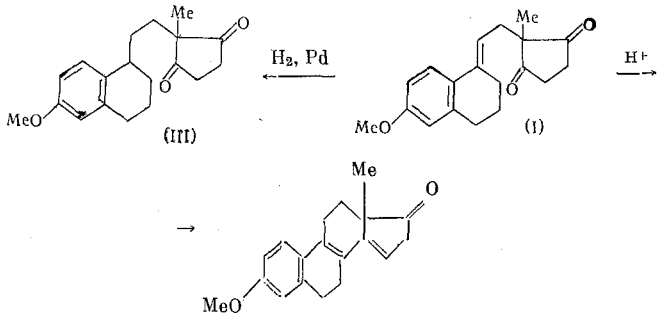
CYCLIZATION OF 3-METHOXY-$\Delta^{1,3,5(10)}$-8,14-SECOESTRATRIENE-14,17-DIONE

S. N. Ananchenko, R. N. Chigir, and I. V. Torgov

UDC 542.91:547.92

Previously [1] we had shown that 3-methoxy-$\Delta^{1,3,5(10),9(11)}$-8,14-secoestratetraene-14,17-dione (I) is easily cyclized in the presence of acid agents to give 3-methoxy-$\Delta^{1,3,5(10),8,14}$-estrapentaen-17-one (II) in high yield, which is a key product in the total synthesis of D,L-estrone. It was postulated that such an easy cyclization is due to, first, the close spatial proximity of the keto group to ring B, and second, the activation of the hydrogens of the methylene group by the exocyclic double bond.

It was interesting to ascertain whether this cyclization would occur in a diketone without the activating double bond, but with a retained close spatial proximity of the keto group to ring B or, in other words, will 3-methoxy-$\Delta^{1,3,5(10)}$-8,14-secoestratriene-14,17-dione (III) undergo cyclization. The latter was obtained by the catalytic hydrogenation of (I), in which connection diketone (III) was formed in a yield of 92%.



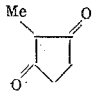
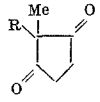
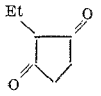
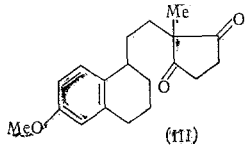
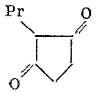
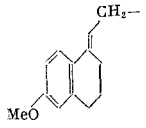
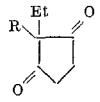
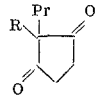
(II)

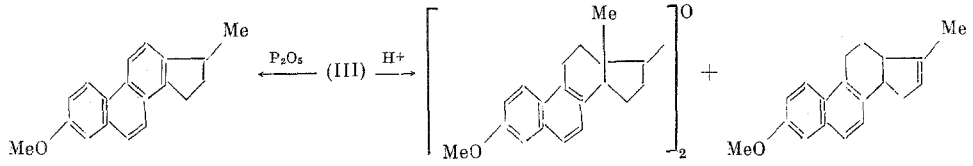
It should be mentioned that in the NMR spectra of (I) and (III), the same as in the case of their analogs (IV) and (V), a singlet appears at 2.63-2.73 ppm, which corresponds to the four methylene protons (Table 1). The same signal, but shifted upfield (2.42-2.43 ppm), was observed by us for the 2-alkylcyclopentane-1,3-diones (VI)-(VIII). These signals are characteristic for the 2-mono- and disubstituted derivatives of 1,3-cyclopentanedione (but not for the 1,3-cyclohexanedione derivatives). The mentioned shift is possibly due to the enolization of the monosubstituted cyclopentanediones [2].

Secodiketone (III), in contrast to (I), is no longer cyclized under mild conditions, for example, by treatment with HCl at 20°C. Under drastic conditions, and specifically by heating with P_2O_5 at 120°, diketone (III) forms a mixture of products, from which we were able to isolate 1-methyl-7-methoxy-2,3-dihydro-1H-cyclopenta[*a*]phenanthrene (IX) in 18% yield, which was identical (in the melting point and the IR and UV spectra) with the by-product that was obtained in [3] by the cyclization of (I). Cyclization also occurs when (III) is heated in either benzene or toluene in the presence of p-toluenesulfonic acid, which is accompanied, the same as when P_2O_5 is used, by dehydration and dehydrogenation reactions. From the reaction mixture were isolated the methoxy ether (X) and 17-methyl-3-methoxy-18-nor-16,17-dehydroequilenane (XI).

M. M. Shemyakin Institute of the Chemistry of Natural Compounds, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 7, pp. 1628-1632, July, 1973. Original article submitted November 21, 1972.

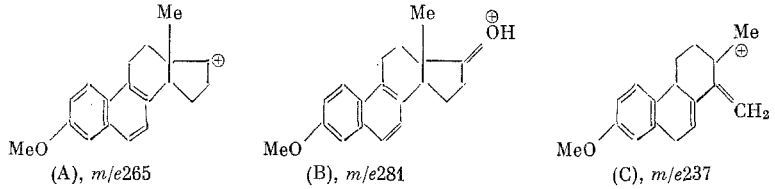
TABLE 1. NMR Spectra of 2-Mono- and 2,2-Dialkyl-Substituted 1,3-Cyclopentanediones

Compound	CH_2-CH_2 signal, ppm	Compound	CH_2-CH_2 signal, ppm
 (VI)	2,45 [2]	 (I)	2,72
 (VII)	2,52	 (III)	2,73
 (VIII)	2,48		
 = R		 (IV)	2,63
		 (V)	2,65



(IX) (X) (XI)

Formula (X) was proposed by us on the basis of the following data. The UV spectrum shows the presence of a naphthalene system. The bands of the hydroxyl and carbonyl groups are absent in the IR spectrum, and only the band of the $\rangle C-O-C\langle$ bond is present. The six-proton singlet in the NMR spectrum upfield (0.74 ppm) suggests a symmetrical structure for the molecule and an angular position of the methyl groups; the signals of vicinal protons are absent. A two-proton multiplet also appears at 3.76 ppm, which should be assigned to the protons at the C_{17}-carbon atoms, attached to oxygen. In the mass spectrum of (X) are present a small molecular peak with m/e 546, the intense peaks of fragments with m/e 265 and 281, which characterize cleavage of the ether linkage with the formation of ions (A) and (B), and a peak with m/e 237, which corresponds to ion (C)



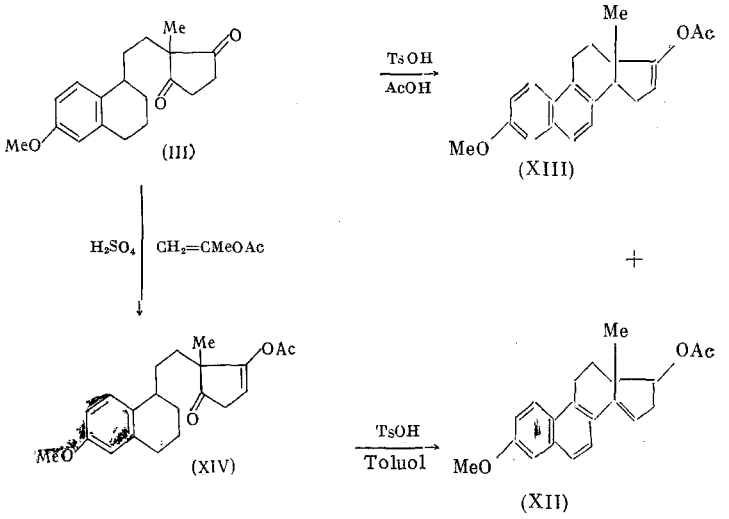
(A), *m/e*265 (B), *m/e*281 (C), *m/e*237

The structure of compound (XI) is supported by the data of the UV spectrum (presence of a naphthalene system) and the IR spectrum (absence of the bands of the hydroxyl and carbonyl groups). The NMR spectrum shows the doublet (1.06 and 1.28 ppm) of a methyl group attached to a double bond and a vinyl proton (5.52 ppm). The molecular weight (264), determined by mass spectrometry, corresponds to formula (XI). It is entirely possible that (XI) is also formed in the reaction with P_2O_5, but as the result of dehydrogenation and migration of the double bonds it is converted to (IX). The ease with which the double bonds in the investigated steroid systems shift is demonstrated with especial clarity when diketone (III) is cyclized under the influence of p-toluenesulfonic acid in a refluxing mixture of CH_3COOH and toluene. Here we were able to isolate the acetate of 3-methoxy-$\Delta^{1,3,5(10),8,14}$-estrapentaen-17β-ol (XII) and the acetate of

3-methoxy-16,17-dehydroisoequilenol (XIII). The formation of both compounds is possible only because of the successive migration of the double bonds that are formed during cyclization and enolization.

Acetate (XII) was previously obtained by a different method [4], and was identified in the usual manner (mixed melting point; comparison of the spectra). The structure of acetate (XIII) was confirmed by the UV spectrum (naphthalene system) and the IR spectrum (presence of an acetoxy group), while the molecular weight (322) corresponds to the given formula. It is possible to assume that rings C and D in acetate (XIII) have a cis-coupling, all the more so since an example of this type of cyclization exists [5], where instead of the $\Delta^{8(9),14(15)}$-diene system the $\Delta^{8(9),15(16)}$-C/D-cis system is formed.

The formation of acetate (XII) apparently goes via the intermediate enol acetate (XIV). The latter was specially synthesized in known manner [6], and it proved that it is cyclized when heated with p-toluenesulfonic acid in refluxing toluene to give (XII) in 36% yield



The reported results show that the spatial factor plays a very important role during intramolecular cyclization and determines the course of reaction even when the $\Delta^{9(11)}$-double bond, which activates the H atoms at C_8, is absent. Naturally, the cyclization proceeds under more drastic conditions, and in view of this is accompanied by a multiple migration of the double bonds (and, consequently, aromatization) and at times by dehydrogenation.

EXPERIMENTAL METHOD

The UV spectra (in alcohol) were taken on a Hitachi-124 instrument, the IR spectra were taken on a UR-10 spectrometer (in Nujol), the NMR spectra were taken on a JNM-4H100 instrument (in $CDCl_3$), and the mass spectra were taken on an MX-1303 instrument, which was equipped with direct insertion into the source. The melting points were determined on a Kofler block and are uncorrected.

3-Methoxy-$\Delta^{1,3,5(10)}$-8,14-secoestratriene-14,17-dione (III). A solution of 7.7 g of (I) in 200 ml of THF was hydrogenated in the presence of 1 g of 10% $Pd/CaCO_3$ until the H_2 absorption ceased. The solution was filtered, the filtrate was evaporated, and the residue was made to crystallize by the addition of ether. We obtained 7.3 g (92%) of diketone (III), mp 69-71° (from methanol). λ_{max} 280, 288 nm (log ε 3.38; 3.35). Infrared spectrum (ν, cm^{-1}): 1725 (2-disubstituted 1,3-cyclopentanedione), and 1610 and 1585 (aromatic). NMR spectrum (δ, ppm): 1.19 singlet (CH_3), 2.74 ($-CH_2-CH_2-$), 3.77 (OCH_3).

Cyclization of Secodiketone (III) in the Presence of P_2O_5. A mixture of 1 g of (III) and 0.4 g of P_2O_5 was heated for 2 h at 110-120° in a vacuum of 20 mm. The mixture was cooled, extracted with $CHCl_3$, and the extract was washed twice with $NaHCO_3$ solution, then with water, dried, and evaporated in vacuo. The obtained oil partially crystallized on cooling. We isolated 160 mg (19%) of 1-methyl-7-methoxy-2,3-dihydro-1H-cyclopenta[*a*]phenanthrene (IX), mp 134° (from 1:4 benzene–petroleum ether) [3]. λ_{max} 263, 286, 294, 304 nm (log ε 3.6; 3.04; 2.99; 2.88). NMR spectrum (δ, ppm): doublet 1.35 and 1.42 (CH_3); 3.94 (OCH_3); mol. wt. 262 (by mass spectrometry).

Cyclization of Secodiketone (III) in Toluene in the Presence of p-Toluenesulfonic Acid. A mixture of 1.2 g of (III), 50 ml of toluene, and 0.5 of p-toluenesulfonic acid was heated under reflux (equipped with a water separator) for 4 h. After the usual workup and evaporation, the residue (1.1 g) was subjected to

preparative chromatography on a plate covered with Al_2O_3 (8:2 benzene–hexane), in which connection three zones were isolated. From the first zone (260 mg) by repeated chromatographing (10:1 hexane–ethyl acetate) we isolated 50 mg [4.5%, when based on reacted diketone (III)] of methoxy ether (X), mp 220-225° (from ethyl acetate). λ_{max} 268, 282, 292, 324, 340 nm (log ε 4.03; 4.01; 3.89; 3.71; 3.89). Infrared spectrum: 1620, 1600 (aromatic) cm^{-1}. NMR spectrum: 0.74 (CH_3); 3.9 (OCH_3) ppm. Mass spectrum: 546 (M), 281, 265, 237. From the second zone (400 mg) was isolated ~50 mg (5%) of 17-methyl-3-methoxy-18-nor-16,17-dehydroequilenane (XI), mp 210-212° (from a 10:1 ethyl acetate–$CHCl_3$ mixture). λ_{max} 268, 279, 311, 324, 338 nm (log ε 3.77; 3.84; 4.19; 4.32). Infrared spectrum: 1610, 1580 (aromatic) cm^{-1}; mol. wt. 264 (by mass spectrometry). NMR spectrum (δ, ppm): 1.06, 1.28 (doublet, CH_3–C=C); 3.83 (OCH_3); 5.52 (C=CH). From the third zone (375 mg) was isolated 225 mg of the starting material (III).

Small amounts of (X) and (XI) were isolated in an analogous manner by the cyclization of (III) in benzene in the presence of p-toluenesulfonic acid (refluxing for 8 h).

Cyclization of Secodiketone (III) in Toluene in the Presence of Acetic and p-Toluenesulfonic Acids. A mixture of 1.2 g of (III), 30 ml of toluene, 4 ml of AcOH, and 0.3 g of p-toluenesulfonic acid was refluxed for 8 h. An additional 0.2 g of p-toluenesulfonic acid and 2 ml of AcOH were added and the mixture was refluxed for another 7 h. After the usual workup the product (1.02 g of oil) was chromatographed on a plate covered with Al_2O_3 (3:97 ether–benzene). From the first zone we isolated 120 mg (26%, when based on reacted diketone) of the acetate of the 3-methyl ether of 16,17-dehydroisoequilenol (XIII), mp 198-202° (from 1:3 alcohol–ethyl acetate). λ_{max} 268, 280, 292, 326, 342 nm (log ε 4.71; 4.76; 4.63; 4.42; 4.44). Infrared spectrum: 1730 (CH_3CO_2), 1625, 1600 (aromatic) cm^{-1}; mol. wt. 322 (by mass spectrometry). From the second zone was isolated 80 mg (17%) of the acetate of 3-methoxy-$\Delta^{1,3,5(10),8,14}$-estrapentaen-17β-ol (XII), mp 112-115°. λ_{max} 310 nm (log ε 4.4). Infrared spectrum: 1738 (CH_3CO_2), 1610, 1590 (aromatic) cm^{-1}. NMR spectrum: 0.98 (CH_3); 2.02 (CH_3CO_2); 3.78 (OCH_3); 4.98 (triplet, C_{17}–H); 5.49 (singlet, C=CH). Acetate (XII) does not depress the mixed melting point with an authentic specimen. From the third zone was isolated 710 mg of the starting material (III).

Enol Acetate (XIV) of Secodiketone. A mixture of 1.3 g of (III), 20 ml of isopropenyl acetate, and 1 ml of the catalyst solution [6], containing 0.02 ml of conc. H_2SO_4 in 1 ml of isopropenyl acetate, was refluxed for 2 h, with a slow distillation of the distillate. Then 10 ml of isopropenyl acetate and 1 ml of the catalyst solution were added, the mixture was refluxed for 4 h, another 10 ml of isopropenyl acetate, and 1 ml of the catalyst solution were added, and the mixture was refluxed for another 6 h. The isopropenyl acetate was vacuum-distilled, while the residue was treated with ice water and then extracted with ether. After the usual workup and removal of the solvent by distillation the product (1.1 g of oil) was chromatographed on a column containing 60 g of SiO_2. From the benzene fraction was isolated 990 mg (67%) of the 17-acetate of 3-methoxy-8,14-seco-$\Delta^{1,3,5(10),16(17)}$-estratetraen-17-ol-14-one (XIV) as an oil. Mass spectrum: 342 (M), 299 (M–43), 282 (M–60).

Cyclization of Enol Acetate (XIV). A mixture of 0.94 g of (XIV), obtained in the preceding experiment, 25 ml of toluene, and 0.25 g of p-toluenesulfonic acid was refluxed for 2.5 h. After the usual workup and removal of the solvent by distillation the oily product was chromatographed on a plate covered with Al_2O_3 (10:2 ethyl acetate–hexane). From the first zone was isolated 240 mg [36%, when based on the reacted (XIV)] of the acetate of 3-methoxy-$\Delta^{1,3,5(10),8,14}$-estrapentaen-17β-ol (XII), mp 108-112°. The mixed melting point with an authentic specimen was not depressed. From the second zone was isolated 0.29 g of (III), mp 68-70°, while from the third zone was isolated 0.28 g of the starting enol acetate (XIV).

CONCLUSIONS

Depending on the conditions, 3-methoxy-$\Delta^{1,3,5(10)}$-8,14-secoestratriene-14,17-dione (III) under the influence of acid agents is cyclized to estradiol, equilenol, 18-norequilenane, and cyclopentanophenanthrene derivatives. As a result, the spatial factor determines the course of the reaction even if the $\Delta^{9(11)}$-double bond, which activates the H atoms at C_7, is absent.

LITERATURE CITED

1. S. N. Anachenko and I. V. Torgov, Tetrahedron Lett., 1553 (1963).
2. K. Hiraga, Chem. Pharm. Bull. Japan, 13, No. 11, 1300 (1965).
3. T. Miki, K. Hiraga, and M. Asako, ibid., 13, No. 11, 1285 (1965).
4. K. K. Koshoev, S. N. Ananchenko, and I. V. Torgov, Khim. Prirodn. Soedin., 172 (1965).
5. D. Ledniger, D. E. Emmert, C. G. Chidester, and D. J. Duchamp, J. Org. Chem., 36, 3260 (1971).
6. J. Fajkos and F. Sorm, Coll. Czech. Chem. Commun., 24, 766 (1959).