STRUCTURE AND AMBIPHILIC REACTIVITY OF INDOLIZINES.

2.* 8(6)-ACETYL- AND CYANOINDOLIZINES

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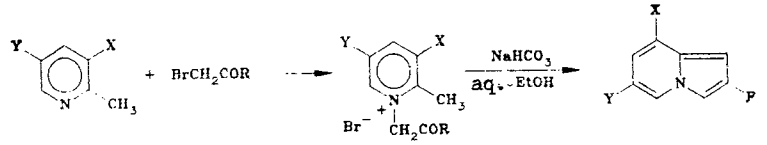
Quaternization of 2-methyl-3(5)-acetyl and cyanopyridines with α-bromoketones followed by cyclocondensation has given a number of 8(6)-acetyl- and cyanoindolizines.

The effects of substituents on the reactivity of indolizines have received little attention. This is particularly true of indolizines substituted in the pyridine ring, for the synthesis of which by the most widely-used Chichibabin reaction [2] difficultly-accessible substituted alkylpyridines are required. At the present time, the Chichibabin reaction has given 6- and 7-cyano-, 6-ethoxycarbonyl and 6-carbamoylindolizines [3], 7- and 8-ethoxycarbonyl [4, 5], and some 6- and 8-nitroindolizines [6], the latter having been subjected to isomerization recyclization to give 5- and 7-nitroindoles respectively [7]. In the synthesis of 8-cyano- [8] and 1,8-dicyanoindolizine [9] and 6-cyano-1-nitro-2-methylindolizine [10], other methods of construction of the indolizine ring have been employed. However, with the exception of the work of Loseva et al. [4, 11, 19] on 6-, 7-, and 8- ethoxycarbonylindolizines, the effects of substituents in different positions of the pyridine ring on the structure and reactivity of indolizines have not been examined. Likewise, no studies have been made on the possible isomerizational recyclization of indolizines with other electron-acceptor substituents (other than the NO_2 group) in positions 6 or 8. It is noteworthy that 6(8)-acylindolizines have not been described.

6- and 8-Acetyl and cyanoindolizines were obtained by the Chichibabin method from α-methyl- β(β')-acetyl and cyanopyridines and α-bromoketones.



Ia-c,g IIa,d-g IIIa-g

a–c R=CH_3, d–g R=C_6H_5; a, f X=CN, b, e, g X=H, c, d X=$COCH_3$; a, c, d, f Y=H, b, e Y=$COCH_3$, g Y=CN

Treatment of the salts (IIa, d-g), isolated in the pure state, with bases has given good yields of the indolizines (Tables 1 and 2). The bromoacetonylates (IIb, c), which could not be purified, were subjected to cyclocondensation without isolation. (The acetonylates of 3-nitro- [6], and of 3- and 5-ethoxy-2-picolines [24, 25], likewise could not be obtained pure, unlike the corresponding bromophenacylates). The compounds were purified by column chromatography. The indolizines (IIIa-g) were orange or yellow in color.

In the IR spectra of indolizines (IIIb-e), the absorption for C=O stretching (1672-1675) corresponded to that in α, β-unsaturated (∿1675) rather than aromatic ketones (∿1690 cm^{-1}), perhaps in consequence of considerable alternation in bond lengths in the pyridine moiety of indolizine (see, e.g., [12]). It is also noteworthy that in 1- and 3-acetylindolizines, in which greater conjugation of the acetyl group with the π-excessive pyrrole ring must occur, the values of the stretching vibrations of the C=O group are smaller, at 1595-1625 cm^{-1} [5].

In the UV spectra (Table 3) of 6- and 8-indolizines, three groups of absorption bands may be discerned (characteristic of indolizines in general), namely at short (221-285),

*For Part 1, see [1].

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TABLE 1. Properties of Salts (II)

Compound	Reaction time, h	Mp, deg C	Found, %		Empirical formula	Calc., %		Yield, %
			C	H		C	H	
IIa	10	200—201	46,3	4,3	$C_{10}H_{11}BrN_2O$	47,1	4,3	40
IId	20	154—156	57,5	5,3	$C_{16}H_{16}BrNO_2$	57,5	4,8	75
IIe	15	199—201	57,3	5,2	$C_{16}H_{16}BrNO_2$	57,5	4,8	72
IIf	20	183—185	56,8	4,1	$C_{15}H_{13}BrN_2O$	56,8	4,1	41
IIg	25	220—222	56,5	4,3	$C_{15}H_{13}BrN_2O$	56,8	4,1	40

TABLE 2. Properties of Indolizines (III)

Compound	Mp, deg C	M^+	$\nu_{C=O}$, cm^{-1}	$\nu_{C\equiv N}$, cm^{-1}	Yield, %
IIIa	35—37	156		2213	100
IIIb	32—33	173	1672		16*
IIIc	15—16	173	1675		98
IIId	163—165	235	1675		57
IIIe	188—190	235	1675		52
IIIf	163—165	218		2235	65
IIIg	194—196	218		2226	70

*Yield based on starting acetylpyridine (Ib).

medium (300-353), and long wavelengths (λ_{max} > 373 nm). As compared with the unsubstituted 2-methyl- and 2-phenylindolizines, all the bands undergo a bathochromic shift. This shift is greatest for the long-wavelength band, and it increases in the order CN < $COCH_3$ < NO_2 both for the 6- and the 8-substituted indolizines (6-substituted 2-phenylindolizines are exceptiona this band appearing as a shoulder in the region 340-450 nm). In the case of the 8-isomers, the long-wavelength region of the spectrum (the first and second absorption bands) undergoes a bathochromic shift as compared with those of the 6-isomers, whereas the short wavelength band is usually shifted towards shorter wavelengths. In the case of 2-methyl-8-substituted indolizines (IIIa, c), the UV spectra are characterized by the appearance of the short-wavelength band appearing as a doublet, which does not occur in the 6-isomers, nor in the 2-phenyl derivatives. A similar double maximum has been observed previously in the methyl derivatives of 8-, but not 6-nitroindolizines [1].

Some of the features of the UV spectra of substituted indolizines may be rationalized in terms of quantum chemical calculations of the indolizine molecule. Using the MO LCAO method, the following values of the π-charges in particular have been obtained for the ground and firs excited singlet states of indolizine: for $C_{(6)}$ 1.00 and 1.08, and for $C_{(8)}$ 0.79 and 1.13 respectively [13]. It has been shown [14] that the long-wavelength band is almost exclusively due (to the extent of 89%) to the HOMO—LUMO transition (of the $\pi \rightarrow \pi^*$-type). It is further suggested that electron-acceptor substituents ($COCH_3$, CN, NO_2) in positions 6 and 8 of indolizine influence only the energies of the molecular orbitals, and do not introduce their own absorption bands (in other words, they are auxochromes rather than chromophores). Since the π-charges at $C_{(6)}$ and $C_{(8)}$ are increased on passing from the ground to the first excited state but to a greater extent for $C_{(8)}$ than for $C_{(6)}$, it may be concluded (cf. [6]) that electron-acceptor substituents in positions 6 and 8 of the indolizine nucleus should deepen the color as compared with pyridine ring-unsubstituted 2-methyl- or 2-phenylindolizines, the 8-isomers being more deeply colored than the 6-isomers, and the λ_{max} values should increase in the sequence $COCH_3$ < CN < NO_2, in accordance with the electronegativity sequence as measured, for example, by their σ constants [15].

These conclusions have in general been confirmed experimentally. In the cyano- and acetylindolizines the long-wavelength bands are close, although the bathochromic shift is somewhat greater in the latter. It is notable that this behavior is not in conflict with the UV spectra of 2-methyl-6- and -8-ethoxycarbonylindolizines (cf. Fig. 1 in [11]).

The PMR spectra of the indolizines prepared here (Table 4) confirm their structures. The 8-acetylindolizine (IIIc) shows a low-field shift of the signal for 1-H under the influenc of the magnetically anisotropic substituent in the peri-position. A similar perishift is

TABLE 3. Groups of Bands in the UV Spectra of Substituted Indolizines (in Ethanol).

Compound*	λ_{max}, nm	lg ε
IIIh[23]**	254,5, 325, 350, 366, 384.5	4,62; 3,27; 3,45; 3,43; 3,15
IIIf	260, 336, **shoulder** 370—420	4,61; 3,95; 3,3—3,0
IIId	256, 350, **shoulder** 415—460	4,60; 2,81; 3,3—3,1
IIIi	248, 378, **shoulder** 450—500	4,62; 3,85; 3,4
IIIg	271, 300—320, **shoulder** 340—435	4,81; 3,99—3,90; 3,78—3,70
IIIe	285, 308—322, **shoulder** 360—435	4,72; 4,18—4,04; 3,20—3,03
IIIj	242, 313, **shoulder** 350—450	4,35; 4,26; 3,90—3,40
IIIk	240, 287, 291, 299, 348	4,50; 3,71; 3,73; 3,75; 3,63
IIIa	248, 265, 315, 321, 394	4,62; 4,66; 3,62; 3,72; 3,28
IIIb	254, 262, 334, 403	4,49; 3,48; 2,81; 2,51
IIIl	258, 265, 353, 480	4,17; 4,18; 3,55; 3,33
IIIe	221, 274, **shoulder** 310, 322, 373	4,41; 4,85; 4,15; 3,97; 2,92
IIIm	226, 303, 436	4,53; 4,51; 3,36

*(IIIh-k), R = C_6H_5; (IIIk-m), R = CH_3; (IIIi, l), X = NO_2, Y = H; (IIIj, m), X = H, Y = NO_2; (IIIh, k), X = Y = H.
**In cyclohexane.

TABLE 4. PMR Spectral Data for Indolizines (III) and Their Cations

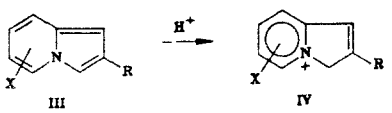
Compound	Solvent	Chemical shifts, δ, ppm						
		1-H	2-R	3-H	5-H	6-H	7-H	8-H
IIIa	CCl_4	6,48	2,30	7,17	7,95	6,36	6,97	—
	CF_3COOH	7,03	2,36	5,50	9,05	7,73	8,60	—
IIIb	CCl_4	6,09	2,30	6,90	8,34	2,16*	6,90	
	CF_3COOH	7,66	3,41	6,29	10,23	3,14*	9,53	8,72
IIIc	CCl_4	7,05	2,31	7,05	7,85	6,28	7,22	2,31*
	CF_3COOH	7,60	2,83	5,30	9,00	7,80	9,00	2,43*
IIId	CF_3COOH	8,36	7,8—8,1	6,06	9,16	7,8—8,1	9,09	2,98*
IIIe	CF_3COOH	7,6—7,8		6,15	9,70	2,95*	9,04	8,20
IIIf	CF_3COOH	7,6—8,0		6,18	9,25	7,85	8,78	—
IIIg	CF_3COOH	7,5—7,9		6,13	9,48	—	8,65	8,19

*For the acetyl CH_3 group.

seen in 8-ethoxycarbonyl-[5] and 8-nitroindolizines [1, 6], but not in 8-cyano-derivatives. The spectra of 8-cyano [8] and 2-methyl-8-cyanoindolizine are similar*.

We have attempted to carry out the base-catalyzed rearrangement of acetylindolizines to the indoles, by analogy with nitroindolizines [7], but it was found that under isomerizational recyclization conditions the indolizines (IIIc-e) were recovered unchanged. Nor were anionic σ-complexes, such as those observed previously with nitroindolizines [7], formed. It is likely that the addition of the HO^- ion followed by recyclization requires the presence in the 6- or 8-position of the indolizine of a nitro-group, or at least a substituent whose electronegativit is no smaller than this.

The protonation of the acetyl- and cyanoindolizines (III) in CF_3CO_2H has been examined by PMR. The appearance in the spectrum of a singlet of double intensity at 5.3-6.3 ppm (Table 4) unambiguously demonstrates [18] that protonation takes place in the 3-position:



III IV

*Note that Jutz et al., [8] inaccurately assigned the signals for 1-H and 3-H, attributing the quadruplet at τ 2.56 ppm (δ 7.44 ppm) to the 1-H proton, probably on the grounds of the smaller value of ^3J (2.8 Hz) [for the quadruplet at τ 3.28 ppm (δ 6.72 ppm) ^3J = 4.0 Hz]. However, in indolizines $^3J_{12} > {}^3J_{23}$ (cf. e.g., [17]), and therefore the signal for the 1-H proton is seen at 6.72, and that for 3-H at 7.44 ppm.

In the case of the 8-substituted cations (IV), a low-field shift of the 1-H proton under the influence of the peri-oriented CH_3CO group is also seen, but this is not the case with the CN group. Protonation at $C_{(3)}$ has been observed previously in carbamoyl- [3], ethoxycarbonyl- [19], and nitroindolizines [1], and hence the introduction of electron-acceptor groups into the 6- or 8-position does not affect the mode of protonation of indolizines.

EXPERIMENTAL

PMR spectra were obtained on Tesla BS-467 (60 MHz) and XL-100 instruments, in CCl_4 or CF_3CO_2H, internal standard TMS. UV spectra were recorded on a Specord M-40 in 96% ethanol, and IR spectra on a UR-20 in Vaseline oil. Mass spectra were obtained on an MX-1303 (E = 70 eV) with direct sample introduction. The purities of the compounds obtained were checked by chromatography on Silufol plates.

The starting acetyl- and cyanopyridines (Ia-c, g) were obtained as described in [20-22].

1-Acetonyl-2-methyl-3-cyanopyridinium Bromide (IIa). A mixture of 0.8 g (6.8 mmole) of 2-methyl-3-cyanopyridine (Ia) and bromoacetone 1.7 g (1.1 ml, 13.0 mmole) was boiled in 10 ml of ethyl methyl ketone for 10 h, until no more solid separated. The solution was cooled, and the rose-colored crystals which separated were filtered off, washed with ethyl methyl ketone and ether, and dried to give 0.7 g of the salt (IIa). Similarly obtained were the salts (IId-g) (Table 1). The β-acetylpyridinium salts were difficult to purify, and it was difficult to obtain a satisfactorily pure sample of the salt (IIc) (mp 145-147°C, from methanol; 42%). It was not possible to isolate the bromo-acetonylate of (Ib).

2-Methyl-8-cyanoindolizine (IIIa). A mixture of 0.52 g (2.0 mmole) of the salt (IIa) and a saturated solution of sodium bicarbonate in 75 ml of 20% ethanol was heated for 30 min. After cooling, the mixture was extracted with ether, the extract evaporated, the residue chromatographed on a plate (silica gel L40/100, chloroform), the fraction with R_f 0.7 being collected. There was obtained 0.32 g (2.0 mmole, 100%) of low-melting yellow crystals of (IIIa). Found: C 77.0; H 5.7; H 17.9%. $C_{10}H_8N_2$. Calculated: C 76.9; H 5.1; N 17.9%.

The indolizines (IIIc-g) were obtained in a similar way (Table 2). In the preparation of (IIIb), the mixture obtained by reacting the pyridine (Ib) with bromoacetone was evaporated under reduced pressure and worked up as for (IIa). Compounds (IIId-f) crystallized from ethyl methyl ketone, and (IIIa-c, g) were purified by plate chromatography (silica gel L40/100, chloroform).

Reaction of 2-Methyl-8-acetylindolizine with Alkali. A solution of 0.145 g (0.84 mmole) of the indolizine (IIIc) in 20 ml of 50% ethanol and 2 g (36 mmole) of KOH was boiled for 10 h. After cooling, the mixture was neutralized with HCl to pH 7, and extracted with chloroform. The extract was evaporated and subjected to column chromatography (SiO_2, chloroform) to give 0.069 g (48%) of the starting indolizine (IIIc), R_f 0.51.

On heating with alkali under the same conditions, the indolizines (IIId, e) were recovered in yields of 80 and 74% respectively.

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PORPHYRINS.

21.* SYNTHESIS AND REACTIVITIES OF 13,17-DISUBSTITUTED DERIVATIVES OF 13,17-DESETHYLETIOPORPHYRIN III

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A method was developed for the preparation, from hemin, of a porphyrin with hydroxypropyl substituents in the 13 and 17 positions of the macroring and a number of its derivatives.

In the present research we solved the problem of the preparation, from hemin (I), of a porphyrin (IIa) with hydroxypropyl substituents in the 13 and 17 positions of the macroring and a number of its derivatives. In the synthesis of the substituted porphyrins special attention was directed to obtaining substances that contain tertiary amino groups, since it is known [2-4] that porphyrins that contain amino groups display diverse biological activity.

The preparation of porphyrin IIa from mesoporphyrin IX (IIIa) by reduction of its dimethyl ester (IIIb) with lithium aluminum hydride has been described in the literature [5]; the preparation of an aminoethylporphyrin from porphyrin IIIa by Curtius cleavage of the corresponding azide IIIc has also been described [6]. Porphyrin IIIa can be obtained in turn by treatment of hemin (I) with concentrated HI [7] or, more efficiently, by hydrogenation of it in formic acid on a palladium catalyst [8].

The process that we developed to obtain porphyrin IIa directly from hemin (I) [9] proceeds in up to 90% overall yield without isolation of intermediates; this made it possible to use this porphyrin for further chemical modification.

*See [1] for Communication 20.

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