3-PYRIDINIUMINDOLYL-2-THIOLATES — NEW TYPE OF FUNCTIONALIZED INDOLES

Jozef GONDA and Pavol KRISTIAN

Depar tment of Organic Chemistry,
P. J. Šafárik University, 041 67 Košice

Received September 28th, 1987
Accepted January 12th, 1988

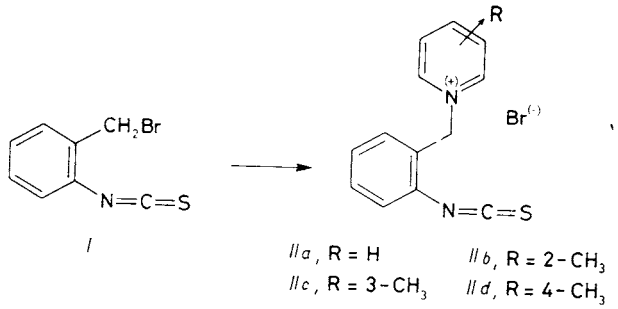
2-Bromomethylphenyl isothiocyanate (*I*) reacts with pyridines to give 2-isothiocyanatobenzylpyridinium bromides *II*. Deprotonation of these compounds with sodium ethoxide in ethanol or sodium hydride in dimethyl sulfoxide afforded novel type of functionalized indoles, 3-pyridiniumindolyl-2-thiolates. Reaction of *II* with KOH or KCN gave products of addition to the NCS group *VII* and *VIII*, respectively. Structure of the obtained compounds was proven by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra and was confirmed by X-ray difraction analysis of 3-pyridiniumindolyl-2-thiolate.

Because of their manifold biological activities and utilization in organic synthesis[1-3], indole derivatives are the subject of constant interest of organic chemists. This is illustrated by a great number of synthetic methods leading to this attractive heterocycle[4-12] that have been developed during the last several years. Save several cases[13-15], all these methods start from substituted benzenes and differ in the type and sequence of reactions used in the construction of the pyrrole ring[2]. One of the most often used methods starting from *ortho*-disubstituted benzenes are the modern modifications of Madelung synthesis[16-19] based on the formation of the C(2)—C(3) indole bond. Besides the syntheses of the indole system itself (most of which are analogous to classical methods), great attention is paid to suitable functionalizations, decisive for biological activity or applicability to a particular synthetic scheme[20,21].

In our previous paper[22] we described the synthesis and some reactions of 3-triphenylphosphoniumindolyl-2-thiolates, obtained by treatment of 2-isothiocyanatobenzyltriphenylphosphonium bromides with bases. The observation[23] that 2-bromomethylphenyl isothiocyanate (*I*) reacted with pyridine to give exclusively 2-isothiocyanatobenzylpyridinium bromide (*IIa*), prompted us to investigate the possible preparation of compounds of this type and their utilization in the synthesis of indole derivatives.

We have found that 2-bromomethylphenyl isothiocyanate (*I*) reacts analogously with methylpyridines to give 2-isothiocyanatobenzylpyridinium bromides *II* in good yields (Table I, Scheme 1). The reaction can be carried out by simple mixing the starting compounds in a solvent of low polarity, preferably in ether. The structure

of the synthesized 2-isothiocyanatobenzylpyridinium bromides *II* has been unequivocally proven by spectral methods (Table I). The products are readily soluble in water without decomposition.



I

IIa, R = H *IIb*, R = 2-CH_3
IIc, R = 3-CH_3 *IId*, R = 4-CH_3

SCHEME 1

The nucleophilic reactions of compounds *II* are similar to those of their triphenylphosphonium analogues[22]. The pyridine ring with deactivated positions α and γ increases the number of possible sites of nucleophilic attack in these isothiocyanates. Compounds *II* react with less basic amines such as anilines to afford thioureas which were previously used in the synthesis of 4*H*-benzo[*d*]-[1,3]thiazines[23].

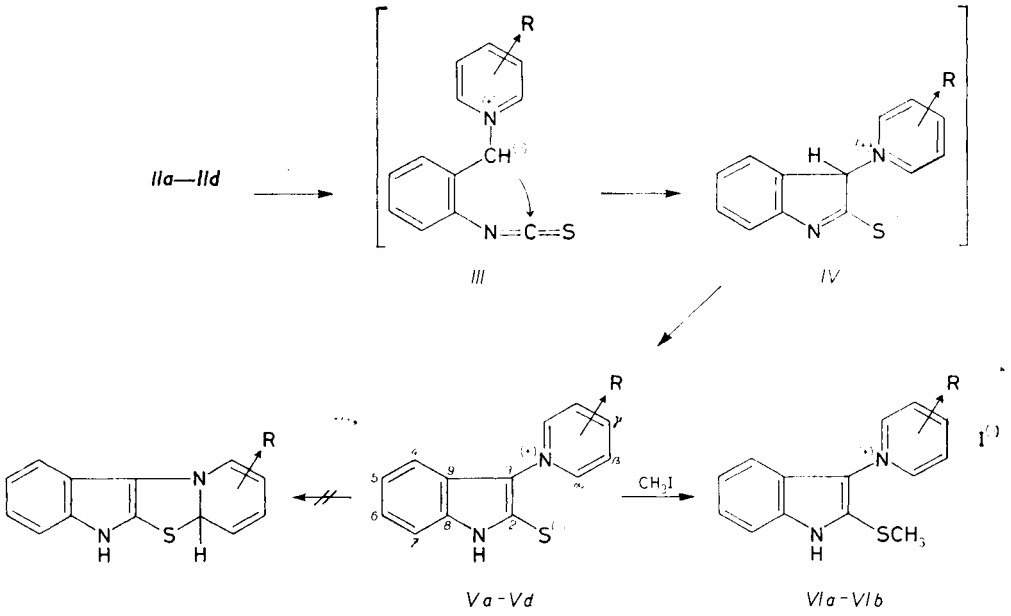
TABLE I

2-Isothiocyanatobenzylpyridinium bromides *IIb*–*d*

Product R	Formula (mol. wt.)	Yield, % (m.p., °C)	$\tilde{\nu}$(N=C=S)[a] cm^{-1}	Calculated/found		
				% C	% H	% N
IIb[b]	$C_{14}H_{13}BrN_2S$	45	2 081	52·35	4·07	8·72
2-CH_3	(321·2)	(113)		52·31	4·15	8·65
IIc[c]	$C_{14}H_{13}BrN_2S$	92	2 095	52·35	4·07	8·72
3-CH_3	(321·2)	(163)		52·30	4·02	8·83
IId[d]	$C_{14}H_{13}BrN_2S$	66	2 092	52·35	4·07	8·72
4-CH_3	(321·2)	(184)		52·34	4·02	8·75

[a] IR spectra measured in $CHCl_3$. [b] ^{1}H NMR ($CDCl_3$): 2·89 s, 3 H(CH_3); 6·21 s, 2 H(CH_2); 7·57–7·83 m, 4 H (benzene); 9·35 d, 1 H (H^{α}-pyridine); 9·21–8·44 m, 3 H (2 H^{β} and H^{γ} pyridine). [c] ^{1}H NMR ($CDCl_3$): 2·75 s, 3 H (CH_3); 6·26 s, 2 H (CH_2); 7·65–7·78 m, 4 H (benzene); 9·31 s, 1 H (H^{α}-pyridine); 9·26 d, 1 H (H^{α}-pyridine); 8·75 d, 1 H (H^{γ}-pyridine); 8·37 m, 1 H (H^{β}-pyridine). [d] ^{1}H NMR ($CDCl_3$): 2·85 s, 3 H (CH_3); 6·25 s, 2 H (CH_2); 7·58–7·81 m, 4 H (benzene); 8·25 d, 2 H (H^{β}-pyridine); 9·21 d, 2 H (H^{α}-pyridine).

However, thanks to the strong electron-acceptor effect of the pyridinium groups, the CH_2 group in the mentioned isothiocyanates behaves as a CH-acid, capable of forming the corresponding carbanion in reactions with strong bases such as alkali metal alkoxides (Method *A*) or sodium hydride in dimethyl sulfoxide (Method *B*, Table II). Intramolecular addition of the formed carbanion *III* to the NCS group, followed by aromatization of the intermediate *IV*, affords 3-pyridiniumindolyl-2--thiolates *V* as the final products (Scheme 2, Table II). Compounds *V* form deep--violet crystals soluble only in polar organic solvents. They react quantitatively with methyl iodide to give 2-methylthioindolyl-3-pyridinium iodides *VI*.



SCHEME 2

Infrared spectra of compounds *V* exhibit characteristic bands at 3 200 cm^{-1} and 1 445 cm^{-1} due to stretching vibrations of the NH and NHCS grouping, respectively. Proton NMR spectra of these derivatives show that during the transformations the pyridine ring remained intact, and that no products of intramolecular addition of the thiolate anion into α-position of pyridine took place (Scheme 2).

A comparison of chemical shifts in the ^{13}C NMR spectra of compounds *V* (Table III) with those of analogous phosphorus derivatives[22] indicates the preservation of a strong polarization of the system N—C=C—$S^{(-)}$, and thus their betaine character. This explains the considerable difference in chemical shifts of the C-2

and C-3 signals (e.g. for *Va*: δ(C-2) = 153, δ(C-3) = 115) which, however, does not achieve such extreme values as reported for the analogous phosphorus derivatives[22]. With S-methyl derivatives *VIa,b* this difference is even smaller (Table III).

The betaine structure of compounds *V* has been unequivocally confirmed by X-ray analysis[24] of *Va* (Fig. 1), according to which the C(2)—C(3) bond length (139·2 pm) is

TABLE II

3-Pyridiniumindolyl-2-thiolates *Va—d* and 2-methylthioindolyl-3-pyridinium iodides *VIa,b*

Product R	Formula (mol. wt.)	Yield, % (method) (m.p., °C)	$\tilde{\nu}$(NH)[a], cm^{-1} $\tilde{\nu}$(CS)[a], cm^{-1}	Calculated/found		
				% C	% H	% N
Va[b]	$C_{13}H_{10}N_2S$	81(*A*), 46(*B*)	3 200	68·99	4·45	12·38
H	(226·3)	(207—209[c])	1 445	68·90	4·39	12·42
Vb	$C_{14}H_{12}N_2S$	36(*A*), 21(*B*)	3 203	69·96	5·03	11·65
2-CH_3	(240·3)	(131—132[c])	1 440	69·95	5·12	11·58
Vc	$C_{14}H_{12}N_2S$	85(*A*), 73(*B*)	3 200	69·96	5·03	11·65
3-CH_3	(240·3)	(221—223[c])	1 443	69·95	5·10	11·57
Vd	$C_{14}H_{12}N_2S$	61(*A*), 41(*B*)	3 202	69·96	5·03	11·65
4-CH_3	(240·3)	(163—165[c])	1 440	59·89	5·00	11·68
VIa	$C_{14}H_{13}N_2IS$	100	3 180	45·66	3·55	7·60
H	(368·2)	(263—264)	—	45·61	3·51	7·68
VIb	$C_{15}H_{15}N_2IS$	100	3 185	47·13	3·95	7·32
3-CH_3	(382·5)	(291—293)	—	47·10	3·87	7·35

[a] IR spectra measured in $CHCl_3$. [b] Mass spectrum, *m/z* (%): 226 (M^+, 8), 193 (M^+ — 33, 100). 165 (38), 132 (49), 105 (66), 104 (61), 79 (98), 52 (91). [c] Decomposition.

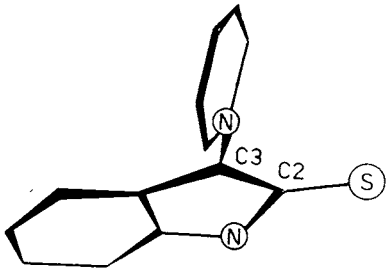


FIG. 1

X-ray structure of *Va*: $C_{13}H_{10}N_2S$ M_r = = 226·29, monoclinic, $P2_1/c$, a = 1 003·7(4), b = 807·6(3), c = 1 412·4(4) pm, β = = 104·59(3)r, V = 1 107·9 . 10^3 pm, Z = 4, D_m = 1·34(1), D_x = 1·36 g cm^3, λMoK_α) = = 71·069 pm, μ_{Mo} = 2·6 cm^{-1}, $F(000)$ = = 472, T = 295 K, R = 0·039 for 2 057 observed reflexions. Sulfur is hydrogen bonded to the neighbouring symmetrically related molecule. The pyridine ring is rotated out of the indole plane by 57°

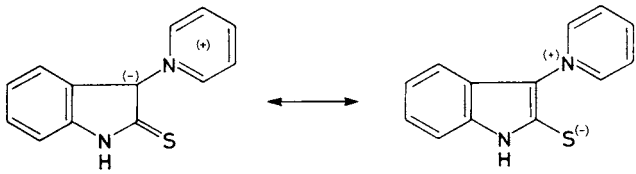
TABLE III

Spectral data of 3-pyridiniumindolyl-2-thiolates *Va—d* and 2-methylthioindolyl-3-pyridinium iodides *VIa,b*

Product R	^{13}C NMR (δ, $(CD_3)_4SO$)					^{1}H NMR (δ, $CDCl_3$: $(CD_3)_2SO$ = 5 : 1)			
	C-2	C-3	C-9	C-8	CH_3	H-benzene(m)	H-pyridine	CH_3(s)	NH(s)
Va[a] H	153·1	115·2	121·9	133·3	—	6·91—7·42	α 9·64 (d) β, γ 7·89—8·13 (m)	—	10·79
Vb[b] 2-CH_3						7·05—7·53	α 9·51 (d) β, γ 8·21 (m)	2·78	11·00
Vc[c] 3-CH_3	153·6	115·0	122·3	133·2	17·7	7·00—7·52	α_1 9·55 (s) α_2 9·51 (d) β, γ 8·15 (m)	2·71	11·21
Vd[b] 4-CH_3						7·00—7·51	α 9·50 (d) β 8·07 (d)	2·75	11·12
VI[d,e] *a* H	134·5	120·9	121·1	127·4	18·3	7·33—7·80	α 9·50 (d) β 8·55 (m) γ 9·08 (m)	2·76	—[g]
VIb[d,f] 3-CH_3	134·0	121·1	121·9	127·8	17·6 18·1	7·35—7·82	α_1 9·48 (s) α_2 9·41 (d) β 8·5 (m) γ 8·82 (d)	2·71 2·78	—[g]

[a] Other data: 108·7, 110·7, 119·2, 119·3 (C-4, C-5, C-6, C-7); 141·1 (C-α); 126·7 (C-β); 139·4 (C-γ). [b] Decomposition in $(CD_3)_2SO$ solution. [c] Other data: 108·7 (C-4), 119·2 (C-6 and C-7), 143·2 (C-α_1), 141·5 (C-α_2), 126·1 (C-β_1), 135·7 (C-β_2), 139·1 (C-γ). [d] ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$. [e] Other data: 111·7, 115·7, 121·4, 123·8 (C-4, C-5, C-6, C-7); 146·3 (C-α), 218·3 (C-β), 146·1 (C-γ). [f] Other data: 111·6, 115·4, 121·4, 123·7 (C-4, C-5, C-6, C-7); 145·8 (C-α_1), 143·7 (C-α_2), 129·3 (C-β_1), 137·9 (C-β_2), 142·8 (C-γ). [g] Signals of NH protons not observed.

typical for an aromatic double bond, whereas the S—C(2) bond length (171·9 pm) is characteristic of a single bond C—S. Consequently, of the two mesomeric structures, derivatives *V* prefer the betaine one (Scheme 3).



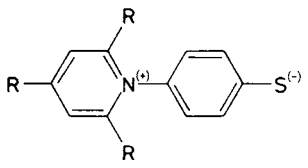
ylide betaine

SCHEME 3

Ultraviolet spectra of compounds *V* display a characteristic absorption band of low intensity ($\varepsilon \approx 320\ l\ mol^{-1}\ cm^{-1}$) in the visible region which is shifted toward shorter wavelengths with increasing solvent polarity. This hypsochromic shift (growing transition energy $E_T \approx 1/\lambda_{max}$), amounting to 110 nm for *Va* (Table IV) indicates an $n \rightarrow \pi^*$ transition. We have not found this solvatochromic effect for analogous phosphorus derivatives[22]. An even more pronounced hypsochromic shift has been observed with betaines of the type *A* ($\lambda_{max} = 350$ nm), structurally close to the discussed derivatives[25-29].

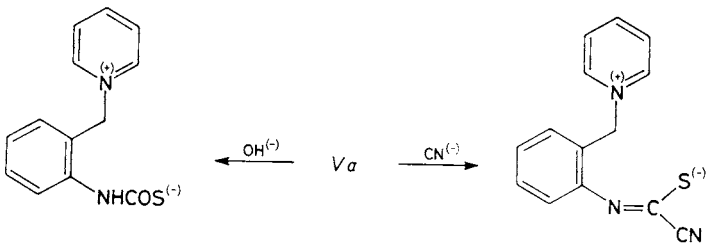
TABLE IV
Values of ν_{max} for compound *Va*

Solvent	λ_{max}, nm	E_T, kJ mol^{-1} (25°C)
Water	451	265·3
Methanol	498	240·1
Ethanol	506	236·4
1-Propanol	518	231·0
Nitromethane	530	225·5
Acetonitrile	532	224·7
N,N-Dimethylformamide	540	221·3
Acetone	543	220·1
Pyridine	550	217·2
Chloroform	553	216·3
Dioxane	558	214·2
Piperidine	561	212·9



A

Surprisingly, reaction of 2-isothiocyanatobenzylpyridinium bromide (*IIa*) with sodium hydroxide or potassium cyanide in aqueous methanol afforded products of addition of these nucleophiles to the NCS group (Scheme 4). The formation of the betaines *VII* and *VIII* proves that the electron deficit on the NCS carbon atom is greater than in the positions α and γ of the pyridine nucleus in isothiocyanates *II*.



VII *Va* *VIII*

SCHEME 4

EXPERIMENTAL

IR spectra of the synthesized compounds were measured on an IR-75 (Zeiss, Jena) double-beam spectrometer in chloroform or KBr pellets in the region 800–4 000 cm^{-1}. ^1H and ^{13}C NMR spectra were taken on a Tesla BS 497 (80 MHz) and a Tesla BS 567 (25·12 MHz) instrument in $CDCl_3$ and $(CD_3)_2SO$ or their mixtures, with tetramethylsilane as internal standard. Signals in the ^{13}C NMR spectra were assigned by the selective proton decoupling technique. Mass spectra were determined on an MS 902 S (AEI, Manchester) spectrometer (70 eV, direct inlet).

2-Bromomethylphenyl isothiocyanate (*I*) was prepared according to ref.[30], 2-isothiocyanatobenzylpyridinium bromide according to ref.[23]. Pyridine, 2-methyl-, 3-methyl-, and 4-methylpyridine were dried over potassium hydroxide and distilled prior to use.

2-Isothiocyanatobenzylpyridinium Bromides *IIb–d*

The corresponding methylpyridine (0·01 mol) was added to 2-bromomethylphenyl isothiocyanate (*I*; 0·01 mol) in anhydrous ether (50 ml), the reaction mixture was stirred and set aside for 48 h. The separated quaternary salt was filtered, washed with ether and crystallized from chloroform–ether. The compound *IId* was purified by precipitation with light petroleum from chloroform solution. Properties of the obtained compounds are given in Table I.

3-Pyridiniumindolyl-2-thiolates *Va—d*

A) A solution of sodium ethoxide (prepared from 0·01 mol of sodium and 30 ml of ethanol) was added at −30°C to a stirred solution of isothiocyanate *IIa—d* in anhydrous ethanol (25 ml). After stirring at −30°C for 0·5 h, the separated solid product was collected, washed with a small amount of cold water and crystallized from ethanol or 2-propanol. For properties of the products see Table II.

B) Sodium hydride (0·01 mol) was dissolved in dry dimethyl sulfoxide at 40—50°C under nitrogen with intermittent shaking. The solution was added at room temperature to a solution of *IIa—d* (0·01 mol) in dimethyl sulfoxide (30 ml) during 10 min. The product was filtered and worked up as described under *A*).

2-Methylthioindolyl-3-pyridinium Iodides *VIa, c*

Methyl iodide (0·015 mol) was added to a suspension of betaine *Va* or *Vc* (0·01 mol) in ethanol (40 ml) and the mixture was stirred until the solid dissolved. The yellow solution was warmed to 40—50°C and peroxide-free ether (30 ml) was added. After cooling, the crystalline product was collected and dried. For properties of the products see Table II.

N-(2-(1-Pyridiniummethyl)phenyl) Thiocarbamate (*VII*)

Potassium hydroxide (0·01 mol) in water (20 ml) was added to the isothiocyanate *IIa* (0·01 mol) in methanol (30 ml). After standing overnight, the crystalline product was collected and dried, m.p. 166—168°C (decomp.); yield 91%. For $C_{13}H_{12}N_2OS$ (244·31) calculated: 63·91% C, 4·95% H, 11·47% N; found: 63·85% C, 4·91% H, 11·55% N. IR spectrum (KBr) cm^{-1}: 3 378 (NH), 1 643 (CO), 1 441 (NHCS). ^1H NMR (CD_3COOD): 5·76 s, 2 H (CH_2); 6·75—7·28 m, 4 H (benzene protons); 8·02 m, 2 H (H^{β}-pyridine); 8·48 m, 1 H (H^{γ}-pyridine); 8·81 d, 2 H (H^{α}-pyridine).

N-(2-(1-Pyridiniummethyl)phenyl) Cyanothioformimidate (*VIII*)

Potassium cyanide (0·01 mol) in water (40 ml) was added to a solution of *IIa* (0·01 mol) in methanol (40 ml). After standing for 16 h, the yellow crystals were collected on filter, washed with water and dried; m.p. 135—136°C (decomp.); yield 86%. For $C_{34}H_{11}N_3S$ (253·3) calculated: 66·37% C, 4·37% H, 16·59% N; found: 66·42% C, 4·42% H, 16·63% N. IR spectrum (KBr) cm^{-1}: 2 237 (CN). ^1H NMR (CD_3COOD): 5·87 s, 2 H (CH_2); 7·23—7·58 m, 4 H (benzene); 8·06 m, 2 H (H^{β}-pyridine); 8·51 m, 1 H (H^{γ}-pyridine); 8·80 d, 2 H (H^{α}-pyridine).

The authors are indebted to Dr K. Huml and Dr J. Hašek, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague, for the X-ray structural analysis and to Dr J. Leško, Laboratory of Mass Spectrometry, Slovak Technical University, Bratislava, for mass spectral measurements.

REFERENCES

1. Herbert R. B.: *Indoles, Part Four* (J. E. Saxton, Ed.), Vol. 25, Chapter 1. Wiley-Interscience, New York 1983.
2. Brown R. T., Joule J. A., Sames P. S.: *Comprehensive Organic Chemistry* (D. R. Barton and W. D. Ollis, Eds), Vol. 4, p. 411. Pergamon Press, Oxford 1979.
3. Robinson B.: *The Fischer Indole Synthesis.* Wiley-Interscience, New York 1982.

4. Smith III A. B., Visnik M.: Tetrahedron Lett. *26*, 3757 (1985).
5. Kozikovsky A. P., Cheng X.-M.: Tetrahedron Lett. *26*, 4047 (1985).
6. Taylor E. C., Katz A. H., Salgado-Zamora: Tetrahedron Lett. *26*, 5963 (1985).
7. Hewson A. T., March L. A., Nowell I. W., Richardson S. K.: Chem. Commun. *1985*, 618.
8. Martin P.: Helv. Chim. Acta *67*, 1647 (1984).
9. Blechert S.: Tetrahedron Lett. *25*, 1547 (1984).
10. Vedachalam M., Mohan M., Srinivasen P. C.: Tetrahedron Lett. *24*, 3531 (1983).
11. Ito Y., Kobayashi K., Seko N., Saegusa T.: Bull. Chem. Soc. Jpn. *57*, 73 (1984).
12. Wender P. A., White A. W.: Tetrahedron *22*, 3767 (1983).
13. Hayakawa K., Yasukouchi T., Kanematsu K.: Tetrahedron Let.. *27*, 1837 (1986).
14. Hayakawa K., Yodo M., Ohsuki S., Kanematsu K.: J. Am. Chem. Soc. *106*, 6735 (1984).
15. Hayakawa K., Yamaguchi Y., Kanematsu K.: Tetrahedron Lett. *26*, 2689 (1985).
16. Verboom W., Berga H. J., Trompenaars W. P., Reinhoudt D. N.: Tetrahedron Lett. *26*, 685 (1985).
17. Bergman J., Sand P., Tilstam U.: Tetrahedron Lett. *24*, 3665 (1983).
18. Bergman J., Sand P., Tilstam U.: Heterocycles *21*, 523 (1984).
19. Schulenberg J. W.: J. Am. Chem. Soc. *90*, 7008 (1968).
20. Sundberg R. J.: *The Chemistry of Indoles.* Academic Press, New York 1970.
21. Springer J. P., Clardy J.: Tetrahedron Lett. *28*, 231 (1980).
22. Gonda J., Kristián P., Imrich J.: Collect. Czech. Chem. Commun. *52*, 2508 (1987).
23. Gonda J., Kristián P.: Collect. Czech. Chem. Commun. *51*, 2810 (1986).
24. Hašek J., Huml K., Kutschabsky L.: Acta Crystallogr., in press.
25. Dimroth K., Reichardt C., Siepmann T., Bohlmann F.: Liebigs Ann. Chem. *661*, 1 (1963).
26. Reichardt C.: Angew. Chem. *77*, 30 (1965).
27. Reichardt C.: Angew. Chem., Int. Ed. *4*, 29 (1965).
28. Dimroth K., Reichardt C., Siepmann T., Bohlmann F.: Z. Anal. Chem. *215*, 344 (1966).
29. Cram D. J., Rickborn B., Kingsbury C. A., Haberfield P.: J. Am. Chem. Soc. *83*, 3678 (1961).
30. Gonda J., Kristián P.: Collect. Czech. Chem. Commun. *51*, 2802 (1986).

Translated by M. Tichý.