AZAINDOLE DERIVATIVES.

66.* 1,6-DISUBSTITUTED 4-METHYL-5-CYANO-7-AZAINDOLINES

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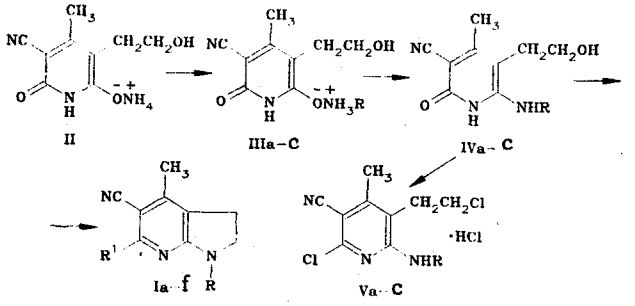
A general method was developed for the synthesis of 1,6-disubstituted 4-methyl-5-cyano-7-azaindolines from the readily available ammonium salt of 2,6-dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine through the corresponding N-substituted ammonium salts and N-substituted 2-amino-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridines with treatment of the latter by $POCl_3$. This method gives a 40% yield of 4-methyl-5-cyano-7-azaindoline compounds containing various aralkyl or alkyl substituents at N-1 and a hydroxy group or halogen atom at C-6 in three steps.

In a continuation of our studies of 7-azaindoline compounds [1, 2], we developed a new general method for the synthesis of 1,6-disubstituted 4-methyl-5-cyano-7-azaindolines (I) having various aralkyl or alkyl groups at N-1 and a hydroxy group or halogen atom at C-6.

The starting compound for these syntheses is the readily available ammonium salt of 2,6-dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine (II) obtained by the condensation of cyanoacetamide with α-acetobutyrolactone [3, 4]. Heating of ammonium salt II with aralkyl or alkyl primary amines due to the elimination of the more volatile and less basic ammonia by these amines leads to substituted ammonium salts III in 90-94% yields.

As noted in our previous work [1], similar reactions with primary aromatic amines which are weaker amines do not proceed and the corresponding arylammonium salts are not obtained by this method.



I a,d R=C_4H_9; b,e R=$CH_2C_6H_5$; b, f R=$CH(CH_3)CH_2C_6H_5$; a-c R^1=OH; d-f R^1=Cl;
III-Va R=C_4H_9; b R=$CH_2C_6H_5$; c R=$CH(CH_3)CH_2C_6H_5$

Treatment of the substituted ammonium salts III by a mixture of the corresponding primary amine and phosphorus pentoxide for 12 h at 150-170°C for the aralkyl amines and 190-200°C for the aliphatic amines leads to 50-73% yields of N-substituted 2-amino-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridines (IV).

The closure of the pyrroline ring in IV with the formation of 1,6-disubstituted 4-methyl-5-cyano-7-azaindolines (I) is achieved by heating with $POCl_3$ in the presence of dimethylanaline. Heating IV with $POCl_3$ even with the addition of phosphorus pentoxide for 10 h and more does not give complete cyclization and more than 50% IV is recovered unchanged. The yield of azaindoline Ib, as noted previously [1], is 41% for IVb. Carrying out the reaction in a sealed glass ampule at up to 170-180°C for 5 h gives azaindoline compounds Ib (26% yield) and

*For Communication 65, see [1].

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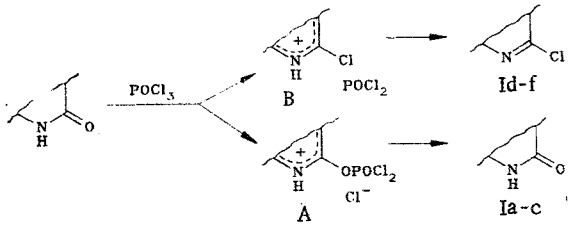
Ie (18% yield), as well as the hydrochloride salt of 2-benzylamino-3-(β-chloroethyl)-4-methyl-5-cyano-6-chloropyridine (Vb) (26% yield). Heating of hydrochloride salt Vb with water is accompanied by the loss of two HCl molecules and closure of the pyrroline ring with formation of chloroazaindoline Ie. A similar effect apparently occurs upon heating Vb and in the direct inlet system of a mass spectrometer. The spectrum of Vb shows only peaks characteristic for 7-azaindoline compounds Ie ($[M]^+$ = 283) and hydrogen chloride. The molecular ion peak corresponding to the base of Vb is lacking in the mass spectrum.

The reaction of hydroxyaminopyridine compounds IV with $POCl_3$ in the presence of catalytic amounts of dimethylaniline in all cases lead to both 6-hydroxy(Ia-c) and corresponding 6-chloro-7-azaindoline derivatives (Id-f). A series of ten experiments showed that a significant increase in the excess of $POCl_3$ (up to 50 moles per mole IV), reaction time and temperature up to 200°C (the reaction products are completely converted to a tar above this temperature), the ratios between the amounts of 6-hydroxy and 6-chloro derivatives of I are hardly altered. The same ratios are also obtained in the treatment of 6-hydroxy-7-azaindolines Ia-c with $POCl_3$. These findings indicate that the reaction of hydroxy derivatives I and IV with $POCl_3$ at the hydroxy group of the pyridine ring proceeds with the formation of intermediates A and B which are characteristic for this type of reaction [5]. The treatment of complex A with water gives hydroxy compounds Ia-c (in the oxo form) and the treatment of complex B with water gives chloro derivatives Id-f.



EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer spectrometer in vaseline oil. The PMR spectra were taken on a JNH-4H-100 spectrometer with TMS as the internal standard. The mass spectra were taken on an Varian MAT-112 spectrometer at 70 eV.*

Butylammonium Salt of 2,6-Dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine (IIIa). A mixture of 2.1 g (10 mmoles) ammonium salt II and 2.2 g (30 mmoles) butylamine was stirred for 4 h at 80-90°C. The cooled reaction mass was triturated with 50 ml ether. The precipitate was filtered off and washed with 20 ml acetone to yield 2.46 g (92%) butylammonium salt IIIa as colorless crystals, mp 214-215°C (from 2-propanol). This compound is soluble in water, DMF, and hot alcohols but insoluble in ether, benzene and acetone. IR spectrum: 3060, 3180, 3340 (NH, NH_2), 2170 (C≡N), 1600 cm^{-1} (CO). Mass-spectrum†: 194 $[M]^+$ (17), 176 $[M - H_2O]^+$ (21), 163 $[M - CH_2OH]^+$ (100), (41), 175 $[M - H_2O, -H]^+$ (25), 73 $[M_2]^+$ (10)‡, 30 $[M_2 - C_3H_7]$ (100). PMR spectrum (DMSO-D_6): 0.88 (t, 3H, $NH_2C_3H_6\mathbf{CH_3}$); 1.34 + 1.50 (two m, 4H, $NH_2CH_2\mathbf{C_2H_4}CH_3$); 2.80 (t, 2H, $\mathbf{NH_2}$–$\mathbf{CH_2}$–C_3H_7); 3.30 + 2.47 (two t, 2H + 2H, J = 8 Hz, $\mathbf{CH_2CH_2}OH$); 2.04 ppm (s, 3H, $\mathbf{CH_3}$). Found: C 58.6; H 8.0; N 16.1%. $C_{13}H_{21}N_3O_3$. Calculated: C 58.4; H 7.9; N 15.7%.

*The PMR spectra were taken by K. F. Turchin. The IR spectra were taken by Yu. I. Pomerantsev. The mass spectra were taken by O. S. Anisimova at the Physicochemical Methods Laboratory of the All-Union Pharmaceutical Chemistry Research Institute directed by Yu. N. Sheinker. The microanalysis was carried out by the group directed by R. A. Dubinskii. The authors express their sincere gratitude to these workers.

†The m/z values are given for the molecular peaks and some of the characteristic fragments. The intensities are given as % of the maximum peak.

‡The mass spectra of salts such as three are sums of the spectra of the corresponding base and acid. Upon temperature fractionation of the sample in the ion source, the spectrum of the corresponding amine $[M_2]^+$ is initially observed and upon further heating we find the spectrum of the corresponding dihydroxypyridine derivative ($[M]^+$ 194).

Phenylisopropylammonium Salt of 2,6-Dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine (IIIc). Analogously, 3 g (14.2 mmoles) ammonium salt II and 5.75 g (42.6 mmoles) phenylisopropylamine gave 4.2 g (90%) IIIc as colorless crystals, mp 213-214°C (from methanol). This compound is soluble in water, DMF and hot alcohols but insoluble in ether, benzene and acetone. IR spectrum: 3080, 3200 (NH, NH_2), 2190 (C≡N), 1635 cm^{-1} (CO). Mass spectrum: 194 $[M]^+$ (18), 176 $[M - H_2O]^+$ (48), 175 $[M - H_2O, -H]^+$ (29), 163 $[M - CH_2OH]^+$ (100), 135 $([M_2]^+)$(<4), 91 $[C_6H_5CH_2]^+$ (70), 44 $[CH(CH_3)NH_2]$ (100). PMR spectrum (D_2O): 1.28 d,[3H, $CH(CH_3)CH_2C_6H_5$], 2.38 + 3.53 (two t, 2H + 2H, CH_2CH_2OH, J = 8 Hz), 2.92 [d, 2H, $CH(CH_3)CH_2C_6H_5$], 3.53 [m, 1H, $CH(CH_3)CH_2C_6H_5$], 7.35 [m, 5H, $CH(CH_3)CH_2C_6H_5$], 2.04 (s, 3H, CH_3). Found: C 65.4; H 7.0; N 12.8%. $C_{18}H_{23}N_3O_3$. Calculated: C 65.6; H 7.0; N 12.8%.

2-Butylamino-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridine (IVa). A mixture of 6 g (22.5 mmoles) butylammonium salt IIIa, 5.0 g (67.5 mmoles) butylamine, and 3.2 g (22.5 mmoles) phosphorus pentoxide was maintained for 12 h at 190-200°C in a sealed steel vessel. The reaction mass was treated after cooling with 60 ml boiling water and cooled. The precipitate was filtered off and washed with 25 ml acetone to yield 3.04 g (54.3%) IVa as colorless crystals, mp 285-286°C (dec., from DMF). This compund is soluble in concentrated sulfuric and acetic acids, DMSO, and hot DMF but insoluble in ordinary organic solvents and in water. IR spectrum: 3080, 3020 (NH), 2190 (C≡N), 1645 cm^{-1} (CO). PMR spectrum (DMSO-d_6): 0.89 (t (3H, $C_3H_6CH_3$), 1.32 + 1.54 (two m, 2H + 2H, $CH_2CH_2CH_2CH_3$), 2.56 + 3.32 (two t, 2H + 2H, CH_2CH_2OH, J = 7 Hz), 2.88 (m, 2H, $NHCH_2C_3H_7$). Mass spectrum: 249 $[M]^+$ (18), 231 $[M - H_2O]^+$ (21), 206 $[M - C_3H_7]^+$ (50), 188 $[M - H_2O, -C_3H_7]^+$ (85), 177 $[M - NHC_4H_9]$ (100). Found: C 62.7; H 7.8; N 17.3%. $C_{13}H_{19}N_3O_2$. Calculated: C 62.7; H 7.6; N 16.9%.

2-(β-Phenylisopropylamino)-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridine (IVc). A mixture of 3.1 g (9.5 mmoles) phenylisopropylammonium salt IIIc, 1.35 g (9.5 mmoles) phosphorus pentoxide, and 3.85 g (28.5 mmoles) phenylisopropylamine was maintained for 12 h at 150-170°C. The reaction mass was treated with 20 ml boiling water and the precipitate was filtered off and recrystallized from DMSO to give 1.39 g (49%) IVc as colorless crystals, mp 292-293°C (dec.). IR spectrum: 3060, 3200 (NH), 2200 (C≡N), 1645 cm^{-1} (CO). Mass spectrum: 311 $[M]^+$ (3), 220 $[M - CH_2Ph]^+$ (73), 202 $[M - CH_2Ph - H_2O]^+$ (18), 177 $[M - NHCH(CH_3)CH_2Ph]^+$ (100), 91 $[CH_2Ph]^+$ (9.6). Found: C 69.4; H 7.0; N 13.6%. $C_{18}H_{21}N_3O_2$. Calculated: C 69.4; H 6.8; N 13.5%.

The synthesis of the benzylammonium salt of 2,6-dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine (IIIb) and 2-benzylamino-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine (IVb) was described in our previous work [1].

Reaction of 2-Butylamino-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridine (IVa) with $POCl_3$. A mixture of 1 g (4 mmoles) aminopyridine IVa, 3 ml (11.5 mmoles) $POCl_3$ and 0.5 ml dimethylaniline was heated in a sealed glass tube for 5 h at 170-180°C. The reaction mass was poured into 60 g ground ice and heated at reflux for 10 min. After cooling, the reaction mass was made basic by the addition of 50% aq. KOH. The precipitate was filtered off, washed with 30 ml benzene and recrystallized from methanol to give 0.45 g (48%) 1-butyl-4-methyl-5-cyano-6-hydroxy-7-azaindoline (Ia) as colorless crystals, mp 270-271°C (dec.). This compound is soluble in DMF, DMSO, and hot alcohols but is insoluble in benzene, acetone, and ether. IR spectrum: 2210 (C≡N), 1635 cm^{-1} (CO). PMR spectrum (DMSO-d_6): 0.91 (t, 3H, $C_3H_6CH_3$), 1.28 + 1.50 (two multiplets, 2H + 2H, $CH_2CH_2CH_2CH_3$), 2.05 (s, 3H, CH_3), 2.82 + 3.65 (two triplets, 2H + 2H, CH_2CH_2N, J = 8.5 Hz), 3.32 (t, 2H, $CH_2C_3H_7$), 11.7 ppm (t, 1H, NH). Mass spectrum: 231 $[M]^+$ (21), 188 $[M - C_3H_7]^+$ (100), 175 $[M - C_4H_9]^+$ (5), 174 $[M - C_4H_6]^+$ (4). Found: C 67.8; H 7.5; N 18.2%. Calculated for $C_{13}H_{17}N_3O$: C 67.5; H 7.4; N 18.2%.

The aqueous filtrate was extracted with three 50-ml portions of benzene. The combined benzene extracts and the wash benzene were dried over magnesium sulfate and evaporated in vacuum. The residue was recrystallized from hexane to give 0.3 g (30%) 1-butyl-4-methyl-5-cyano-6-chloro-7-azaindoline (Id) as white crystals, mp 82-83°C. This compound is soluble in benzene, chloroform and acetone but has low solubility in alcohols and water. IR spectrum: 2200 cm^{-1} (C≡N). PMR spectrum ($CDCl_3$): 0.96 (t, 3H, $C_3H_6CH_3$), 1.34 + 1.58 (two multiplets, 2H + 2H, $CH_2CH_2CH_2CH_3$), 2.28 (s, 3H, CH_3), 2.96 + 3.70 (two triplets, 2H + 2H, CH_2CH_2N, J = 7.5 Hz), 3.44 ppm (t, 2H, $CH_2C_3H_7$). Mass spectrum: 249* $[M]^+$ (15), 206 $[M - C_3H_7]^+$ (100), 193 $[M - C_4H_8]^+$ (7), 192 $[M - C_4H_9]^+$ (6). Found: C 62.4; H 6.4; N 16.9; Cl 14.3%. Calculated for $C_{13}H_{15}N_3Cl$: C 62.8; H 6.0; N 16.9; Cl 14.3%.

*The mass numbers of the ions containing the ^{35}Cl isotope are given for the chlorine-containing compounds.

Analogously, the reaction of 1 g (3.2 mmoles) 2-(β-phenylisopropylamino)-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridine (IVc) with 4 ml (15.6 mmoles) $POCl_3$ and 0.5 ml dimethylaniline gave 0.43 g (46%) 1-(β-phenylisopropyl)-4-methyl-5-cyano-6-hydroxy-7-azaindoline (Ic) and 0.26 g (26%) 1-(β-phenylisopropyl)-4-methyl-5-cyano-6-chloro-7-azaindoline (If). Oxoazaindoline Ic was obtained as colorless crystals, mp 237-238°C (dec., from methanol). This compound is soluble in DMSO, DMF, and hot methanol but insoluble in ether, benzene, acetone, and water. IR spectrum: 2200 (C≡N), 1610 cm^{-1} (CO). PMR spectrum (DMSO-d_6): 1.16 [d, 3H, $CH(CH_3)CH_2C_6H_5$], 2.72 + 3.68 (two triplets, 2H + 2H, CH_2CH_2N, J = 8.5 Hz), 2.70 [d, 2H, $CH(CH_3)CH_2C_6H_5$], 7.26 [m, 5H, $CH(CH_3)CH_2C_6H_5$], 4.50 [m, 1H, $CH(CH_3)CH_2C_6H_5$], 2.04 ppm (s, 3H, CH_3). Mass spectrum: 293 $[M]^+$ (9), 278 $[M - CH_3]^+$ (3), 202 $[M - CH_2Ph]^+$ (100), 91 $[CH_2Ph]^+$ (7). Found: C 73.7; H 6.6; N 14.2%. Calculated for $C_{18}H_{19}ON_3$: C 73.7; H 6.5; N 14.3%.

Chloroazaindoline If was separated from the benzene extract upon chromatography on a column with 1.5 cm diameter packed with a 30-cm layer of silica gel L100/160 using 4:5 ethyl acetate–benzene as the eluent as yellow crystals, mp 175-176°C (from hexane–benzene). IR spectrum: 2200 cm^{-1} (C≡N). Mass spectrum: 311 $[M]^+$ (42), 220 $[M - CH_2Ph]^+$ (100), 91 $[CH_2Ph]^+$ (8). Found: C 69.1; H 5.6; N 13.1; Cl 11.1%. $C_{18}H_{18}N_3Cl$. Calculated for $C_{18}H_{18}N_3Cl$: C 69.5; H 5.8; N 13.5; Cl 11.3%.

Reaction of 2-benzylamino-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridine (IVc) with $POCl_3$. a) A mixture of 3 g (10.5 mmoles) aminopyridine IVa, 15 ml (58.5 mmoles) $POCl_3$ and 1.5 ml dimethylaniline was heated in a sealed glass tube for 5 h at 170-180°C. The reaction mass was poured into 30 g ice and treated with saturated aq. KOH to pH 7-8. The resultant precipitate after drying (3.9 g) was heated at reflux in 150 ml hexane. The hot hexane solution was filtered. Cooling gave precipitation of 0.59 g (18%) 2-benzylamino-4-methyl-5-cyano-6-chloro-7-azaindoline (Ie) as greenish crystals, mp 129-130°C. This compound is soluble in benzene, acetone, and chloroform but has low solubility in hexane, alcohols, and water. IR spectrum: 2200 cm^{-1} (C≡N). PMR spectrum ($CDCl_3$): 2.26 (s, 3H, CH_3), 2.90 + 3.57 (two triplets, 2H + 2H, CH_2CH_2N, J = 9.5 Hz), 4.62 (s, 2H, CH_2Ph), 7.30 ppm (m, 5H, $CH_2C_6H_5$). Mass spectrum: 283 $[M]^+$ (18), 206 $[M - Ph]^+$ (7), 192 $[M - CH_2Ph]^+$ (5), 91 $[CH_2Ph]^+$ (100). Found: C 67.5; H 4.8; N 14.8; Cl 12.6%. Calculated for $C_{16}H_{14}N_3Cl$: C 67.8; H 4.9; N 14.8; Cl 12.4%.

The residue, which is insoluble in boiling hexane, was heated at reflux with 50 ml methanol and again filtered to yield 0.95 g (39%) 1-benzyl-4-methyl-5-cyano-6-hydroxy-7-azaindoline (Ib) which was identical in its mixed melting point and IR spectrum to an authentic sample [1].

The methanolic solution obtained after the separation of hydroxyazaindoline Ib was evaporated and the residue was washed with 25 ml hot acetone to give 0.88 g (26%) hydrochloride salt of 2-benzylamino-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-chloropyridine as colorless crystals, mp 224-225°C (from methanol). IR spectrum: 2210 cm^{-1} (C≡N). The mass spectrum corresponds to that of chloroazaindoline Ie and hydrogen chloride and lacks a molecular ion peak $[M]^{+\bullet}$ with m/z 357. Found: C 53.9; H 4.8; N 11.7; Cl 30.1; Cl^- 9.9%. Calculated for $C_{16}H_{15}N_3Cl_2 \cdot HCl$: C 53.9; H 4.5; N 11.8; Cl 29.9; Cl^- 10.0%.

Heating Vb with water leads to chloroazaindoline Ie which was identical in its mixed melting point and IR spectrum to an authentic sample.

b) A mixture of 5 g (17.5 mmoles) aminopyridine IVa, 15 ml (58.5 mmoles) $POCl_3$ and 2.5 ml dimethylaniline was heated in a sealed glass tube for 5 h at 170-180°C. The reaction mass was poured into 150 g ice, heated at reflux for 10 min and made basic with 10% aq. KOH. The resultant precipitate was filtered off, washed with 50 ml benzene and dried to give 1.53 g (33%) hydroxyazaindoline Ib which was identical in its mixed melting point and IR spectrum to an authentic sample [1]. The aqueous mother liquor was additionally extracted with five 10-ml portions of benzene. The combined benzene extracts and the wash benzene were dried over magnesium sulfate and evaporated. The residue was recrystallized from cyclohexane to give 1.61 g (32%) chloroazoindoline Ie which was identical in its mixed melting point and IR spectrum to an authentic sample.

In an analogous experiment, heating of a mixture of 1.4 g (5 mmoles) hydroxyazaindoline Ib with 4 ml (15.6 mmoles) $POCl_3$ and 0.7 ml dimethylaniline in a sealed glass tube for 5 h at 170-180°C gave 0.47 (34%) hydroxyazaindoline Ib and 0.50 g (36%) chloroazaindoline Ie.

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HYDROACRIDINES AND RELATED COMPOUNDS.

22.* SYNTHESIS OF COMPOUND WITH 2,6-EPIDIOXYPIPERIDINE STRUCTURE

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The addition of hydrogen peroxide to a series of 1,4-dihydropyridine derivatives proceeds with the formation of derivatives of 6,7-dioxa-8-azabicyclo[3.2.1]octane. Such compounds may be obtained by the reaction of alicyclic 1,5-diketones with amines and hydrogen peroxide.

The nucleophilic addition to protonated 1,4-dihydropyridines (DHP) has been reported by Kuthan et al. [2, 3] but the addition of bifunctional nucleophiles to these compounds has been described only for the reaction of hydrogen peroxide to two DHP derivatives [4]. In the present work, this reaction is examined in detail.

Compounds Ia-k which are derivatives of 1,2,3,4,5,6,7,8,9,10-decahydroacridine, 1,4,5,6,7,8-hexahydroquinoline and their analogs were used as the DHP. Compounds Ic,d,f,i-k, which are reported for the first time, were obtained by the reaction of the corresponding pyridinium salts IIa-f with benzylmagnesium chloride or phenylmagnesium bromide (salt IIe which has not been described previously was prepared by the oxidation of Id using CCl_4). The reaction of the pyridinium salts with Grignard reagents may occur at C-2 or C-4 of the pyridinium structure [2, 3]. In our cases, this reaction proceeds only at C-4. In particular, the reaction of perchlorate IIa with phenylmagnesium bromide gave the known compound Ia, while the reaction of 1,5-diketone III with aniline gave Ih. (Formula, top, following page.)

The IR spectra of the newly synthesized DHP has C=C group bands at 1635-1645 and 1675-1685 cm^{-1}. This is in accord with the reported data for Ia,b, e, g. The PMR spectra of the new DHP lack signals for vinyl protons. The signals for the benzyl group protons at C-9 are at 2.68 ppm for Ii, 3.28 for Ij, and 2.85 ppm (4H) for Ik. The signal for these protons in the spectrum of Ic gives a doublet at 3.80 ppm. These findings indicate the symmetrical nature of the hydroacridine structure related to these benzyl groups. The protons at C-4 of the DHP ring in the spectra of 4-phenylsubstituted DHP If and Ih gives singlets at about 3.5 ppm (1H).

Hydrogen peroxide adds to Ia-h in the presence of acetic acid. The reaction does not proceed in the absence of this acid. The addition of sodium acetate facilitates the reaction. The role of this salt may lie in the generation of the highly nucleophilic hydroperoxide anion. The products of the reaction are cyclic aminoperoxides IVa-h, which are derivatives of 4a,10a-epidioxyperhydroacridine, 2,8a-epidioxyperhydroquinoline and their analogs. The yields of aminoperoxides IV are mostly preparative and only IVd is formed in low yield. The products of the addition of H_2O_2 could not be isolated in the case of DHP Ii-k and complex mixtures are formed, possibly as a result is related to the lower stability of the perhydroacridine structure with a benzyl group at C-9; this structure has definite repulsion of the hydrogen atoms in the benzyl groups and at positions 1 and 8 of hydroacridine. The instability is greater when there is a second substituent at C-9 as in Ii-k. The cyanide anion in acetic acid could be added to Ii and Ik with the formation of the corresponding derivatives of 4a,10a-dicyanoperhydroacridine Va and Vb. Cyanide ion does not add to Ij.

*For Communication 21, see [1].

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