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SYNTHESIS OF 17*a*-ETHOXIMINO DERIVATIVES OF 8-AZA-D-HOMOGONA-12,17*a*-DIONES BY ANNELATION OF 3,4-DIHYDROISOQUINOLINES WITH 2-ACETYL-3-ETHOXIMINO-5,5-DIMETHYLCYCLOHEXANONE

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[2+4] Cyclocondensation of 3,4-dihydroisoquinolines with 2-acetyl-5,5-dimethyl-3-ethoximinocyclohexanone has been used to synthesize the previously unavailable 17a-ethoximino derivatives of 8-aza-D-homogona-12,17a-diones.

Cyclocondensation of cyclic Schiff bases with 2-acylcycloalkanones, 2-acylcycloalkane-1,3-diones, 5-acylbarbituric acids, and other β- di- or β,β'-tricarbonyl compounds gives condensed azines, which are structurally related to steroids [1-5]. These compounds show a marked effect on the immune function of an organism in the absence of hormonal effects and present theoretical and practical interest in the development of low molecular, nonantigenic remedies of regulating immunity in man and in animals [6-7]. The structural and functional transformations in the CD-fragment of the ABCD-tetracyclic 8-azasteroid framework can affect both the degree and the course of their immune activity to give substances with both immunostimulating and immunodepressing activity [8-9]. However, methods for regioselective modification of the 2,17*a*-β-dicarbonyl group of immunotropic 8-azasteroids are very scarce [10-11], preventing the preparation of novel compounds in this series and, as a consequence, limiting the structure-functional interactions and also the development of more safe and more efficient immunomodulating agents.

With this in mind, the development of approaches to the synthesis of a modified β-dikarbonyl group-containing 8-azasteroids, based on their reaction with Schiff bases, not on β,β'-triketones themselves [2, 4, 5] but on their derivatives involving carbonyl groups of both the acyl and cyclic fragments, appears to be important. Such a route was partly achieved by cyclocondensation of 3,4-dihydroisoquinolines with 2-(1-aminoethylidene)-cyclohexane-1,3-diones [12]. Inclusion in a similar reaction of 2-acylcycloalkane-1,3-dione derivatives at the carbonyl groups of the cyclic fragment has not been studied previously and considering the foregoing is of great interest.

As the most suitable compounds of the mentioned type we chose the available oximino derivatives [13], in which the 2-acetylcycloalkanone β-dicarbonyl group essential for condensation was retained. In the present work, we examined the novel route on examples of interaction of 3,4-dihydroisoquinolines (Ia,b) with 2-acetyl-3-ethoximino-5,5-dimethylcyclohexanone (II). The choice of this O-ethyloxime II rather than oxime is explained by the fact that similar oximes are readily cyclized to isoxazoles [14] and this may prove a disadvantage for carrying out the proposed cyclocondensation. It should also be mentioned that, in contrast to reaction with 2-acyl-cycloalkane-1,3-diones [2, 4, 15] which are generally complete after 3-7 hours of refluxing or in 12-24 h at room temperature, in this case reaction completion needs 15-20 h of refluxing and this indicates to a lower reactivity of compound II when compared with its β,β'-triketone precursor. The likely products of the reaction were expected to be 12-oxo-17a-ethoximines (IIIa,b) but in result of reaction their 9(11)-dehydro derivatives (IVa,b) have been obtained which are the secondary reaction products according to TLC data.

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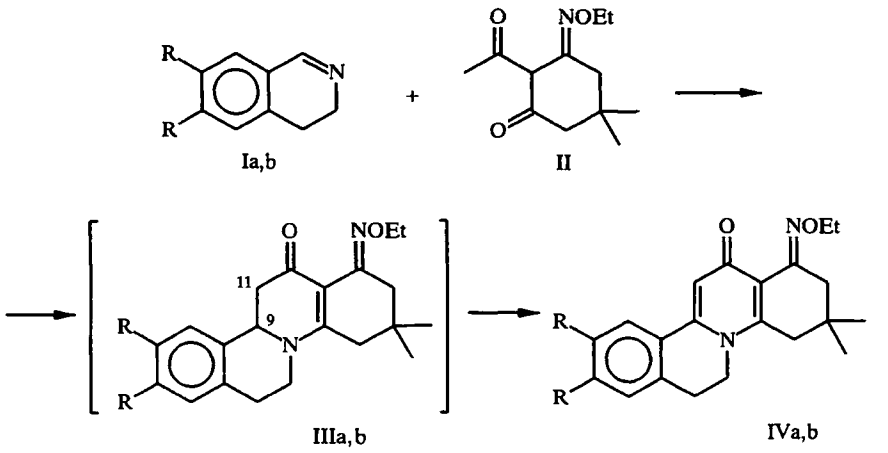

I, III, IV a R = H, b R = OMe

Such an unexpected result of spontaneous dehydrogenation in the course of reaction is evidently connected with the specific nature of the formed compound III. It was notable that dehydrogenation was not observed at the annelation of 3,4-dihydroisoquinolines Ia,b by 2-acylcycloalkanones [1] and this confirms our proposal concerning the effect of the ethoximino group on stability of the proposed annelation products III.

The structure of compounds IVa,b was confirmed by the results of elemental analysis and from spectral data. Hence, in their mass spectra molecular ion signals corresponding to the calculated values are present. In their IR spectra absorption bands for the carbonyl groups of the γ-pyridone ring at 1639-1628 cm^{-1} [16] are observed. In the UV spectra typical γ-pyridone absorption bands at 260-265 nm [17] are present.

Most information about the structure of compounds IVa,b comes from their PMR spectra, in which the methyl group triplet (δ 1.31-1.33 ppm, J = 7.0 Hz) and the methylene group quartet (δ 4.32-4.34 ppm, J = 7.0 Hz) belonging to the ethoxy substituent are observed. Instead of the ABX spin system typical of the protons at $C_{(9)}$ and $C_{(11)}$ in derivatives of III [2] there is found a low field singlet proton signal assigned to $C_{(11)}$ of the γ-pyridone ring of 8-azasteroids at δ 6.74-6.94 ppm [18]. In agreement with the proposed structure, the ^{13}C NMR spectra have a number of carbon nuclei resonance signals, in particular in the low field region for carbonyl groups one CO group signal is found which is shifted to high field (δ 174-175 ppm) and in the high field region a signal corresponding to the $C_{(17a)}$ methyl group of the ethoximino substituent (δ 14 ppm) is observed.

Also of note were the rather low (relative to those of 8-azasteroid 12,17a-dioxo derivatives [2, 15, 18]) melting points of compounds IVa,b that vary in the range of 85-100°C and this may be connected with the disordered nature of their crystal structures.

Hence we have shown that modification of one of the carbonyl groups in the cyclohexane fragment of 2-acylcyclohexane-1,3-diones does not present their cyclocondensation with cyclic Schiff bases and opens up a direct, single stage route to the synthesis of 8-azasteroid derivatives with the purposefully modified functionality in the pharmacologically important CD-fragment.

EXPERIMENTAL

The course of the reaction and the product purity were monitored by TLC on Silufol UV-254 plates using chloroform-methanol (9:1) eluent with visualization in UV light or iodine vapors with subsequent heating at 250-300°C. Melting points were measured on a Boetius heating block. IR spectra were taken on a UR-20 instrument for KBr tablets. UV spectra were obtained on a Specord M-400 spectrophotometer for solutions in methanol. PMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument (200 and 90 MHz respectively) for solutions in $CDCl_3$ using TMS as internal standard. Mass spectra were measured on a Varian MAT-311 mass spectrometer with direct introduction of the sample and an electron ionization energy of 70 eV.

17*a*-Ethoximino-16,16-dimethyl-8-aza-D-homogona-1,3,5(10),9(11),13-pentaen-12-one (IVa). Mixture of 3,4-dihydroisoquinoline Ia (0.39 g, 3 mmol) and acetylcyclohexanone II (0.68 g, 3 mmol) in isopropanol (15 ml) was refluxed for 20 h. The reaction mass was then evaporated to dryness and the residue dissolved in chloroform and flash chromatographed on silica gel (5/40 μ, 7 g) eluting with chloroform-methanol mixture (49:1). The combined eluates were evaporated and the residue crystallized from mixture of ethanol and ether to give the product IVa (0.74 g, 74%) as colorless, needle like crystals with mp 87-91°C. IR spectrum: 3000-2850, 1628, 1610 sh, 1586, 1560, 1491, 1472, 1460, 1058, 873, 780 cm^{-1}. UV Spectrum, λ_{max} (ε): 215 (15090), 265 nm (40720); λ_{min} (ε): 232.7 nm (5630). Mass spectrum: 336 (M^+). Found, %: C 74.75; H 7.08; N 8.24. $C_{21}H_{24}N_2O_2$. Calculated, %: C 74.97; H 7.19; N 8.33.

17*a*-Ethoximino-2,3-dimethoxy-16,16-dimethyl-8-aza-D-homogona-1,3,5(10),9(11),13-pentaen-12-one (IVb). Similarly to the synthesis of compound IVa by refluxing of mixture of 3,4-dihydroisoquinoline Ib (0.48 g, 2.5 mmol) and acetylcyclohexanone II (0.56 g, 2.5 mmol) in ethanol (10 ml) for 17 h and subsequent treatment of the reaction mass the product IVb (0.7 g, 71%) was obtained as pale yellow, fine prisms with mp 87-97°C. IR spectrum: 3000-2830, 1639, 1618, 1525 sh, 1515, 1475, 1362, 1275, 1218, 1159, 1066, 876 cm^{-1}. UV spectrum, λ_{max} (ε): 231.6 (21240), 275 (21040), 324.3 nm (13700); λ_{min} (ε): 217.7 (19125), 260 (15745), 301.9 nm (11255). Mass spectrum: 396 (M^+). Found, %: C 69.71; H 7.09; N 7.00. $C_{23}H_{28}N_2O_4$. Calculated, %: C 69.67; H 7.12; N 7.07.

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