $C_{20}H_{24}O_7$), which has absorption bands in the IR spectrum at 1735 cm^{-1} and 3500 cm^{-1}, characteristic of CO and OH groups. Substance (VII) gives a 2,4-dinitrophenylhydrazone with m.p. 250–252° and does not color a solution of triphenyltetrazolium chloride.

Upon hydroxylation of (IVb) with osmium tetroxide, substance (VIb, $R_1 = R_2 = R_3 = H$) was obtained, m.p. 193.5-194.5°, $R_f = 0$.

$C_{16}H_{22}O_5$.	Found, %:	C 65.63; H 7.66
	Calculated, %:	C 65.29; H 7.54

On acetylation of VIb, triacetate (VIc, $R_1 = R_2 = R_3 = COCH_3$) was formed, m.p. 121-122°, $R_f = 0.8$.

$C_{22}H_{28}O_8$.	Found, %:	C 63.09; H 6.68
	Calculated, %:	C 62.85; H 6.71

The latter gives a depression of the melting point with Va and contains absorption bands in the IR spectrum at 1732 and 3450 cm^{-1}, characteristic of CO and OH groups. After acetylation of substance (VIa), a triacetate was also obtained with m.p. 121-122°, which did not give a depression of the melting point with triacetate (VIc).

In obtaining (Va), we started from the trans-keto acid (I). In the course of the synthesis described above, isomerization could have occurred and a more stable cis system could have formed from the trans-hydrindane system. To establish the configuration of the fusion of the five-membered and six-membered rings, we carried out ozonolysis of IVb. As a result of the reaction, acetoxyketone (VIII) was obtained, m.p. 153.5-154.5°, $R_f = 0.9$. Yield 57%.

$C_{16}H_{18}O_4$.	Found, %:	C 69.83; H 6.77
	Calculated, %:	C 70.04; H 6.61

The acetoxyketone was subjected to alkaline isomerization in order to obtain the stable isomer. As a result of the reaction, acetoxyketone (IX) was isolated, m.p. 80.5-81.5° (found, %: C 69.64; H 6.72). Since the stable configuration for the hydrindane system is the cis configuration, it follows that compound (IVb) and all compounds preceding the latter have the labile trans configuration characteristic of steroid hormones.

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Note: Figure translations are in progress. See original paper for figures.