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6,11-DIOXA-D-HOMOANALOGS OF STEROIDS BY REACTION OF 2-ACETYL-2-CYCLOHEXEN-1-ONES WITH 4-HYDROXYCOUMARINS

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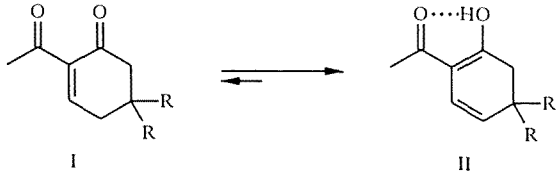
Unsubstituted 2-acetyl-2-cyclohexen-1-one reacts with 4-hydroxycoumarin following the pattern of a Diels–Alder heterodiene condensation to form 12-methyl-6,11-dioxa-9-hydroxy-D-homo-1,3,5(10),12-tetraene-7,17a-dione. In the case of 2-acetyl-5,5-dimethyl-2-cyclohexen-1-one, reaction with both 4-hydroxy- and 4,7-dihydroxycoumarin follows the pattern of a Michael addition with the formation of 3-(2-acetyl-5,5-dimethyl-3-oxocyclohexyl)-4-hydroxy- and 4,7-dihydroxy coumarin respectively. Dehydration of both types of adduct gives 6,11-dioxa-D-homoanalogs of steroids.

In the development of routes for the total synthesis of steroids and their heterocyclic analogs we studied the reaction of 2-acetyl-2-cyclohexen-1-ones (I), occurring in ketodienol form (II), with cyclic β-diketones [1], and β-enaminoketones [2, 3]. These reactions led to new partially hydrogenated dibenzopyran, isoquinoline, and phenanthridine structures.



I II

I, II a R = H, b R = Me

The present work is devoted to a study of the reaction of 2-acetyl-2-cyclohexen-1-ones I with 4-hydroxycoumarin (IIIa) and 4,7-dihydroxycoumarin (IIIb), the objective being the preparation of new tri- and tetracyclic compounds since it is known [4, 5] that coumarins with condensed rings are of great interest to biochemists on account of their broad spectrum of biological activity.

It was found that the unsubstituted endione Ia reacts with hydroxycoumarin IIIa by a Diels–Alder reaction giving the tetracyclic compound IV. Reaction of this endione with enolic ethers takes place in a similar manner, as reported in [6]. At the same time, in the absence of catalyst the endiene Ib does not react with 4-hydroxycoumarins – the Michael reaction occurs in the presence of catalytic quantities of metallic sodium in methanol and leads to the adducts V.

In the PMR spectra (Table 1) of compounds Vb and c there is a signal for the proton of the OH of the cis-ketoenol form (15.2 ppm) of the acetylcyclohexane fragment but in the PMR spectrum of the hydroxydiketone IV the proton of the hydroxyl group appears at 6.60 ppm. In the ^{13}C NMR spectrum of the latter an unequivocal assignment of the signals is possible, including the carbons of the keto group $C_{(4)}$ (210.59 ppm), the lactone carbonyl $C_{(10)}$ (161.91 ppm), and the semiketal $C_{(14)}$ (99.44 ppm). The relative configuration of the substituents in positions 8, 9, and 14 of the dioxasteroid IV was assigned on the basis of the stereochemical features of the diene condensation. In accordance with the rule of cis-addition and the Alder endo rule, one should assign a cis-syn-BCD configuration to the compound [7].

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TABLE 1. Characteristics of Compounds Prepared

Compound	Empirical formula	M^+	M_{calc}	mp, °C	IR spectrum, cm^{-1}	NMR spectrum, ppm*	Yield, %
IV	$C_{17}H_{16}O_5$	300	300	178...180	1572, 1620, 1673, 1713, 3300	210,59 (C_{17a}); 162,26 (C_7); 161,91 (C_5); 153,00 (C_{12}); 132,19 (C_1); 124,06 (C_3); 123,11 (C_2); 116,61 (C_4); 114,64 (C_{13}); 103,19 (C_{10}); 99,44 (C_9); 53,42 (C_8); 38,48 (C_{17}); 32,70 (C_{14}); 29,79 (C_{16}); 27,71 (Me); 18,61 (C_{15})	80
Vc	$C_{19}H_{20}O_5$	328	328	181...183	1578, 1625, 1700, 1713, 3365	1,00 (s, 5'-CH_3); 1,10 (s, 5'-CH_3); 1,20...4,00 (4H, m); 7,30...8,10 (4H, m, Ar); 15,00 (s, OH)	93
Vb	$C_{19}H_{20}O_6$	344	344	224...230 (decomp.)	1568, 1620, 1662, 1722, 3420	1,02 (6H, s, 5'-CH_3); 2,02 (s, $\underline{CH_3}CO$); 0,80...3,50 (m, $5\underline{H}$); 6,80...6,90 (2H, m, Ar); 7,90 (1H, d, Ar, J = 8); 15,20 (1H, s, OH)	92
VIa	$C_{17}H_{14}O_4$	282	282	146...148	1392, 1610, 1665, 1715	201,29 (C_{17a}); 161,32 (C_7); 154,82 (C_5); 122,57 (C_2); 116,67 (C_4); 114,45 (C_{13}); 113,57 (C_8); 21,60 (C_{16}); 17,25 (Me)	95
VIb	$C_{19}H_{18}O_5$	326	326	256...268 (decomp.)	1613, 1655, 1695, 1715, 3340	1,00 (16-CH_3); 1,08 (16-CH_3); 2,24 (s, 12-CH_3); 3,70 (8,14-H, J = 10,0); 1,10...2,40 (m, 4H); 7,64 (d, Ar, J = 8,0)	91
VIc	$C_{19}H_{18}O_4$	310	310	197...199	1585, 1615, 1650, 1715	201,16 (C_{17a}); 161,02 (C_7); 155,02 (C_5); 152,70 C_{12}); 151,16 (C_9); 132,11 (C_1); 124,23 (C_3); 122,50 (C_2); 116,73 (C_4); 114,53 (C_{13}); 113,65 (C_8); 104,23 (C_{10}); 55,19 (C_{15}); 43,27 (C_{17}); 32,20 (C_{16}); 32,11 (Me); 29,27 (C_{14}); 28,08 (Me); 16,92 (Me)	97

*Atoms in compounds IV and VI numbered according to steroid nomenclature.

Dehydration of compounds IV and Vb, c gave 6,11-dioxa-analogs of the steroids. In the ^{13}C NMR spectra of compounds VIa and b all the signals could be unequivocally assigned, including lactones (161.02 and 161.32 ppm) and 17a-ketones (201.16 and 201.29 ppm) respectively. The formation of compounds VIb and c rather than an alternative structure of the type of VII is in accordance with the greater activity of the ketone compared with the lactone carbonyl: in the majority of cases the reaction of 4-hydroxycoumarin and its aza- and thiaanalogs takes place with participation of the ketone function [8].

EXPERIMENTAL

Infrared spectra were run on a UR-20 instrument in KBr disks. NMR spectra were recorded on a Bruker WM-360 with TMS as internal standard. Molecular weights were determined on a Varian MAT-311 mass spectrometer with an ionization energy of 70 eV.

The results of elemental analyses were in agreement with those calculated.

12-Methyl-6,11-dioxa-9-hydroxy-D-homo-1,3,5(10)-tetraen-7,17a-dione (IV). To a solution of 1.62 g (10 mmole) 4-hydroxycoumarin IIIa in 60 ml chloroform was added 1.38 g (10 mmole) freshly-prepared [1] acetylcyclohexenone Ia in 150 ml ether and the mixture held at +10°C for 24 h. The solvent was evaporated and the residue separated on a chromatograph column (silica gel 100/160m, *l* 6 cm, ethyl acetate). The yield was 2.4 g (80%) hydroxydiketone IV and 0.12 g (9%) of the dimer [2] of acetylcyclohexenone.

3-(2-Acetyl-5,5-dimethyl-3-oxocyclohexyl)-4-hydroxycoumarin (Vc). To a solution of 70 mg (3.1 mmole) sodium metal in 30 ml ethanol was added, after cooling, 1.5 g (9.23 mmole) 4-hydroxycoumarin IIIa and, 30 min later, 1.53 g (9.23 mmole) endione Ib [1] and the mixture kept at room temperature. After 24 h the methanol was evaporated in vacuum and the residue treated with 5% HCl (30 ml) and extracted with chloroform and the extract dried over magnesium sulfate. Evaporation of the solvent yielded 2.82 g (93%) triketolactone Vc.

A similar procedure was used for the reaction of 4,7-dihydroxycoumarin (IIIb) [9] with the endione Ib to obtain 3-(2-acetyl-5,5-dimethyl-3-oxocyclohexyl)-4,7-dihydroxycoumarin (Vb).

12,16,16-Trimethyl-6,11-dioxa-D-homo-1,3,5(10),8,12-pentaen-7,17-dione (VIc). To a solution of 0.656 g (2 mmole) triketolactone Va in 200 ml benzene was added 1.0 g P_2O_5 and the mixture heated 3 h at bp and then filtered through a 1 cm layer of Al_2O_3. The solvent was evaporated and the residue recrystallized from a mixture of chloroform and ether. Yield 0.59 g (97%) tetracycle VIc.

A similar procedure was used to prepare 12-methyl-6,11-dioxa-D-homo-1,3,5(10),8,12-pentaen-7,17a-dione (VIa) and 12,16,16-trimethyl-6,11-dioxa-3-hydroxy-D-homo-1,3,5(10),8,12-pentaen-7,17a-dione (VIb).

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