APPROACH TO SYNTHESIS OF 8-AZASTEROIDS

COMMUNICATION 1. SYNTHESIS AND SOME PROPERTIES OF BENZO[*a*]CYCLOALKANO[f]QUINOLIZINES*

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The recently conducted systematic study of the chemistry of triacylmethane compounds led us to the need of studying the reaction of the 3,4-dihydroisoquinolines (VI) with 2-acetyl-1,3-cycloalkanediones (I)-(V). This reaction, similar to the well-known transformations of enolizable β-diketones under the influence of Schiff bases, leads in the case of cyclohexane β-triketones (III)-(V) to dibenzo[*a*,f]quinolizines (VII)-(X) [1, 2]. In view of the ease of formation of the latter and their obvious structural relationship to the biologically highly active isoquinoline alkaloids of the tetrahydroberberine (XIII) and chelidonine (XIV) series it seemed of interest to study the reaction of dihydroisoquinoline (VIa) with cyclopentane β-triketones (I) and (II). The corresponding benzo[*a*]cyclopentano[f]quinolizines (XI) and (XII) are formed as the result of the progress of this reaction. The indicated compounds should apparently possess the properties of quinolizines (VII)-(X), but they can also be regarded as being the 8-aza analogs of estrone (XV), from which they differ by the absence of an angular methyl group at C_{13}.

The relative availability of the vinylog lactams (VIII)-(XII) made it possible to study their behavior in certain transformations, mainly under the influence of various electrophiles, in order to approach the synthesis of compounds belonging to the 8-azaestrone series.

When alcohol solutions of equivalent amounts of β-triketones (III)-(V) and dihydroisoquinoline (VIa) were heated the corresponding cyclodehydration products were obtained in 50-60% yield. Their absorption spectra testify to the presence of the enaminodicarbonyl grouping in the molecules, which appears in the IR spectra as a characteristic set of bands in the 1500-1700 cm^{-1} region, and in the UV spectra as two intense bands in the 260-310 nm region. The similarity of these spectra with the corresponding spectra of the vinylog amides of the (XVII) [3] and quinolizine (VII) [2] series makes it possible to consider the mentioned cyclodehydration products as being quinolizines (VIII)-(X). The formation of the latter evidently includes, as an intermediate step, salt formation between the base (VIa) and the vinylogs of carboxylic acids, which the enolic forms of the β-triketones (III)-(V) actually are. An intermediate compound of this type, obtained from 2-acetyl-1,3-cyclopentanedione (I), proved to be quite stable. Long heating of this compound leads to the cyclodehydration product in ~35% yield; here no advantages were observed when compared with using the starting components (I) and (VIa), without isolating the corresponding ammonium salt, in the reaction. An analogous end product is formed when base (VIa) is reacted with the bicyclic β-triketone (II). A comparison of the IR and UV spectra of the obtained compounds with those of the previously synthesized by us [4] vinylog amides of the cyclopentane series (XVI) indicates that the same enaminodicarbonyl grouping is present in the former. On this basis the compounds formed from β-triketones (I) and (II) and hydroisoquinoline (VIa) are regarded as respectively being benzoquinolizines (XI) and (XII).

The structure of the vinylog lactams (VIII)-(XII) was confirmed by the data of the mass spectra and the NMR spectra. The intense peaks of molecular ions are present in the mass spectra of all of the studied

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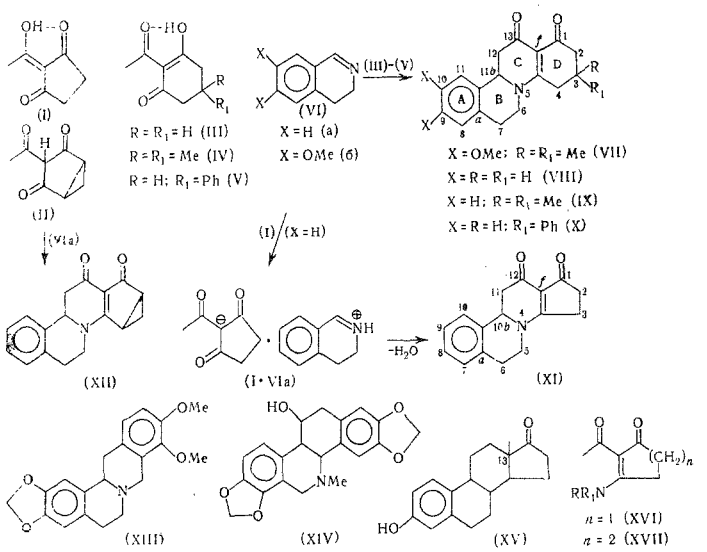
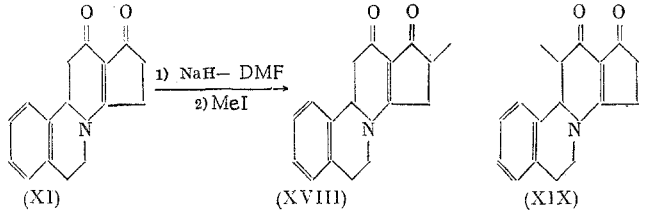


compounds. Their subsequent fragmentation depends on the nature of the D ring of the quinolizidine molecule. In particular, the spectrum of the pentacyclic product (XII) apparently indicates the initial aromatization of the D ring, since the spectrum of the dimethyl derivative (IX) is characterized by two intense peaks, which correspond to the cleavage of a methyl group (m/e 280) and retrodiene decomposition (m/e 239). Further decomposition proceeds with a cleavage of ring C, which leads in all cases to the formation of the dihydroisoquinoline fragment with m/e 130.

The NMR spectra of the discussed compounds exhibit in the region δ 4.9-5.1 ppm the characteristic resonance signal of an angular benzyl proton at C_{11b} for (VIII)-(X), or at C_{10b} for (XI) and (XII). The signal has the shape of four lines of approximately equal intensity, with J 5-6 and 12-14 Hz. It was shown by the double resonance method that this quartet represents the X part of the ABX spectrum, which is formed by the coupling of the mentioned benzyl proton with the protons of the adjacent methylene group at C_{11} (C_{12}). In this connection the shape and position of the signal make it possible to assume that the dihedral angles with the methylene protons are approximately 180 and 60° [5], in which connection the benzyl proton itself should occupy a predominantly quasiaxial position [2, 6-11]. Bohlmann bands are absent in the IR spectra of all of the quinolizidines (VIII)-(XII) in the 2700-2800 cm^{-1} region [12, 13].

Vinylog lactams (VIII)-(XII), similar to enaminodiketones (XVI) and (XVII), proved to be very inert compounds chemically. The main efforts to effect their structural modification reduced to attempting to insert an angular alkyl (mainly methyl) substituent in order to enter the series of 8-azaestrane derivatives. However, the various known methods for the C-alkylation of vinylog amides used by us failed to lead to the desired results in the cases of (VIII)-(XII). In addition, the theoretically possible N- and O-alkylation products of these compounds were not detected. This result is unexpected, especially if it is considered that various techniques for the alkylation of vinylog lactams of the type of (VIII) or (XI), but not containing the additional keto function, are described in the literature [8, 14, 15]. The presence of the latter apparently causes a stronger delocalization of the unshared pair of electrons than in the vinylog lactams, which should lead to an increase in the activation energies of processes involving such a grouping (cf. [10, 16]). The anionoid C-methylation of quinolizine (XI) observed by us can serve as some confirmation of this. The reaction proceeds under drastic conditions and leads to the formation of product (XVIII) in less than 5% yield.

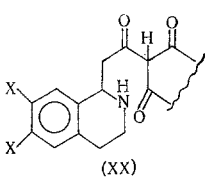


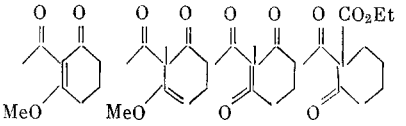
The structure of (XVIII) follows from the data of the vibrational spectra and the NMR spectrum (in $CDCl_3$), in which, in particular, is present a doublet signal (J = 7 Hz) from the protons of the methyl group (δ 1.3 ppm), while the above indicated ABX spin system is retained, with the X part at 5.0 ppm (center of quadruplet). The latter would be impossible in the case of the alternate structure (XIX), which contains a methyl

substituent at C_{11}. Our attempts to accomplish the independent synthesis of the methylated product (XVIII) (or its isomer) by the reductive cleavage under various conditions of the cyclopropane ring in the pentacyclic base (XII) proved unsuccessful. In particular, this compound, the same as the other quinolizines (VIII)-(XI), proved to be stable under either catalytic or ionic hydrogenation conditions. In addition, they are all stable toward acids and bases.

According to [2], the mechanism for the formation of the quinolizidines discussed here include as the controlling step the reaction of the methyl group of the acetyl in the β-triketone with the C=N bond in the dihydroisoquinoline molecule. As a result, the intermediate amino triketone (XX) should be formed in this step in the form of the corresponding preferred tautomer. This can explain, for example, the above mentioned slower progress of the reaction of base (VIa) with 2-acetylcyclopentadione (I) when compared with the cyclohexane β-triketones, which exist almost completely in the form of enols of the (III)-(V) type. Actually, in contrast to them, the cyclopentane analogs, being stronger acids, are characterized by an appreciable portion of α-hydroxyethylidene tautomers of the (I) type, with an exocyclic double bond [17]. Consequently, the activation of the methyl group of the acetyl in (I), which reacts with the C=N bond, should be correspondingly lower than in the cyclohexane series.

On the basis of this scheme, it could be expected that the condensation of the dihydroisoquinolines (VI) with the O- and C-methyl derivatives (XXI)-(XXIII) of the β-triketone (III), previously synthesized by us [18, 19], will proceed in an analogous manner. As a result, the formation of products, which cannot be obtained by the above discussed modification of the vinylog lactam (VIII), could be expected from the nonenolizable di- (XXII) and triketone (XXIII)


(XX)


(XXI) (XXII) (XXIII) (XXIV)

As it proved, ether (XXI), which possesses acid properties [18, 20], gives with base (VIa) a hygroscopic saltlike compound, which, however, fails to undergo further changes even on long heating. The condensation of the dihydroisoquinolines (VI) with methyl ketones (XXII) and (XXIII) under various conditions also failed to lead to the desired results. The reaction between these components, which proceeds to noticeable degree in polar protic media, is accompanied by cleavage of the triacylmethane grouping. Such cleavage during reaction with base (VIb) was described for diketo ester (XXIV) [11], and was also observed by us under other conditions in the cases of (XXII) [18] and (XXIII) [19].

As a result, the discussed data indicate the need for seeking other ways of modifying the quinolizidine molecules (VIII)-(XII) in order to enter the series of 8-azaestrane compounds, which will be discussed by us in subsequent communications.

EXPERIMENTAL METHOD

The melting points were determined on a Kofler block. The IR spectra were obtained on an UR-10 instrument as KBr pellets, the UV spectra were taken on an ERS-2 spectrophotometer in alcohol solution, while the NMR spectra were taken on a Varian DA-60 spectrophotometer in trifluoroacetic acid solution, using HMDS as the internal standard. The mass spectra were obtained on an MKh-1303 spectrometer, with direct insertion of the sample into the source.

Preparation of 18-Nor-8-aza-D-homo-$\Delta^{1,3,5(10),13(14)}$-estratetraene-12,17$\alpha$-diones (VIII)-(X). A solution of 3 g of 2-acetyldihydroresorcinol (III) [21] and 2.6 g of dihydroisoquinoline (VIa) [22] in 100 ml of alcohol was refluxed for 3 h, after which the obtained precipitate was filtered, washed on the filter with chilled alcohol, and recrystallized from the same solvent. We obtained 3 g (56%) of 2,3,4,7,8,11b,12,13-octahydro-1H-dibenzo-[a, f]-1,13-quinolizinedione (VIII) as colorless prisms with mp 212-214°. Found: C 76.06; H 6.40; N 5.31%. $C_{17}H_{17}NO_2$. Calculated: C 76.38; H 6.41; N 5.24%. Infrared spectrum (ν, cm^{-1}): 1530, 1595, 1670. Ultraviolet spectrum (λ_{max}, nm): 266 (ε 15,400), 306 (ε 17,300).

In a similar manner, when an alcohol solution of equimolar amounts of 2-acetyldimedon (IV) [23] and dihydroisoquinoline (VIa) was refluxed for 5 h we obtained a 55% yield of 3,3-dimethyl-2,3,4,7,8,11b,12,13-octahydro-1H-dibenzo[a, f]-1,13-quinolizinedione (IX) with mp 195-197° (from alcohol). Found: C 77.15;

H 7.35; N 5.21%. $C_{19}H_{21}NO_2$. Calculated: C 77.26; H 7.17; N 4.74%. Infrared spectrum: (ν, cm^{-1}): 1520, 1600, 1680. Ultraviolet spectrum (λ_{max}, nm): 267 (ε 13,200), 310 (ε 17,500).

In a similar manner, from β-triketone (V) [23] and base (VIa) when refluxed for 3 h we obtained a 50% yield of 3-phenyl-2,3,4,7,8,11b,12,13-octahydro-1H-dibenzo[*a*, f]-1,13-quinolizinedione (X) as colorless needles with mp 262-263° (from alcohol). Found: C 80.41; H 5.98; N 3.88%. $C_{23}H_{21}NO_2$. Calculated: C 80.44; H 6.16; N 4.08%. Infrared spectrum (ν, cm^{-1}): 1515, 1612, 1680. Ultraviolet spectrum (λ_{max}, nm): 268 (ε 16,000), 308 (ε 19,200).

Preparation of 18-Nor-8-aza-$\Delta^{1,3,5(10),13(14)}$-estratetraene-12,17-diones (XI) and (XII). To a stirred solution of 2.8 g of freshly distilled dihydroisoquinoline (VIa) in 10 ml of ether was added a solution of 3 g of freshly recrystallized β-triketone (I) [24] in 50 ml of ether. A pale yellow crystalline precipitate was obtained, which was filtered, washed on the filter with hexane, and dried in vacuo. We obtained about 5.8 g of the 3,4-dihydroisoquinoline salt of 2-acetyl-1,3-cyclopentadione (I·VIa) with mp 177-179°. Found: C 71.07; H 6.40; N 5.16%. $C_{16}H_{17}NO_3$. Calculated: C 70.83; H 6.32; N 5.16%. Infrared spectrum (ν, cm^{-1}): 1425, 1445, 1500, 1600, 1670, 2700-3200 (broad band).

A solution of 5.8 g of the (I·VIa) salt in 350 ml of methanol was refluxed for 3 h, after which it was evaporated in vacuo and the residue was recrystallized from alcohol. We obtained 1.8 g of 1,2,3,5,6,10b,11,12-octahydrobenzo[*a*]cyclopentano[f]-1,12-quinolizinedione (XI) as colorless plates with mp 295-297°. Found: C 75.78; H 6.07; N 5.63%. $C_{16}H_{15}NO_2$. Calculated: C 75.87; H 5.97; N 5.53%. Infrared spectrum (ν, cm^{-1}): 1485, 1565, 1590, 1625, 1695. Ultraviolet spectrum (λ_{max}, nm): 259 (ε 28,800), 293 (ε 17,600).

A solution of 3.2 g of β-triketone (I) and 3 g of dihydroisoquinoline (VIa) in 150 ml of alcohol was refluxed for 5 h, after which the obtained precipitate was filtered, washed on the filter with chilled alcohol, and recrystallized from the same solvent. We obtained 3 g (52%) of quinolizine (XI) with mp 290-295°, which failed to depress the mixed melting point with the above-described sample of (XI).

In a similar manner, when an alcohol solution of equimolar amounts of the bicyclic β-triketone (II) [25] and dihydroisoquinoline (VIa) was refluxed for 3 h we obtained a 55% yield of 2,3-methyleno-1,2,3,5,6,10b,11,12-octahydrobenzo[*a*]cyclopentano[f]quinolizine-1,12-dione (XII) with mp 284-286° (from alcohol). Found: C 76.58; H 5.71; N 5.09%. $C_{17}H_{15}NO_2$. Calculated: C 76.96; H 5.70; N 5.28%. Infrared spectrum (ν, cm^{-1}): 1485, 1565, 1590, 1615, 1680. Ultraviolet spectrum (λ_{max}, nm): 272 (ε 11,100), 303 (ε 12,700).

Methylation of Quinolizine (XI). A mixture of 1.5 g of quinolizine (XI) in 100 ml of DMF, previously distilled over calcium hydride, and 380 mg of 70% NaH was stirred in an argon atmosphere for 25 min at room temperature, and then for 30 min at 50-70°, in which connection the liberated hydrogen was collected; the yield was 102 ml (75% of theory). To the obtained solution of the Na salt at room temperature was added 4 ml of MeI, the mixture was let stand for 15 min, and then it was evaporated in vacuo, treated with water, and extracted with chloroform. The extract was worked up in the usual manner and the substance was purified by the passage of an acetone solution through a bed of Al_2O_3 to give 280 mg of mixed products with mp 240-250°. Repeated recrystallization of this mixture from methanol gave ~50 mg of 2-methyl-1,2,3,5,6,10b,11,12-octahydrobenzo[*a*]cyclopentano[f]-1,12-quinolizinedione (XVIII) with mp 213-215°. Found: N 5.26%; mol. wt. 267 (mass-spectrometrically). $C_{17}H_{17}NO_2$. Calculated: N 5.24%; mol. wt. 267.3. Ultraviolet spectrum (λ_{max}, nm): 260 (ε 40,000), 294 (ε 27,500).

CONCLUSIONS

1. Benzo[*a*]cycloalkano[f]quinolizines were obtained by the condensation of 2-acetyl-1,3-cycloalkenediones with 3,4-dihydroisoquinoline.

2. Some routes for the modification of quinolizines were investigated in order to effect the synthesis of products belonging to the 8-azaestrane series.

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