CHEMISTRY OF 1,5-DIKETONE DERIVATIVES.

1. OXIDATION OF 8a-METHOXY-4a,5,6,7,8,8a-HEXAHYDROCHROMENES BY MONOPERPHTHALIC ACID

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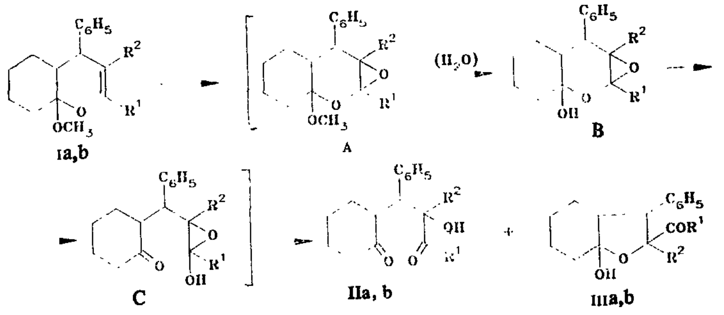
UDC 547.442.5'814.1'728.2'638.2:541.63

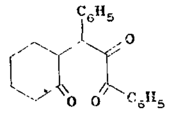
2-(2-Oxo-3-hydroxy-1,3-diphenylpropyl)cyclohexanone, 2-(2,3-dioxo-1,3-diphenylpropyl)cyclohexanone, and 2-benzyl-7a-hydroxy-3-phenylperhydrobenzofuran are formed by the action of monoperphthalic acid on 8a-methoxy-2,4-diphenyl-4a,5,6,7,8,8a-hexahydrochromene. Under analogous conditions, 4a-methoxy-10-phenyl-1,2,3,4,4a,6,7,8,9,10a-decahydroxanthene forms 7a-hydroxy-3-phenyloctahydrobenzo[b]furan-2-spiro-1'-cyclohexan-2'-one and its dehydration product. The behavior of the compounds obtained toward acetic anhydride and a methanolic solution of HCl was studied. The configurations of the reaction products and the reaction path are considered.

The ability of several 1,5-diketones to exist in the form of 2-hydroxy-2,3-dihydro-4H-pyrans [1] or to give methyl ethers [2] corresponding to the latter was previously shown. In the course of studying the chemistry of these compounds, we investigated the action of monoperphthalic acid (MPPA) on the methoxyhydropyrans (Ia, b). We obtained the products (IIa), (IIIa), and (IV) from compound (Ia); oxidation of compound (Ib) gave the products (IIIb) and (V).

The breakdown of molecular ions in the mass spectra of compounds (IIa), (IIIa) includes loss of a molecule of water (m/z 304), phenyl (m/z 245), and benzoyl (m/z 217). In the mass spectrum of compound (IIIa), the peak at m/z 199 corresponds to loss of the C_6H_5CO group with a fragment ion m/z 304.

The IR spectra of compounds (IIa) and (IIIa) contain absorption peaks of the hydroxyl and carbonyl groups (cf. Table 1).

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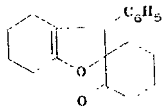
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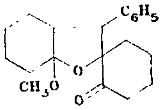
VIII

Far-Eastern State University, Vladivostok 690600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 177-181, February, 1985. Original article submitted April 23, 1984.

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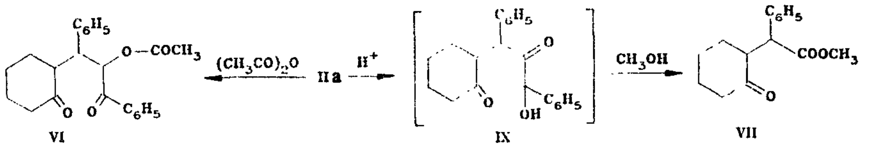
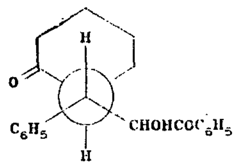
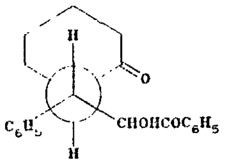


I—III a $R^1 = C_6H_5$, $R^2 = H$; b $R^1 + R^2 = -(CH_2)_4-$

In the PMR spectrum of the hydroxydiketone (IIa), the signal of the hydroxyl group proton appears as a doublet at 3.73 ppm (J = 6.5 Hz) and disappears on addition of deuteromethanol. The signal of the proton at $C(_{2'})$ appears as a doublet of doublets at 3.72 ppm (J = 2.0, 6.5 Hz) and degenerates into a doublet (J = 2 Hz) on addition of deuteromethanol. Therefore, the constant 6.5 Hz corresponds to the spin–spin interaction of the proton at $C(_{2'})$ with the proton of the hydroxyl group. An analogous effect is observed for α-hydroxyacetophenones [3] and indicates a strong hydrogen bonding of hydroxyl to the oxygen of the carbonyl group. The type of signal at 3.40 ppm (triplet of doublets, J = 4.0, 12.0, and 12.0 Hz) can be assigned to the proton at $C(_2)$, and favors the assumption that this proton occupies an axial position in the cyclohexane ring (constants 4.0 and 12.0 Hz). The second large constant, equal to the spin–spin coupling constant of the benzyl proton (cf. Table 1), indicates a transoid disposition of the proton at $C(_2)$ and the benzyl proton. The two configurations D and E correspond to this condition. In the latter, the hydroxyl group and the cyclohexane carbonyl are adjacent; this should lead to ready cyclization to compound (IIIa). Since the hydroxydiketone (IIa) is not converted to the hydroxyperhydrobenzofuran (IIIa), it is considered probable that our configuration D corresponds to (IIa) and that (IIIa) is a derivative of the alternative configuration E.



D



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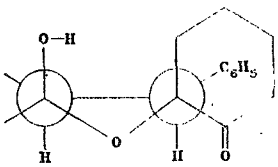
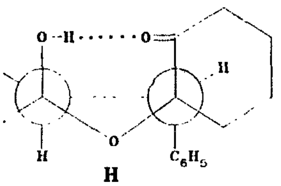
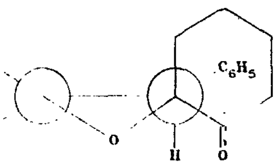


G



H



F

In the ^{13}C NMR spectrum of the hydroxydiketone (IIa), the signals of C=O occur at 200.9 and 214.3 ppm. Carbon bound to hydroxyl gives a signal at 73.9 ppm, while benzyl carbon registers at 43.5 ppm. Signals at 49.6 and 50.8 ppm correspond to atoms situated in the α positions to the ring carbonyl. In the PMR spectrum of the hydroxyhydrofuran (IIIa), the signals of the hydroxyl proton are observed as a singlet at 2.80 ppm. The proton at $C(_2)$ registers at 5.46 ppm (J = 8.5 Hz).

We reacted compound (IIa) with acetic anhydride in pyridine and obtained the expected acetate (VI). The fragment ion, m/z 305, in its mass spectrum corresponds to loss of the CH_3COO group. Absorption of the hydroxyl group is absent in the IR spectrum. In the PMR spectrum, the signal of the proton at $C(_2)$ appears as a doublet at 6.62 ppm (J = 2.0 Hz).

In order to clarify whether compound (IIa) can cyclize to the ring form (IIIa), we reacted the hydroxydiketone (IIa) with a solution of HCl in methanol to take into account the isolation of the methyl ether of the cyclic form (IIIa). However, instead of the expected product, we isolated a compound of composition $C_{15}H_{18}O_3$. The data of its IR and mass spectra (in the latter, fragment ions m/z 215 and 187 correspond to loss of fragments OCH_3 and $COOCH_3$ by the molecular ion) correspond to the structure (VII). The formation of this compound can be explained as follows. The configuration of compound (IIa) is such that cyclization into the form (IIIa) appears difficult. An alternative process is the

TABLE 1. Characteristics of Compounds (II-VIII)

Compound	mp, °C[a]	R_f[b]	IR spectrum		PMR spectrum C_6H_5CH		Found			Empirical formula	Calculated			Yield, %
			νOH	νC=O	δ, ppm	J, Hz	C, %	H(N), %	M^+		C, %	H(N), %	M^+	
IIa	123—124	0,20	3470	1705, 1682	3,56	2,0; 12,0	78,3	7,1	322	$C_{21}H_{22}O_3$	78,2	6,9	322	42
IIIa	131—132	0,13	3580, 3425	1689	3,63	8,5; 8,5	78,2	7,1	322	$C_{21}H_{22}O_3$				7
IIIb[c]	129—130	0,42	3592, 3420	1720—1715	4,22	12,5	76,3	7,9 (16,8)	300	$C_{19}H_{24}O_3$	76,0	8,0 (17,0)	300	62
IV	104—106	0,43	—	1708, 1705, 1671	4,58	12,0	79,1	6,7	320	$C_{21}H_{20}O_3$	78,7	6,3	320	21
V	96—98	0,52	—	1720—1715	4,50	s	80,7	8,0	282	$C_{19}H_{22}O_2$	80,8	7,8	282	20
VI	151—152	0,15	—	1746, 1705	3,70	2,0; 10,0	75,7	6,3	364	$C_{23}H_{24}O_4$	75,8	6,6	364	70
VII	102—103	0,39	—	1731, 1705	—	—	73,1	7,6	246	$C_{15}H_{18}O_3$	73,2	7,3	246	20
VIII	87—88	0,70	—	1718	4,22	12,5	76,5	8,4	314	$C_{20}H_{26}O_3$	76,4	8,3	314	55

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[a] Compounds (IIIa), (IIIb), and (V) are recrystallized from a mixture of petroleum ether—EtOAc. Compound (IV) is recrystallized from petroleum ether. Compound (VIII) is recrystallized from methanol with added HCl. The remainder are recrystallized from ethanol.

[b] On Silufol in a 7:2 petroleum ether—EtOAc mixture.

[c] bis-2,4-DNPH, mp 206-207°C (with decomposition, from DMF—ethanol mixture).

cleavage of the C—C bond in the fragment CHOH—CO, typical acyloins [4]. Evidently, when methanol and HCl act on the molecules of compound (IIa), there is initial rearrangement with formation of the intermediate (IX). Subsequent breaking of the C—C bond with addition of methoxyl and hydrogen leads to the formation of compound (VII).

In the mass spectrum of the triketone (IV), the molecular ion breaks down with cleavage of C_6H_5CO (m/z 215) and C_6H_5COCO (m/z 187). The IR and PMR spectrum correspond to the structure (IV). In the ^{13}C NMR spectrum, there are signals of three carbonyl carbons at 190.0, 198.1, and 211.7 ppm, signals of six sp^3-hybridized carbon atoms at 25.1, 27.7, 31.8, 41.6, 53.0, and 55.7 ppm, and also signals of the aromatic ring carbons. The signal at 73.9 ppm, characteristic of the spectrum of the hydroxydiketone, is absent here.

Compound (Ib) is converted by MPPA into the cyclic hemiacetal (IIIb) and its dehydration product (V). The mass spectra of the compounds correspond to the proposed formulas. In the spectrum of compound (IIIb), there is a fragment ion, m/z 282, corresponding to the loss of a molecule of water. The absorption of carbonyl groups is noted in the IR spectra of the ketones (IIIb) and (V). The absorption of the hydroxyl group is present in the spectrum of the hemitacetal (IIIb), but is absent from the spectrum of the vinyl ether (V). In the ^{13}C NMR spectrum of compound (IIIb), the following signals are present: 86.3 ppm (C_2), 104.5 ppm (C_{7a}), and 209.9 ppm (C=O). Compound (V) has signals at 91.4 ppm (C_2), 108.9, 150.6 ppm (C=C), and 208.5 ppm (C=O).

Compound (IIIb) is methylated by HCl in methanol to the methoxyl derivative (VIII). The spectral characteristics of the latter (cf. Table 1) correspond to the proposed structure. The molecules of compounds (IIIb) and (VIII) have four chiral centers, namely, at $C_{(2)}$, $C_{(3)}$, $C_{(3a)}$, and $C_{(7a)}$. The first two are present in the molecule of compound (V). Their configuration can be established on the basis of the following data. The ready dehydration of the hemiacetal (IIIb), which proceeds by the action of acetic anhydride in pyridine and leads to the unsaturated ether (V), enables a trans-disposition of hydroxyl and hydrogen at $C_{(3a)}$ to be postulated. The high-field region of the PMR spectra of compounds (IIIb), (V), and (VIII) contains a signal with an intensity corresponding to one proton. This occurs at 1.13 ppm (V), 0.84 ppm (IIIb), and 0.73 ppm (VIII). The signal has a set of constants [3.0, 14.0, 14.0 Hz for compounds (IIIa), (VIII), and 3.0, 11.0, 14.0 Hz for compound (V)] corresponding to the axial proton of a methylene group adjoining a methylene group on one side, and an atom of carbon, not linked to hydrogen atoms, on the other. The protons at atoms $C_{(7)}$ and $C_{(6)}$ correspond to this condition. It is difficult to find a reasonable explanation for the high-field shift of the signal of the proton at $C_{(7)}$. In contrast, the shift of the signal of the proton at $C_{(6')}$ is readily explained by entry of the proton into the shielding cone of the benzene nucleus at $C_{(3)}$, if it exists in a skewed conformation in relation to the atom $C_{(6)}$. Analogous examples are known [5]. The shift of the signals of the benzyl protons to weak field, compared to their usual position (cf. Table 1), serves to confirm this. Inspection of models shows that the benzyl protons enters the deshielding cone of the carbonyl group. Therefore, the configuration of compound (V) is determined as F. Regarding the configurations of compounds (IIIb) and (VIII), they can be depicted by formulas G and H. Intramolecular hydrogen bonding between hyroxyl and carbonyl is possible in the configuration H. The IR spectrum of compound (IIIb) indicates the absence of an intramolecular hydrogen bond ($\nu OH = 3600\ cm^{-1}$ in 10^{-4} M solution in CCl_4). This cannot serve as unambiguous evidence for the configuration G since the hydrogen bond may also not be present for other reasons. However, it is more probable for compound (IIIb).

Compound (IIIb) is the cyclic form of the 2-hydroxyl-1,5-diketone (IIb). Although we could not isolate the latter, we established that compound (IIIb) forms a bis-2,4-dinitrophenylhydrazone, i.e., it can react in the diketone form.

The path of the reaction of compound (Ia) and (Ib) with MPPA can be represented as follows. There is initial epoxidation of the double bond with formation of the intermediate A. Substitution of methoxyl by hydroxyl leads to the intermediate B. The opening of rings in B leads (via intermediate C) to the formation of the 2-hyroxy-1,5-diketone (II) and further, to the cyclic hemiacetal (III).

EXPERIMENTAL

IR spectra were taken with a Specord 75-IR instrument (in $CHCl_3$, CCl_4, and mineral oil). NMR spectra (in deuterochloroform) were taken with Bruker WH-250 (for ^1H) and Bruker HX-90E (for ^{13}C) instruments at 250 and 22.63 MHz, respectively. Chemical shifts are given relative to tetramethylsilane. Mass spectra were taken with an LKB 9000S instrument at 32 eV.

The initial compounds (Ia) and (Ib) were obtained according to methods in [1] and [2]. A 0.53 M solution of MPPA, obtained according to [6], was utilized for oxidation.

The characteristics of the compounds are presented in Table 1.

Action of MPPA on Compound (Ia). To a suspension of 4.8 g (0.15 mole) of compound (Ia) in 50 ml of ether is added, with stirring, 30 ml of a solution of MPPA in ether. The reaction mixture is stirred for 1 h; then a further 27 ml of the solution of MPPA is added, and the reaction is conducted for a further 3 h. In the course of the reaction, the initial compound gradually dissolves. A residue of phthalic acid separates out on the sides of the reaction vessel, and the solution is colored yellow-green. After the disappearance of the spot of the initial compound from the chromatogram of the reaction mixture, 30 ml of a saturated solution of Na_2CO_3 is added to it. After shaking, the ether layer is separated and washed twice with a solution of sodium carbonate and then with water until neutrality. After drying with magnesium sulfate, the ether is distilled. To the oily residue, 20 ml of ethanol is added. The crystals precipitated by this are separated, and 1.55 g of 2-(2-hydroxy-3-oxo-1,3-diphenylpropyl)cyclohexanone (IIa) is obtained. The solvent is removed from the alcoholic mother liquor, and the residue (3.23 g) is chromatographed on 150 g of silicagel L 100/250 in a column 47 cm by 3 cm. Eluting with a mixture of petroleum ether and ethyl ether (30:1) gave 1.0 g of 2-(2,3-dioxo-1,3-diphenylpropyl) cyclohexanone (IV). A 20:1 mixture gave 0.6 g of the diketone (IIa), and a 10:1 mixture gave 0.25 g of 2-benzoyl-7a-hydroxy -3-phenyloctahydrobenzo[b]furan (IIIa). Resinous material (0.9 g) is washed out from the column with ethyl ether.

Action of MPPA on Compound (Ib). After dissolving 5.96 g (0.02 mole) of compound (Ib) in 40 ml of ether, 30 ml of the solution of MPPA is added with stirring. The mixture is self-heated to 34°C, cooled to 0°C, and a further 20 ml of MPPA solution is added after 3 h. The initial compound is absent from the reaction mixture at 2 h following the introduction of the second portion of the peracid. The reaction mixture is shaken with 30 ml of Na_2CO_3 solution prior to separation of the ether layer, washed twice with Na_2CO_3 solution, and washed with water until neutrality. The ether solution is dried with magnesium sulfate. After evaporating the ether, 5.8 g of the mixture of reaction products is obtained. The mixture is dissolved, with heating, in 30 ml of a mixture of petroleum ether and ethyl acetate (7:2). The residue which crystallized out on cooling was filtered off and washed with the same mixture. A yield of 2.8 g of 7a-hydroxy-3-phenylooctahydrobenzo[b]furan-2-spiro-1'-cyclohexan-2'-one (IIIb) is obtained. The residue present in the mother liquor (2.9 g) is chromatographed on 120 g of silicagel in a column 30 cm by 3 cm. Elution is performed as above. A mixture (0.4 g) of unidentified reaction products is washed out with petroleum ether. Compound (V) (1.2 g) is washed out with a mixture of petroleum ether and ethyl ether (30:1). Compound (IIIb) (0.9 g) is washed out with a 10:1 solvent mixture.

3-Phenyl-2,3,4,5,6,7-hexahydrobenzo[b]furan-2-spiro-1'-hexan-2'-one (V). The alcohol (IIIb) (0.5 g) is dissolved in 1 ml of dry pyridine prior to adding 1 ml of acetic anhydride. The reaction mixture is left at room temperature for 72 h. After diluting with water, the reaction product is filtered off, rinsed on the filter with water, and recrystallized from ethanol. The resulting compound (V) (0.25 g, 50%) is identical to that obtained in the preceding experiment.

In an analogous experiment, 0.4 g of 2-(2-acetozy-3-oxo-1,3-diphenylpropyl)cyclohexanone (VI) is obtained from 0.55 g of compound (IIa), 2 ml of pyridine, and 2 ml of acetic anhydride after 30 h reaction time.

Methyl 2-(2-Oxocyclohexyl)-2-phenylacetate (VII). To 1 g of compound (IIa) is added 3 ml of a 0.54% solution of HCl in absolute methanol. The mixture is held at room temperature for 72 h prior to the removal of methanol *in vacuo* without heating. The residue is dissolved in ether. The ether solution is washed with a solution of $NaHCO_3$, and with water until neutrality, and dried with magnesium sulfate. After the removal of the ether, 4 ml of ethanol is added to the resulting 0.9 g of oily product. On standing, 0.2 g of compound (VII) crystallizes out.

In an analogous experiment, 5 ml of a 1% solution of HCl in methanol is added to 0.8 g of compound (IIIb). After keeping at room temperature for 2 h, the methanol is evaporated. The residue is recrystallized from methanol with added HCl. The product is 7a-methoxy-3-phenyloctahydrobenzo[b]furan-2-spiro-1'-cyclohexan-2'-one (VIII).

Action of 2,4-Dinitrophenylhydrazine on Compound (IIIb). To a solution of 0.4 g of 2,4-dinitrophenylhydrazine in 2 ml of DMF is added a solution of 0.2 g of compound (IIIb) in 0.5 ml of DMF and 2 drops of conc. HCl. The precipitate of dinitrophenylhydrazine is filtered off after 4 h.

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13-AMINO-1,4,7,10-BENZOTETRAOXA-15-CYCLODODECENE

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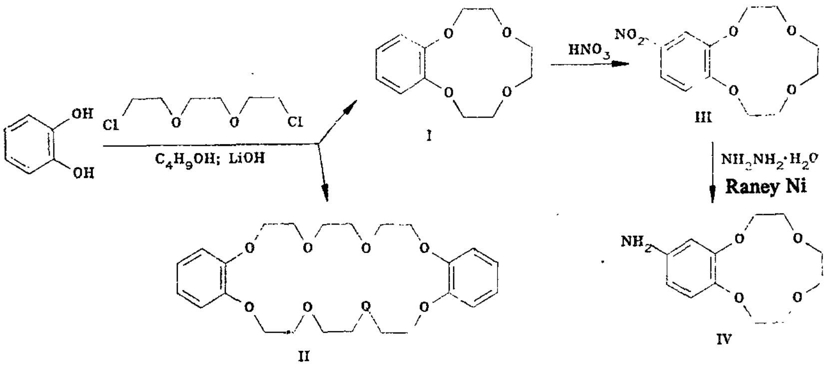
UDC 547.898.07

A separation was performed for benzo-12-crown-4 and dibenzo-24-crown-8 obtained as a mixture by the reaction of pyrocatechol with 1,8-dichloro-3,6-dioxaoctane. Nitro and amino derivatives of benzo-12-crown-4 were obtained.

13-Amino-1,4,7,10-benzotetraoxa-15-cyclododecene (IV) is a starting material for the synthesis of derivatives with substitution in the benzene ring. Product IV was obtained by the following scheme:



A matrix synthesis of benzo-12-crown-4 (I) by the reaction of pyrocatechol with 1,8-dichloro-3,6-dioxaoctane under high dilution conditions gave dibenzo-24-crown-8 (II). The separation of these macrocycles through their nitro derivatives was described by Shinkai et al. [1]. We have been able to separate I and II using the high solubility of I in ether.

The purity of the compounds obtained was confirmed by mass spectral analysis. The molecular ions with m/z 224 and 448 correspond to the molecular masses of I and II. The high stability of the molecular peaks relative to electron impact is characteristic of crown ethers containing aromatic rings, and the fragmentation, which is analogous to the

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All-Union Scientific-Research Institute for Chemical Reactants and High-Purity Chemicals, Moscow 107258. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 182-183, February, 1985. Original article submitted February 20, 1984.

0009-3122/85/2102-0147$09.50