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SYNTHESIS OF PYRIDINE DERIVATIVES BY THE THREE-COMPONENT CONDENSATION OF A β-DICARBONYL COMPOUND, β-ENAMINOCARBONYL COMPOUND, AND ETHYL ORTHOFORMATE

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The major products of the three-component condensation of a β-dicarbonyl compound, β-enaminocarbonyl compound, and ethyl orthoformate are pyridine derivatives. The reaction of 1,3-cyclohexanedione or dimedone, the enamino ketones obtained from these diones, and ethyl orthoformate gives octahydroacridinediones, while the reaction of dimedone, ethyl β-aminocrotonate, and ethyl orthoformate gives a tetrahydroquinoline derivative. The structures of the minor products were established in some cases. The reduction of 3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydro-1,8-acridinedione by $LiAlH_4$ proceeds with retention of the pyridine ring and leads to the corresponding octahydroacridinediol.

3,5-Diacylpyridines I are obtained by the oxidation of the corresponding 1,4-dihydropyridines, which are products of the Hantzsch reaction [1]. Substituted pyridine Ia [2, 3] and octahydroacridine Ib [4] have been obtained by this method. Products Ia and Ib were also synthesized in two steps by the condensation of ethyl acetoacetate (IIa) and dimedone (IIb) with ethyl orthoformate and subsequent reaction of the products with ammonia [5, 6]. Octahydroacridines Ib and Ic were obtained [7] by the condensation of enamino ketones IIIb and IIIc from dimedone and 1,3-cyclohexanedione (IIc) with ethyl orthoformate in acetic acid. The maximum yields were 44% for Ia, 53% for Ib, and 21% for Ic (Table 1). Analysis of these methods for the preparation of symmetrical pyridine derivatives Ia-c led us to study the reaction of a three-component system consisting of a β-dicarbonyl compound II, β-enaminocarbonyl compound III, and ethyl orthoformate with the aim of increasing the yield of products Ia-c as well as to obtain new products I, including asymmetric derivatives.

The reaction of ethyl orthoformate with β-dicarbonyl compounds IIa-c presumably leads to the formation of unsaturated diketoesters IVa-c, which, as shown [5] in the case of ethyl ethoxymethylenacetoacetate (IVa), react with enamines IIIa-c (obtained from IIa-c, respectively) to give products I.

The reaction was carried out in the presence of acetic acid in accordance with the procedure described [8] for the synthesis of β-enamino diketones from β-diketones, primary amines, and ethyl orthoformate. Indeed, pyridine derivatives Ia-e were obtained as the major products. Minor products, namely, tricarbonyl compounds Va,b,d as well as tetrahydropyridine derivative VI (obtained when IIa and IIIa were the starting reagents) (Scheme I) were also isolated from the reaction mixture in the reaction with ethyl orthoformate, ethyl acetoacetate, dimedone, and the resultant enamines (IIa and IIIa, IIb and IIIb, and IIb and IIIa).

The structures of these products were established by the spectral and elemental analysis data (Tables 1 and 2). Thus, the PMR spectra of IIa-e have a characteristic singlet for 4-H at 8.68-8.82 ppm and signals, whose position, shape, and intensity correspond to the substituent protons. The PMR spectra of imines Va,b,d have characteristic

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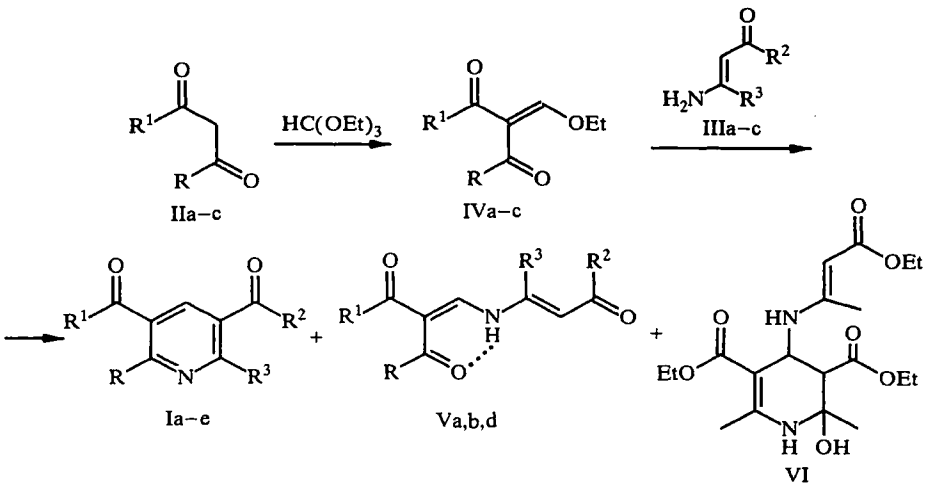


I–V, VI a R = R^3 = Me, R^1 = R^2 = OEt; b R + R^1 = R^2 + R^3 = $-CH_2CMe_2CH_2-$;
c R + R^1 = R^2 + R^3 = $-(CH_2)_3-$; d R + R^1 = $-CH_2CMe_2CH_2-$; R^2 = OEt, R^3 = Me;
e R + R^1 = $-CH_2CMe_2CH_2-$; R^2 + R^3 = $-(CH_2)_3-$

doublets for the NH proton at 12.42-14.14 ppm and the coupled olefinic proton at 8.14-8.28 ppm (J = 12.5-13.0 Hz). The structure of octahydroacridinediones Ic and Ie was supported by their ^{13}C NMR spectra. The data of the corresponding spectrum of hydroacridine Ib [6] were used in assigning these signals. The PMR spectrum of tetrahydropyridine VI has a doublet for the proton bound to the acyclic nitrogen atom at 4.97 ppm and triplet for the coupled heterocyclic proton 4-H at 4.58 ppm. A three-proton singlet for the methyl group at $C_{(2)}$ in the heterocycle is also found in this spectrum at 1.70 ppm.

The absorption band at 210-227 nm is the more intense one in the UV spectra of Ia-e. A long-wavelength band at 364-367 nm is found in the UV spectra of imines Va,b,d as in the spectra of 3,5-diacyl-1,4-dihydropyridines with a structurally similar π-electron system [9]. This band is much stronger than in the case of 1,4-dihydropyridines. Similar to the latter compounds, Va,b,d fluoresce in ethanolic solution upon the ultraviolet radiation. Thus, emission maxima are observed at 434, 441, and 425 nm, respectively, upon excitation at the wavelength corresponding to the UV absorption maximum (364-367 nm). A strong maximum at 270 nm for the two enaminocarbonyl fragments is noted in the UV spectrum of tetrahydropyridine VI.

The IR spectra of these compounds have bands corresponding to carbon-carbon and nitrogen-carbon double bonds (1580-1630 cm^{-1}) and carbonyl functions (1640-1742 cm^{-1}).

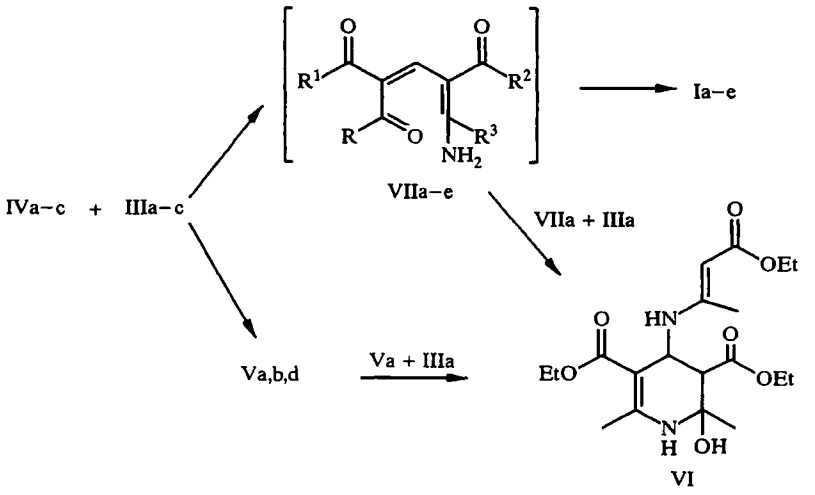
Comparison of the PMR spectra of minor products Va,b,d with the spectra of compounds also containing enaminocarbonyl and enaminodicarbonyl fragments makes possible some conclusions concerning the three-dimensional structure of these compounds. Thus, the coupling constant of the vicinal protons of the CH–NH fragment (12.5-13.0 Hz) indicate that these protons are in *anti* position in the favored conformation [10, 11]. The mutual arrangement of the substituents at the double bonds in Vb is unequivocally detremined by the existence of two rings in this molecule. The chemical shift of the NH proton in Va (13.94 ppm) and Vd (14.14 ppm) indicates an intramolecular hydrogen bond with the oxygen atom of keto group [10, 13]. The proposed formation of such a bond with the ketonic carbonyl group was established [14] in other structures containing an enaminodicarbonyl fragment as in Va. Both (*E*)- and (*Z*)-configurations are possible for the enamino ester fragment $-N-C(CH_3)=CHCO_2Et$ in Va,d. The hydrogen bond of the NH proton in the (*Z*)-isomer is formed with two oxygen atoms simultaneously [12, 13, 15]. The rotational barrier about the single and double bonds of the enaminocarbonyl systems is relatively low [16]. Thus, we may discuss the most occupied conformation with a certain configuration of the double bonds under the given conditions (solution in $CDCl_3$).

The formation of Ia-e, Va,b,d, and VI probably proceeds as follows. The reaction of β-dicarbonyl compounds IIa-c with ethyl orthoformate leads to their ethoxymethylene derivatives IVa-c, which react with enamines IIIa-c, involving either the carbon nucleophilic centre of the latter, which leads to dienamines VIIa-e, and or

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (Ref. mp)	[M+]	Yield, %	Yield, % [Ref.]
		C	H	N				
Ia					72-73 73-74 [3]	251	73	44 [2] 41 [3] 42 [5]
Ib					147-148 144-146 [6]	271	71	49 [4] 53 [6] 41 [7]
Ic					142-144 144 [7]	215	25	21 [7]
Id	$C_{15}H_{19}O_3N$	68.87 68.94	7.41 7.33	5.47 5.36	58-59	261	37	—
Ie	$C_{15}H_{17}O_2N$	73.92 74.05	7.16 7.04	5.84 5.76	101-103	243	52	—
Va					102-103 101-102 [5]	269	10	8 [5]
Vb	$C_{17}H_{23}O_3N$	70.48 70.56	8.14 8.01	4.92 4.84	180-182	289	12	
Vd	$C_{15}H_{21}O_4N$	64.34 64.49	7.62 7.58	5.14 5.01	172-174	279	12	
VI	$C_{19}H_{30}O_7N_2$	57.18 57.27	7.69 7.59	7.16 7.03	115-116	398	5	
X					270-272 270-272 [7]	275	73	74 [7]

the nitrogen nucleophilic centre to give dienamines Va,b,d (Scheme 2). Cyclization with subsequent dehydration of intermediates VIIa-e leads to pyridine structures Ia-e. Addition of aminoester IIIa to unsaturated diesters VIIa or Va and subsequent cyclization give tetrahydropyridine VI.



Thus, this synthetic method permits to obtain symmetrical structures Ia-c, sometimes in higher yields than by reported procedures (see Table 1, ref. [2-7]), as well as previously unknown asymmetrical octahydroacridinedione Ie and tetrahydroquinone Id, which could not be obtained [17] by the standard oxidation of 3-carbethoxy-2,7,7-trimethyl-1,4,5,6,7,8-hexahydro-5-quinolone.

Reduction of octahydroacridinedione Ib by lithium aluminum hydride was described [7] and the reaction product was identified as decahydroacridinediol IX, which raised some doubt since compounds containing a 1,4-dihydropyridine ring, not stabilized at $C_{(3)}$ and $C_{(5)}$ by electron-withdrawing substituents, are unstable and undergo hydrolysis to give 1,5-diketones in the presence of water [18]. Hence, we repeated the reduction of hydroacridinedione Ib by lithium aluminum hydride under the conditions reported [7] and studied the structure of the

TABLE 2. Spectral Characteristics of the Synthesized Compounds

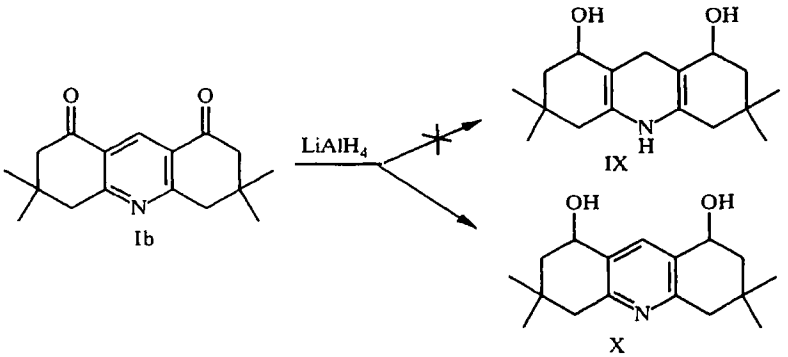
Compound	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (lg ε)	NMR spectrum*	
			spectrum type	chemical shift, δ, ppm, coupling constant (*J*), Hz
1	2	3	4	5
Ia	1595, 1628, 1722	206 (4.47) 235 (4.01) 274 (3.53)	^1H	1.24 (6H, t, *J* = 7.0, $2CH_2\underline{CH_3}$); 2.84 (6H, s, $2CH_3$); 4.42 (4H, q, *J* = 7.0, $2\underline{CH_2}CH_3$) 8.68 (1H, s, 4-H)
Ib	1590, 1630, 1695	224 (4.36) 250 (4.00) 293 (3.86) 299 (3.83)	^1H	1.14 (12H, s, $4CH_3$); 2.58 (4H, s, 2,2- and 7,7-H_2); 3.07 (4H, s, 4,4- and 5,5-H_2); 8.81 (1H, s, 9-H)
Ic	1425, 1590, 1700	224 (4.42) 246 (4.01) 290 (3.79) 298 (3.77)	^{13}C	2.21 (4H, q, *J* = 7.0, 3,3- and 6,6-H_2); 2.71 (4H, t, *J* = 7.0, 2,2- and 7,7-H_2); 3.16 (4H, t, *J* = 7.0, 4,4- and 5,5-H_2); 8.82 (1H, s, 9-H); 21.45 ($C_{(3)}$, $C_{(6)}$); 32.98 ($C_{(2)}$, $C_{(7)}$); 38.43 ($C_{(4)}$, $C_{(5)}$) 127.26 ($C_{(8a)}$, $C_{(9a)}$); 134.54 ($C_{(9)}$); 167.30 ($C_{(4a)}$, $C_{(10a)}$); 196.71 ($C_{(1)}$, $C_{(8)}$)
Id	1557, 1592, 1688, 1730	216 (4.27) 244 (3.91) 283 (3.57) 290 (3.52)	^1H	1.10 (6H, s, 7- and 7-CH_3); 1.44 (3H, t, *J* = 7.0, $CH_2\underline{CH_3}$); 2.56 (2H, s, 6,6-H_2); 2.88 (3H, s, 2-CH_3) 3.02 (2H, s, 8,8-H_2); 4.40 (2H, q, *J* = 7.0, $\underline{CH_2}CH_3$); 8.72 (1H, s, 4-H)
Ie	1560, 1590, 1700	224 (4.30) 246 (3.92) 295 (3.59) 299 (3.56)	^{13}C	1.13 (6H, s, 3- and 3-CH_3); 2.22 (2H, q, *J* = 6.5, 6,6-H_2); 2.56 (2H, s, 2,2-H_2); 2.71 (2H, t, *J* = 6.5, 7,7-H_2); 3.04 (2H, s, 4,4-H_2); 3.17 (2H, t, *J* = 6.5, 5,5-H_2); 8.82 (1H, s, 9-H); 21.45 ($C_{(6)}$) 28.28 (3- and 3-CH_3); 32.77 ($C_{(7)}$); 33.00 ($C_{(3)}$); 38.43 ($C_{(5)}$); 46.63 ($C_{(2)}$); 51.90 ($C_{(4)}$); 126.32 ($C_{(9a)}$) 127.23 ($C_{(8a)}$); 134.07 ($C_{(9)}$); 165.98 ($C_{(4a)}$); 167.67 ($C_{(10a)}$); 196.75 ($C_{(1)}$, $C_{(8)}$)
Va	1580, 1640, 1690, 1710	235 (4.10) 265 (3.89) 342 (4.37) 358 (4.30)	^1H	1.28 (3H, t, *J* = 7.0, $CH_2\underline{CH_3}$); 1.39 (3H, t, *J* = 7.0, $CH_2\underline{CH_3}$); 2.16 (3H, s, CH_3); 2.53 (3H, s, CH_3) 4.24 (2H, q, *J* = 7.0, $\underline{CH_2}CH_3$); 4.26 (2H, q, *J* = 7.0, $\underline{CH_2}CH_3$); 5.21 (1H, s, CO=CH) 8.14 (1H, d, *J* = 13.0, N=CH); 13.94 (1H, d, *J* = 13.0, NH)

TABLE 2 (continued)

1	2	3	4	5
Vb	1585, 1600, 1620, 1670	237 (4.02) 285 (4.10) 359 (4.29) 380 (4.20)	^{1}H	1.10 (6H, s, 2CH$_3$); 1.16 (6H, s, 2CH$_3$); 2.32 (2H, s, CH$_2$); 2.45 (2H, s, CH$_2$); 2.48 (4H, s, 2CH$_2$) 5.88 (1H, s, CO=CH); 8.28 (1H, d, J = 12.5, N=CH); 12.42 (1H, d, J = 12.5, NH)
Vd	1580, 1630, 1650, 1690	233 (4.16) 256 (3.98) 352 (4.46) 374 (4.39)	^{1}H	1.05 (6H, s, 2CH$_3$); 1.29 (3H, t, J = 7.0, CH$_2$CH$_3$); 2.19 (3H, s, CH$_3$); 2.40 (2H, s, CH$_2$) 2.46 (2H, s, CH$_2$); 4.27 (2H, q, J = 7.0, CH$_2$CH$_3$); 5.34 (1H, s, CO=CH) 8.19 (1H, d, J = 13.0, N=CH); 14.14 (1H, d, J = 13.0, NH)
VI	1580, 1630, 1650, 1722 1742	270 (4.49)	^{1}H	1.28 (9H, m, 3CH$_2$CH$_3$); 1.70 (3H, s, 2-CH$_3$); 2.12 (3H, s, CH$_3$); 2.20 (3H, s, CH$_3$) 2.66 (1H, d, J = 3.0, 3-H); 4.17 (6H, m, 3CH$_2$CH$_3$); 4.58 (1H, t, J = 3.0, 4-H) 4.97 (1H, d, J = 3.0, 4-H); 5.34 (1H, s, =CHCO)
X	1450, 1574, 1596, 2980 3100	220 (3.94) 278 (3.73)	^{13}C	1.08 (6H, s, 2CH$_3$); 1.26 (6H, s, 2CH$_3$); 1.78 (2H, t, J = 12.0, 2- and 7-H^a); 2.26 (2H, dd, J_1 = 5.0, J_2 = 12.0, 2- and 7-H^e); 2.94 (4H, s, 4,4- and 5,5-H$_2$); 5.12 (2H, dd, J_1 = 5.0, J_2 = 12.0, 1- and 8-H) 8.94 (1H, s, 9-H); 25.78 (CH$_3$); 31.06 (CH$_3$); 32.10 (C$_{(3)}$, C$_{(6)}$); 41.73 (C$_{(2)}$, C$_{(7)}$); 44.80 (C$_{(4)}$, C$_{(5)}$) 67.14 (C$_{(1)}$, C$_{(8)}$); 137.97 (C$_{(8a)}$, C$_{(9a)}$); 146.00 (C$_{(9)}$); 152.99 (C$_{(4a)}$, C$_{(10a)}$)

* Spectra of compound X taken in CF_3CO_2D, spectra of other compounds taken in $CDCl_3$.

product obtained (Scheme 3). The melting point and IR spectra of this compound coincided with those of the product described. However, the PMR and ^{13}C NMR spectral data correspond to octahydroacridinediol X. Thus, the PMR spectrum has a one-proton downfield singlet for 9-H at 8.94 ppm. The three downfield signals in the ^{13}C NMR spectrum (at 137.97, 146.00, and 152.99 ppm) correspond to the signals of pyridine ring carbon atoms. The coupling constants of the protons bound to $C_{(1)}$ (12.0 Hz) and $C_{(8)}$ (5.0 Hz) indicate their pseudoaxial orientation and, thus, pseudoequatorial orientation of the hydroxyl groups bound to these carbon atoms in the half-chair conformation of the cyclohexene rings. Such a predominant arrangement of the hydroxyl groups results from a considerable 1,3-diaxial interaction of these groups with the axial methyl groups at $C_{(3)}$ and $C_{(6)}$ [19].



EXPERIMENTAL

The reaction course and purity of the products obtained were monitored by TLC on Silufol 254 using 1:2 ether–hexane as the eluent with visualization by UV light or iodine vapor. The melting points were determined on a Boetius block. The IR spectra were taken on a UR-20 spectrometer for KBr pellets. The UV spectra were taken on a Specord M-40 spectrometer for solutions in ethanol. The mass spectra were taken on a Varian MAT-311 mass spectrometer with direct sample inlet. The ionizing voltage was 70 eV. The PMR and ^{13}C NMR spectra were taken on a Bruker AC-200 spectrometer at 200 and 50 MHz, respectively. The ^{13}C NMR spectra were taken with proton decoupling. The fluorescence spectra were taken on a Solar SFL 1211A instrument for solutions in ethanol.

3,5-Diethoxycarbonyl-2,6-dimethylpyridine (Ia), Ethyl α-[(1-Methyl-2-ethoxycarbonylvinylamino)-methylen]acetoacetate (Va), and 3,5-Diethoxycarbonyl-2,6-dimethyl-2-hydroxy-4-(1-methyl-2-ethoxycarbonylvinylamino)-1,2,3,4-tetrahydropyridine (VI). A mixture of ethyl acetoacetate (1.56 g, 12 mmol), ethyl 3-aminocrotonate (IIIa) (1.55 g, 12 mmol), ethyl orthoformate (5 ml, 32 mmol), and acetic acid (2 ml, 35 mmol) was heated at reflux for 1 h in a nitrogen atmosphere. The reaction mixture was evaporated in vacuum. The residue was treated with ether (200 ml) and sat. aq. Na_2CO_3 (50 ml). The etheral extract was dried over Na_2SO_4 and evaporated. The residue was subjected to column chromatography on silica gel 100/160 using 1:5 ether–hexane as the eluent to give Ia (2.20 g), Va (0.32 g), and VI (0.12 g).

The three-component condensations given below were carried out analogously. Thus, compound IIb (1.96 g, 14 mmol), 3-amino-5,5-dimethylcyclohexen-2-one (IIIb) (1.95 g, 14 mmol), ethyl orthoformate (7 ml, 44 mmol), and acetic acid (2.5 ml) gave 2.69 g of **3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydro-1,8-acridinedione (Ib)** and 0.49 g of **1-[(5,5-dimethyl-3-oxo-2-cyclohexen-1-ylamino)methylen]-4,4-dimethylcyclohexane-2,6-dione (Vb).**

A sample of 1,3-cyclohexanedione (IIc) (0.67 g, 6 mmol), 3-aminocyclohexen-2-one (IIIc) (0.66 g, 6 mmol), ethyl orthoformate (3 ml, 19 mmol), and acetic acid (1 ml) gave 0.32 g of **1,2,3,4,5,6,7,8-octahydro-1,8-acridinedione (Ic).**

A sample of dimedone (2.24 g, 16 mmol), enamino ester IIIa (2.06 g, 16 mmol), ethyl orthoformate (10 ml, 53 mmol), and acetic acid (2.5 ml) gave 1.54 g of **3-ethoxycarbonyl-2,7,7-trimethyl-5,6,7,8-tetrahydro-5-quinolinone (Id)** and 0.54 g of **ethyl 3-[(4,4-dimethyl-2,6-dioxocyclohexylidene)methylamino]-2-butenoate (Vd).**

A sample of enaminoketone IIIb (0.97 g, 7 mmol), cyclohexanedione IIc (0.78 g, 7 mmol), ethyl orthoformate (3.5 ml, 22 mmol), and acetic acid (1 ml) gave 0.88 g of **3,3-dimethyl-1,2,3,4,5,6,7,8-octahydro-1,8-acridinedione (Ie).**

3,3,6,6-Tetramethyl-1,2,3,4,5,6,7,8-octahydro-1,8-acridinediol (X) was obtained from octahydroacridinedione Ib by the action of $LiAlH_4$ according to [7].

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