SYNTHESIS OF PYRROLO[3,2,1-d,e]ACRIDIN-6-ONE

T. M. Alyab'eva, T. E. Khoshtariya,
A. M. Vasil'ev, L. G. Tret'yakova,
T. M. Efimova, and N. N. Suvorov

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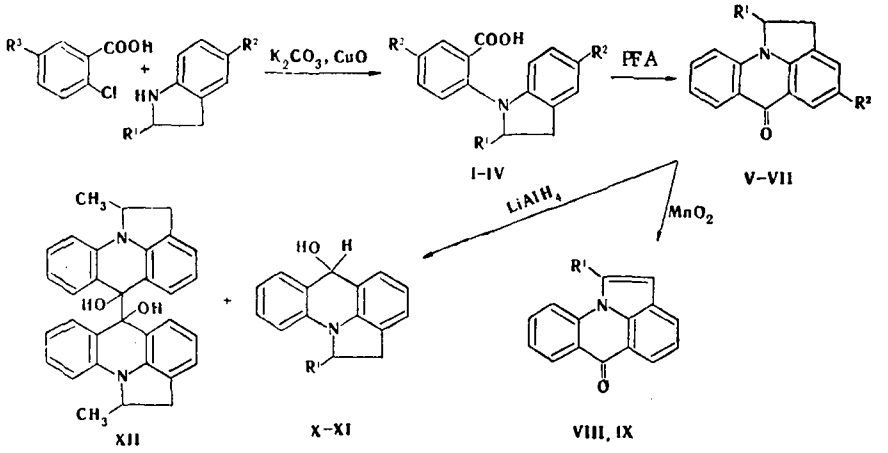
We have previously described the preparation of a pyrroloacridine by hydrazone cyclization under the conditions of the Fischer reaction [1]. Here we report a new method for the synthesis of heterocyclic systems containing acridine and pyrrole rings. It is based on the Jourdan–Ullmann reaction [2], which is widely used for the synthesis of acridines. We used indoline and some of its derivatives as the amino component.



I $R^1=R^2=R^3=H$; II $R^1=CH_3$; $R^2=R^3=H$; III $R^1=R^3=H$; $R^2=OCH_3$; IV $R^1=R^2=H$; $R^3=NO_2$; V $R^1=R^2=H$; VI $R^1=CH_3$; $R^2=H$; VII $R^1=H$; $R^2=OCH_3$; VIII $R^1=H$; IX $R^1=CH_3$; X $R^1=H$; XI $R^1=CH_3$

Condensation of indoline, 2-methylindoline, and 5-acetylindoline with 2-chlorobenzoic acid in the presence of anhydrous potassium carbonate and cupric oxide gave N-2'-carboxyphenyl indoline (I) and its substituted derivatives (II) and (III). The reaction was carried out with a two- or threefold excess of the indoline without solvent. Indoline condenses readily and under comparatively milder conditions than aniline. Only in the case of 5-acetylindoline (Table 1) was a reduction in yield apparent, evidently because of the electron-accepting effect of the acetyl substituent, which reduces the nucleophilicity of the imino group. The major condensation product was accompanied in each case by a small amount of the corresponding indole, formed by partial dehydrogenation of the indoline in the presence of cupric oxide. Condensation of indoline with 2-chloro-5-nitrobenzoic acid (IV) proceeded much more rapidly and in better yield, since here the nucleophilic substitution of the halogen is activated by the nitro group.

Intramolecular cyclization of compounds (I)-(III) in polyphosphoric acid gave respectively 1,2-dihydropyrrolo[3,2,1-d,e]acridin-6-one (V), 1-methyl-1,2-dihydropyrrolo[3,2,1-d,e]acridin-6-one (VI), and 4-acetyl-1,2-dihydropyrrolo[3,2,1-d,e]acridin-6-one (VII). The cyclization of the N-2'-carboxyphenylindolines unsubstituted in the benzene ring with polyphosphoric acid proceeded rapidly and in high yield, whereas the yield of compound (III) was much lower, probably as a result of the accepting effect of the substituent, which inhibits electrophilic substitution. In the case of N-2'-carboxyphenyl-4'-nitroindoline we were unable to generate the acridine ring with either polyphosphoric acid or sulfuric acid. Albert [3] has commented on the difficulties encountered in the cyclization of nitro-substituted diphenylamine-2-carboxylic acids.

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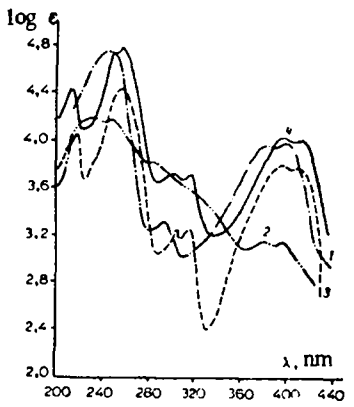

Fig. 1

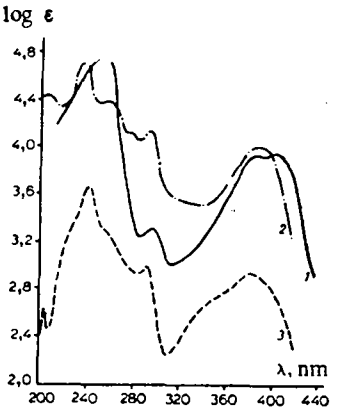

Fig. 2

Fig. 1. UV spectra: 1) 9-acridone; 2) 4-acetyl-1,2-dihydropyrrolo[3,2,1-d,e]acridin-6-one; 3) 1-methyl-1,2-dihydropyrrolo[3,2,1-d,e]acridin-6-one; and 4) 1,2-dihydropyrrolo[3,2,1-d,e]acridin-6-one.

Fig. 2. UV spectra: 1) 9-acridone; 2) pyrrolo[3,2,1-d,e]acridin-6-one; and 3) 1-methylpyrrolo[3,2,1-d,e]acridin-6-one.

Dehydrogenation of compounds (V) and (VI) with manganese dioxide in xylene gave pyrrolo-[3,2,1-d,e]acridin-6-one (VIII) and 1-methylpyrrolo[3,2,1-d,e]acridin-6-one (IX).

The IR spectra of compounds (V) and (VI) have the carbonyl band at 1633 and 1635 cm^{-1} respectively, close to the position of the C=O band in 9-acridone [4]. In compounds (VIII) and (IX) this band is slightly shifted to higher frequency (1685 and 1675 cm^{-1}, respectively).

Since even in nonpolar solvents 9-acridone exists in the oxo form, the UV spectra of N-substituted acridones are extremely similar to that of 9-acridone itself [5]. The absorption spectra of compounds (V) and (VI) also closely resemble that of 9-acridone; the sole exception is a slight bathochromic shift of the long-wavelength maxima (Fig. 1). The introduction of the methyl substituent in compound (VI) does not alter the shape of the curve and affects only the extinction coefficient. The effect of the acceptor substituent in compound (VII) causes smoothing of the vibrational structure in the UV spectrum. The UV spectra of compounds (VIII) and (IX) do not differ greatly from that of 9-acridone (Fig. 2).

The fragmentation of compounds (V) and (VI) is typified by the loss of two protons until the more stable deprotonated system is formed [6]. Compounds (V), (VI), (VIII), and (IX) lose the neutral C=O species, generating a substituted carbazole ion; the subsequent decomposition is typical of carbazoles [7].

In the PMR spectra of compounds (VIII) and (IX) the signal of the 2-H proton lies upfield and is close to the position of the corresponding signal in indole [8]. We identified the signal of the 1-H proton in compound (VIII), which is overlapped by other groups of signals, by double resonance. We assigned the signals of the 3-H, 4-H, and 5-H protons, which lie downfield, on the basis of a comparison with the spectra of indole and its substituted derivatives [8]. The phenyl protons appear as a rather complex multiplet at higher field.

Reduction of compounds (V) and (VI) with lithium aluminum hydride in tetrahydrofuran formed 1,2-dihydro-6H-pyrrolo[3,2,1-d,e]acridin-6-ol (X) and 1-methyl-1,2-dihydro-6H-pyrrolo-[3,2,1-d,e]acridin-6-ol (XI); compound (VI) also gave dimer (XII), which is similar to pinacone in structure.

All three compounds are readily converted by oxidants to the substituted acridones (V) and (VI). The characteristic hydroxyl band in the 3400-3600 cm^{-1} region can be identified in their IR spectra, while their UV spectra resemble that of acridan [10].

In the PMR spectra of compounds (X)-(XII) the hydroxyl proton appears as a sharp singlet at 8.24, 10.1, and 9.8 ppm, respectively.

EXPERIMENTAL

Spectra were recorded on: UV: a Specord UV-vis, in ethanol; IR: a UR-20, in Vaseline oil; PMR: a Varian HA-100D, in acetone-d_6 with hexamethyldisiloxane (HMDS) as internal

TABLE 1. Properties of Substituted N-2'-Carboxyphenylindolines

Compound	mp, °C	UV spectrum, λ_{max} (log ε)	Found, %			Formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
I	125—126	207 (4,52), 294 (4,02)	75,0	5,1	6,0	$C_{15}H_{13}NO_2$	75,3	5,4	5,9	89
II	128—129	208 (4,19), 227 (4,00), 285 (3,65)	75,4	5,8	5,3	$C_{16}H_{15}NO_2$	75,9	5,9	5,5	83
III	119—120*	205 (4,30), 227 (4,42), 298 (3,40)	72,3	5,0	5,1	$C_{17}H_{15}NO_3$	72,6	5,3	5,0	40
IV	164—165	208 (4,41), 273 (4,18), 417 (3,88)	63,2	4,1	9,7	$C_{15}H_{12}N_2O_4$	63,5	4,2	9,9	92

*Silica gel column; elution by ether.

standard. Mass spectra were derived with an MX-1303 with sample insertion into the ion source, cathode emission current 1.5 mA, ionizing voltage 50 eV, and accelerating voltage 2 kV.

N-2'-Carboxyphenylindoline (I) and N-2'-Carboxylphenyl-2-methylindoline (II). A mixture of indoline (11.9 g, 0.1 mole) or 2-methylindoline (13.3 g, 0.1 mole), 2-chlorobenzoic acid (7.8 g, 0.05 mole) anhydrous potassium carbonate (7.8 g, 0.055 mole), and cupric oxide (0.1 g) was heated at 110-120°C for 30 min. The thickened reaction mixture was transferred to refluxing 2% aqueous KOH solution (300 ml). The organic layer was removed. The aqueous layer after extraction with ethyl acetate was filtered and acidified with hydrochloric acid until precipitation of the grayish green crystals of compound (I) was complete. Compound (II) precipitated as an oil that crystallized on cooling. It was purified by reprecipitation from sodium carbonate solution.

N-2'-Carboxyphenyl-5-acetylindoline (III). To a melt of 5-acetylindoline (10 g, 0.06 mole) was added 2-chlorobenzoic acid (3.1 g, 0.02 mole), K_2CO_2 (3.1 g, 0.022 mole), and cupric oxide (0.05 g). The mixture was heated at 140-150°C for 1 h. Compound (III) was isolated in the same way as compounds (I) and (II). It precipitated as an oil and was purified by chromatography.

N-2'-Carboxyphenyl-4'-nitroindoline (IV) was prepared in the same way as compound (I) from indoline (17.8 g, 0.15 mole), 2-chloro-5-nitrobenzoic acid (11 g, 0.055 mole), K_2CO_3 (11 g, 0.078 mole), and cupric oxide (0.15 g) at 90-100°C for 15 min.

1,2-Dihydropyrrolo[3,2,1-d,e]acridin-6-one (V) and 1-Methyl-1,2-dihydropyrrolo[3,2,1-d,e]acridin-6-one (VI). To polyphosphoric acid (100 ml) was added compound (I) or (II) (5 g, 0.02 mole). The reaction mixture was heated at 125-130°C for 30 min with constant stirring and then poured into boiling water (300 ml). The yellow precipitate was filtered off and refluxed for 5 min in 10% Na_2CO_3 solution (100 ml). It was then pressed on the filter and washed thoroughly with water. The yield of compound (V) (4.2 g, 90%), mp 210-212°C (from ethyl acetate). Mass spectrum:* 221 (19), 220 (17), 219 (7), 195 (68), 194 (70), 193 (100), 165 (25). Found: C 81.6; H 5.02; N 6.3%. $C_{15}H_{11}NO$. Calculated: C 81.5; H 5.0; N 6.3%. The yield of compound (VI) was 3.7 g (80%), mp 123°C (silica gel column, elution with ether). Mass spectrum: 235 (72), 234 (6), 233 (10), 220 (100), 219 (31), 192 (7), 165 (10), 164 (6). Found: C 81.5; H 5.2; N 5.9%. $C_{16}H_{13}NO$. Calculated: C 81.7; H 5.4; N 5.9%.

4-Acetyl-1,2-dihydropyrrolo[3,2,1-d,e]acridin-6-one (VII). Compound (III) (2.24 g, 8 mmole) and polyphosphoric acid (50 ml) were heated at 150°C for 1 h. The reaction mixture was poured into water and the precipitate was extracted with ethyl acetate. The extract was dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a silica gel column with elution by ether. The yield was 0.21 g (10%), mp 153°C (from ethyl acetate). IR spectrum: 1700 (CO), 1780 cm^{-1} ($COCH_3$). Found: C 77.3; H 4.5; N 5.2%. $C_{17}H_{13}NO_2$. Calculated: C 77.6; H 4.9; N 5.3%.

Pyrrolo[3,2,1-d,e]acridin-6-one (VIII) and 1-Methylpyrrolo[3,2,1-d,e]acridin-6-one (IX). Compound (V) (2.2 g, 10 mmole) or compound (VI) (2.35 g, 10 mmole) in xylene was refluxed with active manganese dioxide for 36 h and 12 h, respectively. Then the MnO_2 was filtered off and the solvent was evaporated. The precipitate of compound (VIII) was purified by recrystallization from acetone; compound (IX) was purified by chromatography on a silica gel column with elution by ether. The yield of (VIII) was 1.64 g (75%), mp 232°C. Mass spectrum: 219 (100),

*Here and subsequently we quote m/e (intensity of the peak in % relative to the maximum).

191 (22), 190 (20), 164 (34), 163 (41). PMR spectrum: 8.36 (d, J_{12} = 3.5 Hz, 1-H), 7.04 (d, 2-H), 7.8 (d, 3-H), 8.42 (q, J_{54} = 8.1 Hz, J_{53} = 1.6 Hz, 5-H), 7.55* (m, 7-H, 8-H), 8.11* ppm (m, 4-H, 6-H, 9-H). Found: C 81.9; H 4.0; N 6.2%. $C_{15}H_9NO$. Calculated: C 82.2; H 4.1; N 6.4%. The yield of compound (IX) was 1.84 g (78%), mp 198-200°C. Mass spectrum: 233 (100), 232 (47), 205 (11), 204 (50), 177 (7), 176 (10), 150 (8). PMR spectrum: 3.03 (s, CH_3), 6.73 (d, J_{2,CH_3} = 1 Hz, 2-H), 7.78 (d, 3-H), 8.49 (q, J_{54} = 8.1 Hz, J_{53} = 1.6 Hz, 5-H), 7.48* ppm (m, 7-H, 8-H), 8.03* (m, 4-H, 6-H, 9-H). Found: C 82.2; H 4.5; N 5.9%. $C_{16}H_{11}NO$. Calculated: C 82.4; H 4.7; N 6.0%.

1,2-Dihydro-6H-pyrrolo[3,2,1-d,e]acridin-6-ol (X), 1-Methyl-1,2-dihydro-6H-pyrrolo[3,2,1-d,e]acridin-6-ol (XI) and 6,6'-Dihydroxy-1,1'-dimethyl-1,1',2,2'-tetrahydrodipyrrolo[3,2,1-d,e]-6,6'-biacridanyl (XII). To a refluxing suspension of lithium aluminum hydride (0.5 g) in absolute THF (50 ml) was added a solution of compound (V) or (VI) (0.5 g) over a period of 15 min. The reaction mixture was refluxed for 30 min. The mixture was cooled. Excess reductant was decomposed with water (0.5 ml), 15% NaOH solution (0.5 ml), and again with water (0.5 ml). The precipitate was filtered off and washed with THF; the filtrate was evaporated under vacuum. The white precipitate of compound (X) was washed with acetone and recrystallized from DMF. The yield was 0.42 g (84%), mp 260°C. IR spectrum: 3450-3520 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 210 (4.31), 289 nm (3.95). Found: C 80.6; H 5.8; N 6.4%. $C_{15}H_{13}NO$. Calculated: C 80.7; H 5.8; N 6.3%. In the case of compounds (XI) and (XII) the residue after evaporation of THF was dissolved in methanol (30 ml) and the insoluble precipitate of compound (XII) was filtered off; the filtrate was evaporated and chromatographed on a silica gel column with elution by ether—methanol, 1:10. The yield of compound (XI) was 0.36 g (71%), mp 325-328°C. IR spectrum: 3480-3510 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 215 (4.2), 262 (3.6), 290 nm (4.0). Found: C 80.9; H 6.0; N 5.6%. $C_{16}H_{15}NO$. Calculated: C 81.0; H 6.3; N 5.9%. The yield of compound (XII) was 0.11 g (22%), mp 358-362°C (decomposition; from DMF). IR spectrum: 3500-3600 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 212 (4.1), 262 (3.65), 285 nm (3.9). Found: C 81.1; H 5.8; N 5.9%. $C_{32}H_{26}N_2O_2$. Calculated: C 81.3; H 5.9; N 5.9%.

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*We quote the average chemical shift.