OCTAHYDROPYRROLO[4,3,2-m,n]ACRIDINE DERIVATIVES.

I. SYNTHESIS AND MOLECULAR STRUCTURE OF DERIVATIVES OF 2,3,4,5,7,8,9,10-OCTAHYDROPYRROLO[4,3,2-m,n]ACRIDIN-10-ONE, A NEW HETEROCYCLIC SYSTEM

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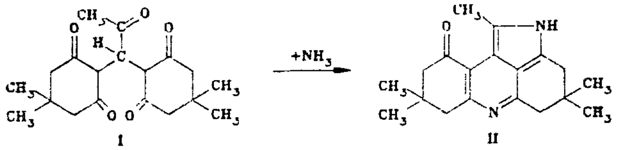
Heating 1,1-bis(5,5-dimethyl-1,3-cyclohexanedion-2-yl)acetone with ammonia gave a new heterocyclic compound, namely, 1,4,4,8,8-pentamethyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-one. Analogously, 3,6-dimethyl-9-benzoyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione gave 4,8-dimethyl-1-phenyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-one. The structures of these products were demonstrated by PMR and IR spectroscopy and x-ray diffraction analysis.

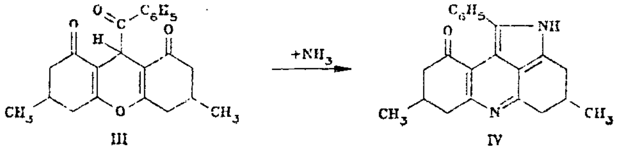
3,3,6,6-Tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-diones are well known hydrogenated nitrogen heterocycles. The corresponding aldehyde and 5,5-dimethylcyclohexane-1,3-dione or the products of their reaction, bis(5,5-dimethylcyclohexane-1,3-dion-2-yl)methane serve as starting reagents for these heterocycles [1]. 1,1-Bis(5,5-dimethyl-1,3-cyclohexanedion-2-yl)acetone (I) [2] upon cyclization with ammonia gives a new heterocyclic system, namely, 1,4,4,8,8-pentamethyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-one (II), whose conjugated fragment is a pyrrolo[4,3-c]pyridine with a carbonyl group fixed in s-trans orientation, instead of the expected 9-acetyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione.



The lack of the acridine-1,8-dione derivative in the reaction mixture indicates that the formation of II proceeds through prior closure of the pyrrole ring.

Acridinone (II) crystallizes with an equimolar amount of ethanol or methanol solvent, which although readily removed by another solvent, is removed only with difficulty (upon heating to over 130°C.

The same heterocyclic system was obtained from 5-methylcyclohexane-1,3-dione, which reacts with phenylglyoxal in the presence of dehydrating agents by analogy to dimedone [3] with the formation of 3,6-dimethyl-9-benzoyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (III). Treatment of III by ammonia at 150°C leads to 4,8-dimethyl-1-phenyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-one (IV), which forms a crystal hydrate containing a mole of water. By analogy to II, this water of crystallization is removed only with difficulty.



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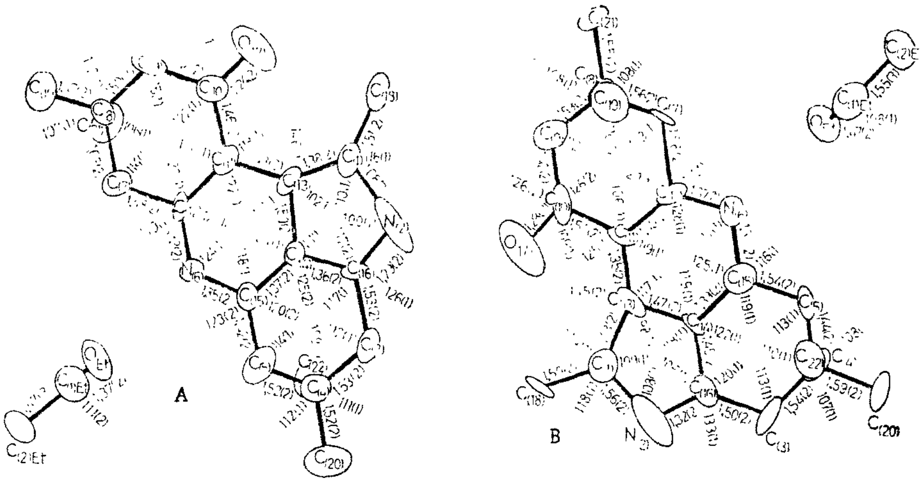

Fig. 1. Geometrical parameters of the solvated dimer of IIa.

$C_{(4)}-C_{(22)}$	1,55(2)	$C_{(4)}-C_{(22)}$	1,51(2)
$C_{(8)}-C_{(21)}$	1,56(2)	$C_{(8)}-C_{(19)}$	1,55(2)
$C_{(21)}-C_{(8)}-C_{(9)}$	113(1)	$C_{(21)}-C_{(8)}-C_{(19)}$	112(1)
$C_{(21)}-C_{(8)}-C_{(7)}$	109(1)	$C_{(22)}-C_{(4)}-C_{(3)}$	107(1)
$C_{(21)}-C_{(8)}-C_{(19)}$	107(1)	$C_{(22)}-C_{(4)}-C_{(5)}$	112(1)
$C_{(22)}-C_{(4)}-C_{(3)}$	110(1)	$C_{(22)}-C_{(4)}-C_{(20)}$	111(1)
$C_{(22)}-C_{(4)}-C_{(5)}$	111(1)	$C_{(19)}-C_{(8)}-C_{(7)}$	109(1)
$C_{(22)}-C_{(4)}-C_{(20)}$	105(1)	$C_{(19)}-C_{(8)}-C_{(9)}$	110(1)

The presence of C=O and NH groups in heterocycles II and IV was indicated by the IR spectra of these compounds in solution: 1650 (C=O) and 3435 cm^{-1} (NH) for II and 1663 (C=O) and 3400 cm^{-1} (NH) for IV. The reduced frequencies of these bands in the IR spectrum of II taken in Vaseline mull indicates the participation of these groups in intermolecular hydrogen bonding. The UV spectra of these compounds indicate a more complex conjugated system in II and IV than in decahydroacridine-1,8-dione derivatives [1].

We attempted to elucidate the nature of the bond of the solvents with II and IV in the crystal, find the orientation of the hydrogen of the NH group in the pyrrole rings, and study the conformation of the condensed heterocyclic system and steric conditions of the close-lying substituents at $C_{(1)}$ and $C_{(10)}$. An x-ray diffraction study was carried out on II and IV in order to clarify these questions.

The crystal of II is a solvate containing two nonequivalent 1,4,4,8,8-pentamethyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-one molecules (A and B) and two ethanol molecules (Fig. 1). By means of intermolecular hydrogen bonds formed by the pyrrole ring NH group and the carbonyl group of the adjacent molecules, molecules A and B are linked in a chain along the diagonal of the ab plane of the unit cell. The solvent molecules form O—H...N hydrogen bonds with the pyridine ring nitrogen atoms of the adjacent molecules (Table 1). Molecules A and B have geometric and conformational differences exceeding experimental error which may be due to their different crystal environment.

The crystallographically independent structure in the crystal of IV has only one water molecule (Fig. 2). In contrast to the structure of II, the molecules in the crystal of IV are not directly linked by hydrogen bonds with each other but rather form a three-dimensional network of hydrogen bonds by means of the water molecules surrounding them (Table 1).

The heterocyclic fragments of A and B in the crystal of II are virtually planar with the exception of $C_{(4)}$ and $C_{(8)}$, which deviate as a pair in each molecule in the same direction; the average deviation is 0.64 Å. The heterocyclic fragment in IV is also close to planar. The angle between the mean planes of the pyrrole and pyridine rings is less than 5° (Table 2). The carbocycle atoms have a common bond with the pyrrole fragment deviate only slightly from the plane of the pyridine ring while the carbocycle containing the carbonyl group is highly deformed. $C_{(8)}$, $C_{(9)}$, and $C_{(10)}$ deviate from the pyridine ring plane by −0.45, 0.22, and 0.33 Å, respectively, and the carbocycle has distorted half-chair conformation.

TABLE 1. X—H...Y Hydrogen Bond Parameters in the Structures of II and IV

Structure	Atom X	Atom Y	Distance X...Y, Å	Distance H...Y, Å	Angle X—H...Y (deg)
II	$N_{(2)}$ (A)	$O_{(17)}$ (B)	2,89	2,24	168
	$O_{(ET)}$ (A)	$N_{(6)}$ (A)	2,87	1,73	172
	$O_{(ET)}$ (B)	$N_{(6)}$ (B)	2,76	1,66	168
	$N_{(2)}$ (B)	$O_{(17)}$ (A)	2,94	2,17	146
IV	$N_{(2)}$	$O_{(H_2O)}$	2,79	1,87	161
	$O_{(H_2O)}$	$O_{(10)}$	2,93	2,15	166
	$O_{(H_2O)}$	$N_{(6)}$	2,84	1,99	155

TABLE 2. Characteristic Angles between Planes in II and IV

Compound	Atoms in planes		Angle, deg	
	plane I	plane II	A	B
II	$C_{(1)}N_{(2)}C_{(16)}C_{(14)}C_{(13)}$	$C_{(11)}C_{(12)}N_{(6)}C_{(15)}C_{(14)}$ $C_{(13)}$	0,8	1,1
	$N_{(2)}C_{(16)}C_{(14)}C_{(15)}N_{(6)}$	$C_{(11)}C_{(12)}N_{(6)}$	3,9	1,0
	$O_{(17)}C_{(10)}C_{(11)}$	$C_{(11)}C_{(12)}C_{(14)}C_{(15)}$	3,3	6,4
	$C_{(12)}N_{(6)}C_{(15)}$	$C_{(11)}C_{(12)}C_{(14)}C_{(15)}$	1,5	1,2
IV	$C_{(1)}N_{(2)}C_{(16)}C_{(14)}C_{(13)}$	$C_{(11)}C_{(12)}C_{(14)}C_{(15)}$	4,5	
	$C_{(12)}N_{(6)}C_{(15)}$	$C_{(11)}C_{(12)}C_{(14)}C_{(15)}$	1,0	
	$C_{(17)} \ldots C_{(21)}$	$C_{(1)}N_{(2)}C_{(16)}C_{(14)}C_{(13)}$	37,1	
	$O_{(10)}C_{(10)}C_{(11)}$	$C_{(11)}C_{(12)}C_{(14)}C_{(15)}$	19,2	
	$O_{(10)}C_{(10)}C_{(11)}$	$C_{(11)}C_{(12)}N_{(6)}$	18,3	

In addition to crystal packing factors, the steric interactions of the carbonyl groups and substituents at $C_{(1)}$ markedly affect the geometry of II and IV. Thus, the distances from $O_{(17)}$ to $C_{(18)}$ in molecules IIA and IIB are 2.89 and 2.85 Å, respectively, and the distance in IV from $O_{(10)}$ to $C_{(22)}$ is 2.88 Å. These distances are shorter than the sums of the van der Waals radii of the given atoms [4]. While steric hindrance in IV leads to deformation of the corresponding carbocycle and $O_{(10)}$ of the carbonyl group and $C_{(17)}$ of the phenyl ring deviate in opposite directions from the pyridine plane (by 0.76 and 0.32 Å, respectively), such interaction in IIA and IIB leads to a significant distortion of the pyrrole rings. Thus, molecules A and B show significant extension of the $C_{(1)}$—$N_{(2)}$ bonds to 1.68 and 1.56 Å and shortening of the $N_{(2)}$—$C_{(16)}$ bonds to 1.29 and 1.32 Å, respectively.

We should also note the conjugated amino—vinyl—imino—vinyl—carbonyl system $N_{(2)}$—$C_{(16)}$—$C_{(14)}$—$C_{(15)}$—$N_{(6)}$—$C_{(12)}$—$C_{(11)}$—$C_{(10)}$—$O_{(10)}$. The bond lengths in this system are markedly equalized as, for example, in the structure of the potassium salt of 3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridine-9-carboxylic acid [5].

EXPERIMENTAL

The PMR spectra were obtained on a Bruker WH-90 spectrometer. The UV spectra were taken on a Hitachi 557 spectrometer. The IR spectra were taken on a UR-20 spectrometer.

The x-ray diffraction structural analyses of II and IV were carried out on a Syntex $P2_1$ diffractometer using $\theta/2\theta$ scan, CuK_α radiation, and graphite monochromator; $2\theta_{max} = 150°$. The unit cell parameters for triclinic monocrystals of II ($C_{19}H_{24}N_2O \cdot C_2H_5OH$): $a = 8.934(2)$, $b = 8.928(2)$, $c = 12.254(2)$ Å, $\alpha = 97.62(2)$, $\beta = 97.68(2)$, $\gamma = 100.44(2)°$, $V = 940.2(4)$ Å^3, $M = 342.6$, d_{calc} 1.21 g/cm^3, $\mu(CuK_\alpha)$ 6.2 cm^{-1}, $Z = 2$, space group P1, $F_{000} = 372$.

The unit cell parameters for monoclinic monocrystals of IV ($C_{22}H_{22}N_2O \cdot H_2O$): $a = 9.724(1)$, $b = 18.803(1)$, $c = 11.197(2)$ Å, $\beta = 111.16(1)°$, $V = 1908.9(4)$ Å^3, M 330.45, d_{calc} 1.15 g/cm^3, $\mu(CuK_\alpha)$ 5.6 cm^{-1}, $Z = 4$, space group $P2_1/c$ $F_{000} = 704$.

Totals of 2931 (for II) and 2990 (for IV) independent reflections were measured, of which 2298 and 2188 reflections with $I \geq 2\sigma_I$ were used in the calculations. The structures were solved using the direct method and the XTL programs and refined by the method of least squared in the full-matrix approximation anisotropically for the nonhydrogen atoms and iso-

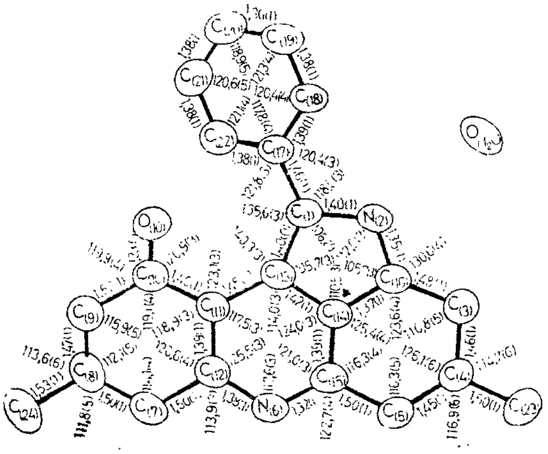

Fig. 2. Geometric parameters of IV.

TABLE 3. Coordinates (×10⁴) of the Non-Hydrogen Atoms in II

Atom*	Molecule A			Molecule B		
	x	*y*	*z*	*x*	*y*	*z*
$O_{(17)}$	4624(2)	1352(2)	4534(2)	−1579(2)	5239(2)	5444(1)
$N_{(2)}$	1092(2)	4691(2)	4480(1)	−4796(2)	8626(2)	5503(1)
$N_{(6)}$	5120(1)	5484(2)	2527(1)	−5684(1)	4676(2)	7544(1)
$C_{(1)}$	2253(2)	3412(2)	4528(1)	−3557(2)	7607(2)	5479(1)
$C_{(3)}$	1217(2)	6982(2)	3482(1)	−7113(2)	8640(2)	6555(1)
$C_{(4)}$	1737(2)	7327(2)	2388(1)	−7472(2)	8081(2)	7649(1)
$C_{(5)}$	3455(2)	7358(2)	2487(2)	−7507(2)	6453(2)	7582(1)
$C_{(7)}$	6976(2)	3831(2)	2496(1)	−3943(2)	2887(2)	7569(1)
$C_{(8)}$	6984(2)	1996(2)	2401(1)	−2192(2)	2863(2)	7628(1)
$C_{(9)}$	6656(2)	1556(2)	3502(1)	−1687(2)	3181(2)	6526(2)
$C_{(10)}$	5300(0)	2060(0)	3883(0)	−2168(2)	4481(2)	6148(1)
$C_{(11)}$	4791(2)	3425(2)	3556(1)	−3530(2)	5924(2)	6450(1)
$C_{(12)}$	5550(2)	4242(2)	2834(1)	−4389(2)	4347(2)	7151(1)
$C_{(13)}$	3405(2)	3777(2)	3000(1)	−3953(2)	6379(2)	6100(1)
$C_{(14)}$	3051(2)	5214(2)	3498(1)	−5285(2)	6870(2)	6513(1)
$C_{(15)}$	3898(2)	6020(2)	2833(1)	−6093(2)	5964(2)	7165(1)
$C_{(16)}$	1768(2)	5581(2)	3866(1)	−5772(1)	8084(1)	6146(1)
$C_{(18)}$	1847(2)	2145(2)	5209(1)	−2269(2)	8044(2)	4842(1)
$C_{(19)}$	8491(2)	1717(2)	2171(2)	−1254(2)	4121(2)	8589(2)
$C_{(20)}$	1355(2)	8841(2)	2116(2)	−9141(2)	8381(2)	7809(2)
$C_{(21)}$	9756(2)	1110(2)	1394(1)	−1968(2)	1218(2)	7792(2)
$C_{(22)}$	821(2)	6091(2)	1421(1)	−6248(2)	9031(2)	8579(1)
O_{Et}	7109(2)	7437(2)	1410(1)	−7601(2)	2725(2)	8571(1)
$C_{(1)Et}$	6635(2)	7003(2)	288(2)	−7108(2)	3261(2)	9776(2)
$C_{(2)Et}$	7662(2)	7912(2)	−331(2)	−8078(2)	2161(2)	10409(1)

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*The numbering of the atoms is given in Fig. 1.

tropically for the hydrogen atoms. The final R = 0.079 (for II) and R = 0.062 (for IV). The coordinates of the nonhydrogen atoms are given in Tables 3 and 4.

1,4,4,8,8-Pentamethyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-one (II). A solution of 2.91 g (8.7 mmoles) 1,1-bis(5,5-dimethyl-1,3-cyclohexanedione-2-yl)acetone in a mixture of 5 ml ethanol and 4 ml (58.8 mmoles) 25% aqueous ammonia was heated in a steel autoclave at 150°C for 5 h. After cooling the reaction mixture gave 2.52 g (86%) II as bright red crystal hydrate IIa containing 1 mole ethanol. mp >190°C (dec.) (from ethanol). IR spectrum (0.07 mole/liter in $CHCl_3$): 1655 (C=O), 3425 cm^{-1} (NH). UV spectrum (in ethanol), λ_{max} (log ε): 203 (4.11), 243 (4.40), 448 nm (3.61). Found, %: C 73.1, H 9.1, N 8.2. $C_{19}H_{24}N_2O \cdot C_2H_5OH$. Calculated, %: C 73.7, H 8.8, N 8.2.

A solution of 0.2 g crystal hydrate IIa in 10 ml methanol was heated at reflux for 10 min and cooled to give 0.1 bright red crystal hydrate IIb containing 1 mole methanol, mp > 200°C (dec.). Found, %: C 73.0, H 8.7, N 8.4. $C_{19}H_{24}N_2O \cdot CH_3OH$. Calculated, %: C 73.1, H 8.6, N 8.5.

In order to remove the solvents, crystal hydrates IIa and IIb were heated in vacuum at 150°C for 1 h to give bright red II not containing alcohol, as indicated by PMR spectroscopy.

TABLE 4. Coordinates ($\times 10^4$) of Non-Hydrogen Atoms in IV

Atom*	x	y	z	Atom*	x	y	z
$O_{(H_2O)}$	9 059(5)	5575(2)	2083(4)	$C_{(12)}$	11 691(4)	2079(2)	1161(4)
$N_{(2)}$	10 451(3)	4286(2)	2033(3)	$C_{(13)}$	11 439(4)	3349(2)	1416(3)
$N_{(6)}$	10 623(3)	1905(2)	1652(3)	$C_{(14)}$	10 306(4)	3138(2)	1861(4)
$O_{(10)}$	13 051(3)	3446(1)	−307(3)	$C_{(15)}$	9 932(4)	2433(2)	1974(4)
$C_{(1)}$	11 527(4)	4087(2)	1541(4)	$C_{(16)}$	9 706(4)	3720(2)	2227(4)
$C_{(3)}$	8 523(6)	3676(2)	2760(6)	$C_{(17)}$	12 504(4)	4641(2)	1381(3)
$C_{(4)}$	8022(8)	2942(3)	2750(9)	$C_{(18)}$	11 960(5)	5315(2)	962(4)
$C_{(5)}$	8 759(6)	2313(2)	2534(6)	$C_{(19)}$	12 886(5)	5840(2)	823(4)
$C_{(7)}$	12 389(5)	1446(2)	788(6)	$C_{(20)}$	14 342(6)	5714(2)	1094(4)
$C_{(8)}$	13 847(7)	1600(3)	670(7)	$C_{(21)}$	14 897(5)	5049(3)	1515(5)
$C_{(9)}$	13 797(6)	2242(2)	−90(5)	$C_{(22)}$	13 991(4)	4520(2)	1660(4)
$C_{(10)}$	13 005(4)	2867(2)	186(4)	$C_{(23)}$	6 907(7)	2835(3)	3375(8)
$C_{(11)}$	12 101(4)	2765(2)	969(3)	$C_{(24)}$	14 464(10)	951(3)	219(8)

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*The numbering of the atoms is given in Fig. 2.

PMR spectrum in $CDCl_3$: 1.12 [6H, s, 8-$C(CH_3)_2$], 1.13 [6H, s, 4-$C(CH_3)_2$], 2.51 (2H, s, 9-CH_2), 2.74 (2H, s, 7-CH_2), 2.77 (2H, s, 5-CH_2), 2.88 (3H, s, 1-CH_3), 2.98 (2H, s, 3-CH_2), 9.54 ppm (1H, br. s, NH).

The PMR spectra of the crystal hydrates were analogous. However, the spectrum of IIa also has ethanol proton signals at 1.22 (3H, t, J = 7.0 Hz, CH_3), 3.70 (2H, q, J = 7.0 Hz, CH_2), 1.75 (1H, s, OH), and the spectrum of IIb has methanol proton signals at 1.65 (1H, s, OH) and 3.47 (3H, s, CH_3).

Solvate IIa dried at 20°C was used for the x-ray diffraction structural analysis.

3,6-Dimethyl-9-benzoyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (III). A solution of 12.6 g (0.10 mole) 5-methyl-1,3-cyclohexanedione and 7.6 g (0.05 mole) phenylglyoxal monohydrate in a mixture of 50 ml acetic acid and 18.4 g (0.18 mole) acetic anhydride was heated at reflux for 1 h. The reaction mixture was cooled and mixed with water. The precipitate formed was washed with water and recrystallized from 1:1 ethanol—water to give 11.2 g (66%) colorless crystalline III, mp 201-203°C. PMR spectrum in $CDCl_3$: 1.08 (6H, d, J = 5.0 Hz, 3,6-CH_3), 1.95-2.73 (10H, m, 2,4,5,7-CH_2 and 3,6-CH), 5.41 (1H, s, 9-H), and 7.35-8.31 ppm (5H, m, C_6H_5). Found, %: C 74.2, H 6.2. $C_{21}H_{22}O_4$. Calculated, %: C 74.5, H 6.6.

4,8-Dimethyl-1-phenyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-one (IV). A solution of 6.8 g (0.02 mole) III in a mixture of 45 ml ethanol and 30 ml (0.44 mole) 25% aqueous ammonia was heated for 6 h in an autoclave at 150°C. After cooling, the precipitate formed was filtered off and dried at 20°C to give 5.7 g (82%) orange IV as a monohydrate with mp 145-148°C (dec.) (from ethanol). Found, %: C 75.6, H 6.9, N 7.9. $C_{22}H_{22}N_2O \cdot H_2O$. Calculated, %: C 75.8, H 6.9, N 8.0.

A sample of monohydrate IV was dried for 30 min in vacuum over P_2O_5 at 138°C to give dark orange anhydrous IV.

IR spectrum (0.07 mole/liter solution in dichloroethane): 1663 (C=O), 3400 cm^{-1} (NH). UV spectrum (in ethanol), λ_{max} (log ε): 205 (4.37), 236 (4.24), 265 (4.38), 311 (3.92), 438 nm (3.59). PMR spectrum of dried IV (in $CDCl_3$): 1.10 (3H, d, J = 5.7 Hz, 8-CH_3), 1.23 (3H, d, J = 5.7 Hz, 4-CH_3), 2.02-3.32 (10H, m, 3,5,7,9-CH_2 and 4,8-CH), 7.18 (5H, s, C_6H_5), 10.39 ppm (1H, br. s, NH). The PMR spectrum of the monohydrate has a signal for the water protons at 2.08 ppm (2H, s). Found, %: C 78.1, H 6.8, N 8.2. $C_{22}H_{22}N_2O$. Calculated, %: C 80.0, H 6.7, N 8.5.

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