PYRROLOINDOLES.

10.* SYNTHESIS OF SOME SUBSTITUTED PYRROLOINDOLES AND TETRAHYDROPYRROLOCARBAZOLES

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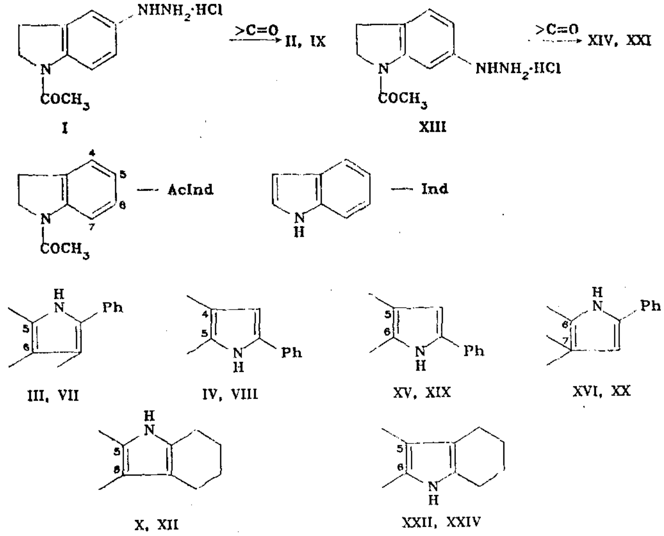
The formation of linear four-ring pyrrolocarbazole systems is observed in the indolization of cyclohexanone 1-acetyl-5-indolinyl- and 1-acetyl-6-indolinylhydrazones, whereas the formation of mixtures of linear and angular pyrroloindoles is observed in the cyclization of the corresponding acetophenone hydrazones.

In order to study the effect of substituents on the formation of pyrroloindole structures we carried out indolization of hydrazones based on acetophenone and cyclohexanone via the Fischer reaction.

Hydrazines I and XIII were obtained by diazotization [3] and subsequent reduction [4] of 1-acetyl-5-aminoindoline and 1-acetyl-6-aminoindoline. The 1-acetyl-5-indolinyl- and 1-acetyl-6-indolinylhydrazones of acetophenone (II, XIV) and cyclohexanone (IX, XXI) (Table 1) were synthesized by condensation of I and XIII with acetophenone and cyclohexanone.

The best results in the cyclization of the hydrazones were obtained when ethyl polyphosphate (EPP) was used as the cyclizing agent.

The cyclization of the hydrazones (II and XIV) based on acetophenone leads to the formation of mixtures of pyrroloindolines with linear (III, XV) and angular (IV, XVI) structures, whereas the formation of only pyrroloindoles with a linear structure (X, XXII) is observed when a cyclohexyl substituent is present in the hydrazone; this can be explained by steric factors.



III, IV, XV, XVI, X, XXII—AcInd; VII, VIII, XIX, XX, XII, XXIV—Ind

$$\begin{tikzcd}
\mathrm{I} \arrow[r] \arrow[d] & \mathrm{IX} \arrow[r] & \mathrm{X} \arrow[r] & \mathrm{XII} & \mathrm{XIII} \arrow[r] \arrow[d] & \mathrm{XXI} \arrow[r] & \mathrm{XXII} \arrow[r] & \mathrm{XXIV} \\
\mathrm{II} \arrow[r] & \mathrm{III+IV} \arrow[r] & \mathrm{VII+VIII} & & \mathrm{XIV} \arrow[r] & \mathrm{XV+XVI} \arrow[r] & \mathrm{XIX+XX} &
\end{tikzcd}$$

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*See [1, 2] for communications 8 and 9.

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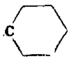
TABLE 1. PMR Spectra of Hydrazones II, IX, XIV, and XXI in $CDCl_3$ (ppm)

Compound	1-H	2-H	3-H	4-H	5-H	6-H	7-H
II	—	4,00 t	3,07 t	—*	—	—*	—*
IX	—	4,10 t	3,17 t	7,52 s	—	7,60 d	8,20 d
XIV	—	4,01 t	3,09 t	7,29 dd	7,74 dd	—	7,87 dd
XXI	—	4,00 t	3,07 t	6,94 d	6,94 d	—	7,71 dd

TABLE 1 (continued)

Compound	NH	$COCH_3$	CH_3		C_6H_5	J, Hz
II	9,0 s	2,20 s	2,10 s	—	6,8—7,8	$J_{23}=8,0$
IX	8,2 s	2,25 s	—	1,81—1,88	—	$J_{67}=8,0$; $J_{23}=8,6$
XIV	7,0 s	2,20 s	2,20 s	—	7,0—7,3	$J_{45}=8,3$; $J_{47}=0,5$; $J_{57}=1,6$; $J_{23}=8,2$
XXI	6,6 s	2,18 s	—	1,64—1,30	—	$J_{47}=0,5$; $J_{57}=1,5$; $J_{23}=8,5$

*The signals of the protons in the 4, 6, and 7 positions are located in the region of the signals of the protons of the phenyl group.

TABLE 2. PMR Spectra of Pyrroloindoles III, IV, VII, VIII, XV, and XVI in d_6-DMSO and XIX and XX in d_6-Acetone (ppm)

Compound	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H
III	11,2 s	—	6,76 d	8,17 d	—	4,06 t	3,12 t	7,70 d
IV	6,61 d	—	11,1 s	7,10 d	7,72 d	—	4,09 t	3,00 t
VII	11,05 s	—	6,90 d	~7,3	10,6 s	~7,3	6,40 d	7,50 d
VIII	6,98 d	—	10,8 s	7,79 d	7,00 d	11,2 s	7,28 dd	6,55 dd
XV	11,1 s	—	7,23 dd	6,66 d	3,13 t	4,07 t	—	8,10 dd
XVI	—	4,10 m	3,09 m	6,89 d	7,08 d	11,1 s	—	7,23 d
XIX	10,1 s	—	6,85 dd	7,29 d	6,40 m	7,18 dd	9,7 s	7,64 m
XX	10,4 s	7,1 dd	6,49 dd	7,24*d	7,37*d	10,6 s	—	7,41 d

TABLE 2 (continued)

Compound	$COCH_3$	C_6H_5	J, Hz
III	2,15 s	7,1—7,8	$J_{13}=2,0$; $J_{48}=0,9$; $J_{67}=8,0$
IV	2,09 s	7,5—7,8	$J_{13}=2,0$; $J_{45}=8,2$; $J_{67}=8,0$
VII	—	7,1—7,8	$J_{13}=2,0$; $J_{48}=1,2$; $J_{67}=3,0$
VIII	—	7,2—7,8	$J_{13}=1,8$; $J_{45}=8,2$; $J_{67}=3,0$; $J_{68}=2,4$; $J_{78}=4,0$
XV	2,17 s	7,2—8,1	$J_{13}=1,8$; $J_{38}\simeq J_{48}=0,9$; $J_{56}=8,1$
XVI	2,22 s	6,8—7,8	$J_{45}=8,3$; $J_{68}=2,2$; $J_{56}=8,2$
XIX	—	7,3—7,9	$J_{13}=1,9$; $J_{38}\simeq J_{48}\simeq J_{58}=0,4$; $J_{56}=3,2$; $J_{57}=2,1$; $J_{67}=2,7$
XX	—	7,1—7,4	$J_{12}=2,5$; $J_{13}=2,1$; $J_{23}=3,0$; $J_{45}=74$; $J_{68}=1,9$

*Or vice versa.

To remove the acetyl protective group in reaction products III, IX, X, XV, XVI, and XXII we carried out their hydrolysis in the presence of hydrochloric acid [5]; V, VI, XI, XVII, XVIII, and XXIII are formed in high yields. Dehydrogenation of the latter over 10% Pd/C gave pyrroloindoles VII, VIII, XII, XIX, XX, and XXIV.

The signals of the 4-H and 5-H protons in the PMR spectra of IV, VIII, XX, and XVI (Table 2) are AB systems with characteristic spin-spin coupling constants (SSCC) J_o = 8.2-8.3 Hz, which indicates the angular structure of these compounds.

Characteristic SSCC J_p = 0.4-1.3 Hz are observed between the 4-H and 8-H and 4-H and 10-H protons in the PMR spectra of III, VII, X, XII, XV, XIX, XXII, and XXIV (Tables 2 and 3); this indicates that these compounds have a linear structure.

TABLE 3. PMR Spectra of Pyrrolocarbazoles X, XII, and XXII in d_6-DMSO and XXIV in d_6-Acetone (ppm)

Compound	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H	10-H	$COCH_3$	J, Hz
X	—	4,03t	3,11 t	6,99 d	10,1 s	1,8—3,2				7,90 d	2,13 s	$J_{410}=1,3$; $J_{23}=7,6$
XII	10,2s	7,26 dd	6,47 m	7,48 d	10,6 s	1,3—2,8				7,37 dd	—	$J_{12}=2,8$; $J_{13}=2,1$; $J_{23}=3,1$; $J_{310}=0,7$; $J_{410}=0,6$
XXII	—	4,04t	3,10 t	7,04 d	1,8—3,2				10,1s	7,93d	2,13 s	$J_{410}=0,9$; $J_{23}=8,0$
XXIV	9,5s	7,12 dd	6,40 d	7,22 m	1,9—2,7				9,0s	7,43d	—	$J_{12}=2,3$; $J_{13}=2,1$; $J_{23}=3,2$; $J_{14}\simeq J_{94}\simeq \simeq J_{410}=0,9$

TABLE 4. Constants and Yields of the Compounds Obtained

Compound	mp, °C	R_f*	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Found				Empirical formula	Calc.				Yield, %
					C, %	H, %	N, %	M^+		C, %	H, %	N, %	M	
II	245—246	0,22 (a)	3295, 1650, 1620	206,8 (4,50), 272,5 (4,05), 320 (4,24), 347,5 (4,31)	73,8	6,6	13,9		$C_{18}H_{19}N_3O$	73,7	6,5	14,3		87
III	266—267	0,41 (b)	3180, 1620	205 (4,53), 235,5 (4,63), 333 (4,62)	78,4	6,0	9,9	276	$C_{18}H_{16}N_2O$	78,3	5,8	10,1	276	30
IV	309—310	0,42 (b)	3240, 1630	206,9 (4,19), 270 (4,63), 317,5 (4,43)	78,5	5,7	9,7	276	$C_{18}H_{16}N_2O$	78,3	5,8	10,1	276	15
VII	320—321	0,5 (c)	3430, 3410	206 (4,35), 228 (4,37), 259,7 (4,23), 325 (4,43)	82,5	5,7	11,7	232	$C_{10}H_{12}N_2$	82,7	5,2	12,1	232	42
VIII	140—141	0,46 (c)			82,2	5,4	12,2		$C_6H_{12}N_2$	82,7	5,2	12,1		25
IX	168—169	0,35 (a)	3000—3300, 1650, 1610	207 (4,26), 241 (4,06), 327,8 (4,15)	70,2	7,2	15,0		$C_{16}H_{21}N_3O$	70,8	7,7	15,4		94
X	263—264	0,43 (b)	3200, 1640	206 (4,25), 254,5 (4,85), 310 (3,93), 316 (3,91), 322 (3,93)	75,2	7,1	11,3	254	$C_{16}H_{18}N_2O$	75,6	7,1	11,0	254	75
XII	176—177	0,18 (b)	3260, 3380	224,7 (3,93), 254 (4,02), 312 (3,83)	79,7	6,3	12,9	210	$C_{14}H_{14}N_2$	80,0	6,7	13,3	210	59
XIV	208—209	0,33 (a)	3260, 1650, 1610	205,2 (4,47), 246 (4,43), 318 (4,37)										88
XV	318—319	0,3 (b)	3270, 1640	206 (4,44), 237 (4,49), 259,6 (4,37), 339 (4,60)	78,5	6,5	10,1	276	$C_{18}H_{16}N_2O$	78,3	5,8	10,1	276	31
XVI	190—191	0,51 (b)	3160, 1650	206 (4,37), 254,6 (4,52), 322 (4,41)	78,4	6,5	10,0	276	$C_{18}H_{16}N_2O$	78,3	5,8	10,1	276	23
XIX	319—320	0,37 (d)	3430, 3400	213 (4,50), 292 (4,29), 284 (4,26), 336 (4,48)	82,3	5,4	11,6	232	$C_{16}H_{12}N_2$	82,7	5,2	12,1	232	20
XX	235—236	0,55 (c)	3430, 3400	205,5 (4,45), 228,3 (4,50), 330 (4,42)	82,5	5,4	11,7	232	$C_{16}H_{12}N_2$	82,7	5,2	12,1	232	41
XXI	157—158	0,27 (a)	3270, 1645, 1612	204,8 (4,24), 242 (4,31), 260 (4,32), 282 (4,27)	70,6	7,8	15,1		$C_{16}H_{21}N_3O$	70,8	7,7	15,4		88
XXII	325—326	0,49 (b)	3230, 3200	224,7 (3,93), 254 (4,02), 312 (3,83)	76,1	7,1	11,1	254	$C_{16}H_{18}N_2O$	75,6	7,1	11,0	254	78
XXIV	195—196	0,24 (c)	3400, 3380	206 (4,38), 235 (4,61), 252 (4,41), 274 (4,05), 307,7 (4,12)	79,7	6,7	13,4	210	$C_{14}H_{14}N_2$	80,0	6,7	13,3	210	34

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*The R_f values were determined in the following systems: benzene—acetone (6:1) (a), benzene—acetone (8:3) (b), petroleum ether—ether (1:1) (c), and benzene—acetone (3:5) (d).

An increase in the intensities of the absorption bands and an 18-20 nm bathochromic shift to the long-wave region are observed in the UV spectra of linear isomers III and XV as compared with the maxima of the long-wave absorption of angular isomers IV and XVI; this is evidently due to the greater conjugation in the linear molecules as compared with the angular molecules.

EXPERIMENTAL

The purity of the compounds was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates. Preparative column chromatography was carried out on silica gel (100-250 μ). The R_f values were determined on Silufol. The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were recorded with a Specord spectrophotometer. The molecular masses were determined mass spectrally with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 50 eV. The PMR spectra were recorded with a Varian CFT-20 spectrometer (80 MHz) with tetramethylsilane as the internal standard. The constants and yields of all of the compounds obtained are presented in Table 4.

Acetophenone 1-Acetyl-5-indolinylhydrazone (II). A solution of 10 g (44 mmole) of hydrochloride I in 1 liter of water was heated to 70°C, after which the pH of the solution was brought up to 3-4 with sodium acetate, and the solution was filtered rapidly. A solution of 6 ml (50 mmole) of acetophenone in 10 ml of ethanol was added to the cooled solution, and the mixture was allowed to stand overnight. The resulting precipitate was removed by filtration, washed with water until the wash water was neutral, and dried. Recrystallization from ethanol gave 11.2 g of hydrazone II. Hydrazones IX, XIV, and XXI were similarly obtained.

5-Acetyl-6,7-dihydro-2-phenyl-1H,5H-pyrrolo[2,3-f]indole (III) and 6-Acetyl-7,8-dihydro-2-phenyl-3H,6H-pyrrolo[3,2-e]indole (IV). A 2-g sample of II was suspended in 20 g of EPP, and the resulting mixture was stirred at 80°C for 1 h. It was then cooled and poured over ice, and the precipitate was removed by filtration, washed with water until the wash water was neutral, and dried to give 1 g (53%) of a mixture of pyrroloindole III and pyrroloindole IV. The mixture was separated with a column in benzene—acetone (5:1). The yields were calculated from the amount of the mixture used.

Mixtures of XV and XVI and X and XXII were similarly obtained. The compounds were isolated with a column with elution by chloroform (X), benzene—ether (4:1) (XV and XVI), and benzene—ether (4:1) (XXII) and were recrystallized from DMF.

2-Phenyl-1H,5H-pyrrolo[2,3-f]indole (VII) and 2-Phenyl-3H,6H-pyrrolo[3,2-e]indole (VIII). A mixture of 1 g of III and IV with 18 ml of concentrated HCl was refluxed for 1 h, after which it was filtered, and excess concentrated KOH was added slowly with cooling. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.4 g (48%) of a mixture of 6,7-dihydro-2-phenyl-1H,5H-pyrrolo[2,3-f]indole (V) and 7,8-dihydro-2-phenyl-3H,6H-pyrrolo[3,2-e]indole (VI). A 0.3-g sample of this mixture and 0.1 g of Pd/C in 20 ml of isopropyl alcohol was refluxed with stirring for 7 h, after which the hot mixture was filtered, and the solution was evaporated to give 0.12 g (41%) of a mixture of VII and VIII, which were separated with a column by elution with petroleum ether—ether (1:1). Compounds XII, XIX, XX, and XXIV were similarly obtained from the following intermediates: XI, mp 214-217°C, 77% yield; XVII, mp 265-267°C, 83% yield; XVIII, mp 190-191°C, 80% yield; XXIII, mp 240-250°C, 80% yield. Compounds XII (elution with benzene) and XXIV [elution with petroleum ether—ether (2:1)] were purified with a column.

LITERATURE CITED

1. D. O. Kadzhrishvili, Sh. A. Samsoniya, E. N. Gordeev, L. N. Kurkovskaya, V. E. Zhigachev, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 8, 1086 (1983).
2. Sh. A. Samsoniya, S. V. Dolidze, N. L. Targamadze, and N. N. Suvorov, Zh. Org. Khim., 19, 441 (1983).
3. R. Ikan and E. Rapoport, Tetrahedron, 23, 3823 (1967).
4. J. V. Braun, Chem. Ber., 49, 1266 (1916).
5. G. I. Zhungietu, V. A. Budylin, and A. N. Kost, The Preparative Chemistry of Indole [in Russian], Shtiintsa, Kishinev (1975), p. 159.