Chemistry of Heterocyclic Compounds, Vol. 38, No. 10, 2002

ALKYLATION OF 6-(3-INDOLYL)-INDOLO[2,3-*b*]CARBAZOLE

L. N. Yudina, E. I. Lazhko, A. M. Korolev, and M. N. Preobrazhenskaya

The methylation and allylation of 6-(3-indolyl)indolo[2,3-b]carbazole were studied, and its trimethyl and mono-, di-, and triallyl derivatives were obtained.

Keywords: 6-(3-indolyl)indolo[2,3-*b*]carbazole, alkylation.

Indolocarbazoles have attracted great attention in recent years since compounds with important biological characteristics have been found among them. Thus, the indolo[2,3-*a*]carbazole nucleus forms the basis of the structure of a group of highly active antibiotics and alkaloids (rebeccamycin, staurosporine, and their synthetic analogs) [1, 2], while indolo[3,2-*b*]carbazole and its 6-formyl derivative are natural ligands of the Ah receptor of aromatic hydrocarbons [3-5]. Whereas the biological characteristics of various indolocarbazoles have been studied for a long time their chemical characteristics remain little studied; the least studied is indolo[2,3-*b*]carbazole [6, 7].

Earlier we showed that uroroseine – a salt of 3-[(3-indolyl)methylene]indolenine – dissociates in methanol or acetic acid with the formation of a mixture in which 6-(3-indolyl)indolo[2,3-*b*]carbazole (**1**) predominates [8, 9]. In the present work the methylation and allylation of the latter were studied.

During the action of dimethyl sulfate or methyl iodide on compound **1** in the presence of sodium hydride the 5,7,1'-N,N,N-trimethyl derivative **2a** was obtained with a yield of 95%. It is not possible to isolate the dimethyl derivative. During the allylation under the same conditions successive substitution of protons occurs at the nitrogen atoms and primarily at the nitrogen atom of the most accessible indole substituent at position 6 with the formation of the product **3**. Then the protons at the nitrogen in the indolocarbazole system are substituted successively, leading to 5-allyl-6-(1'-allyl-3-indolyl)indolo[2,3-*b*]carbazole (**4**) and 5,7-diallyl-6-(1'-allyl-3-indolyl)indolo[2,3-*b*]carbazole (**2b**). It should be noted that the reaction practically stops at the monoallyl derivative **3**, and only with the addition of a large excess of sodium hydride does it take place at the sterically hindered nitrogen atoms $N_{(5)}$ and $N_{(7)}$ of the indolocarbazole ring. The mono-, di-, and triallyl derivatives **3**, **4**, and **2b** were isolated from the reaction mixture by preparative TLC, and their structures were confirmed by data from the ^{1}H NMR and mass spectra (Scheme 1).

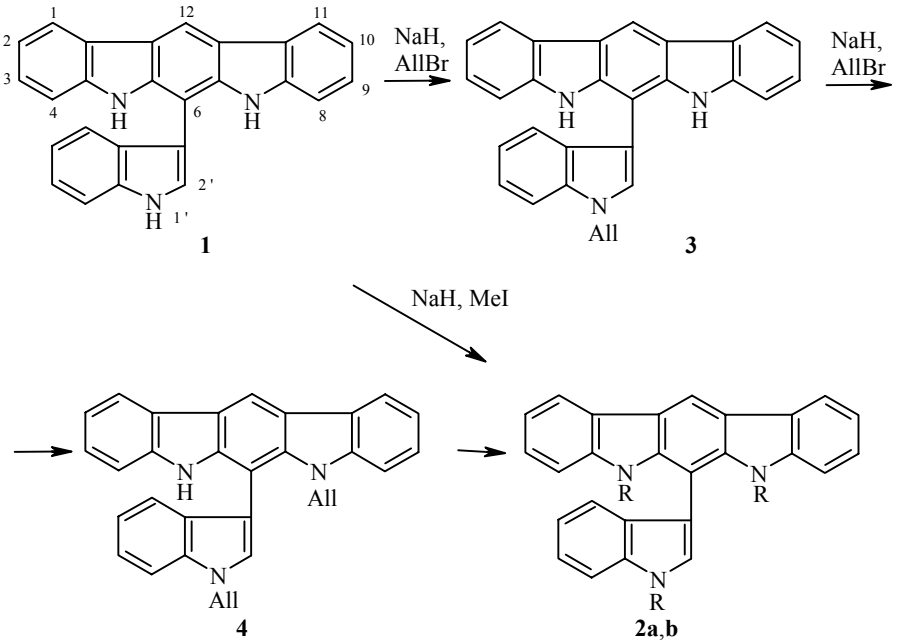
When the indolocarbazole **1** was kept with sodium hydride without addition of the alkylating agent it underwent transformations that apparently affected the skeleton of the molecule. Thus, control of the course of the reaction by TLC or HPLC showed that the initial indolocarbazole **1** is transformed into several new compounds; subsequent methylation of the reaction mixture leads to the formation of a complex set of substances, among which 5,7-dimethylindolo[2,3-*b*]carbazole (**5**) was isolated with a yield of 36%. It was identified by data from the ^{1}H and ^{13}C NMR spectra and also by their comparison with data from the spectra of

---

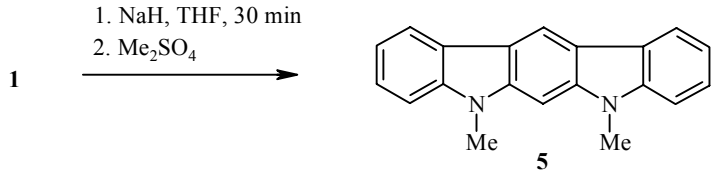
Scientific-Research Institute of New Antibiotics, Russian Academy of Medical Sciences, Moscow 119867, Russia; e-mail: lcta@space.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1364-1368, October, 2002. Original article submitted January 18, 2000. Revision submitted October 3, 2000.

 0009-3122/02/3810-1200$27.00

Scheme 1



related compounds [9]. Since the molecule of compound **5** has a plane of symmetry, the signals of the protons and ^{13}C nuclei at positions 1-4 and also the 5-Me group coincide with the corresponding signals for positions 7-11. On the other hand the signals of the 6-CH and 12-CH groups differ greatly, and the chemical shifts of 6-^{1}H and ^{13}C are in the very downfield region. The presence of unsubstituted 1-methylindole in the reaction mixture and the absence of compound **2a** were also demonstrated by chromatographic methods.



The structure of the alkylation products **2a**,**b**, **3**, **4** was confirmed by comparison of their ^{1}H NMR spectra with the spectrum of the initial indolocarbazole **1** (Table 1). The molecules of **1**, **2a**,**b**, and **3** have planes of symmetry, and the signals of the protons at positions 1-4 and 8-11 respectively therefore coincide. In the spectra of the trialkyl derivatives **2a**,**b** there are no signals characteristic of NH groups, while the ratio of the integral intensities of the signals of the allyl substituents that differ from each other amounts to 1:2. The product of 1'-monoalkylation **3** gives a singlet for the protons of the two NH groups and signals for the protons of one allyl group, indicating substitution of the 6-indole substituent. In the case of the unsymmetrical diallylation product **4** the signals of the protons at positions 1-4 and 8-11 respectively do not coincide, and equally intense signals for two allyl substituents are observed. It is interesting to note that the signals of the allyl group attached to the indolocarbazole fragment have increased multiplicity and lie in the upfield region compared with the signals of the allyl group in the 6-indole substituent. In all the investigated compounds the assignment of the signals for the protons of the indolocarbazole system was made in the following way: The position of the signals of 1- and 11-H was determined by means of an NOEDIF experiment with saturation of the downfield singlet

TABLE 1. The ^{1}H NMR Spectra of Compounds **1-4**

Com-pound*	Chemical shifts, δ, ppm (SSCC, *J*, Hz)												
	1-H, 11-H, d	2-H, 10-H, t	3-H, 9-H, t	4-H, 8-H, d	12-H (1H, s)	2'-H (1H, s)	4'-H (1H, d)	5'-H (1H, t)	6'-H (1H, t)	7'-H (1H, d)	5-H/R	7-H/R	1'-H/R
1	8.17 (2H)	7.13 (2H)	7.26 (2H)	7.40 (2H)	8.79	7.76	7.23	7.02	7.21	7.59	10.42 (2H, s)		11.57 (1H, s)
2a	8.24 (2H)	7.20 (2H)	7.36 (2H)	7.36 (2H)	8.96	7.59	7.17	7.05	7.26	7.63	3.17 (3H, s)	3.17 (3H, s)	3.99 (3H, s)
2b	8.29 (2H)	7.22 (2H)	7.34 (2H)	7.29 (2H)	8,99	7.50	7.11	7.02	7.23	7.61	5.45 (2H, m, 2"-H), 4.81 (2H, d, J_{cis} = 10.0, 3"-H a), 4.56 (2H, d, J_{trans} = 16.8, 3"-H b), 4.42 (2H, dd, J_{gem} = 5.6, $J_{1a",2"}$ = 14.8, 1"-H a), 4.15 (2H, dd, J_{gem} = 5.6, $J_{1b",2"}$ = 15.0, 1"-H b)		6.08 (1H, m, 2"-H), 5.24 (1H, d, J_{cis} = 10.4, 3"-H a), 5.21 (1H, d, J_{trans} = 17.3, 3"-H b), 4.96 (2H, d, J_{gem} = 5.1, 1"-H)
3	8.18 (2H)	7.14 (2H)	7.27 (2H)	7.41 (2H)	8.80	7.79	7.24	7.04	7.26	7.63	10.47 (2H, s)		6.19 (1H, m, 2"-H), 5.39 (1H, dd, J_{trans} = 17.1, J_{gem} = 1.50, 3"-H a), 5.28 (1H, dd, J_{cis} = 10.1, J_{gem} = 1.5, 3"-H b), 5.03 (2H, d, J_{gem} = 6.6, 1"-H)
4	8.24 (1H), 8.18 (1H)	7.23 (1H), 7.16 (1H)	7.25 (1H), 7.28 (2H)	7.35 (1H), 7.38 (2H)	8.90	7.62	7.10	7.01	7.25	7.60	10.29 (1H, s)	5.50 (1H, m, 2"-H), 4.89 (1H, d, J_{cis} = 9.3, 3"-H a), 4.59 (1H, d, J_{trans} = 17.2, 3"-H b), 4.55 (1H, dd, J_{gem} = 5.6, $J_{1a",2"}$ = 15.8, 1"-H a), 4.36 (1H, dd, J_{gem} = 5,6, $J_{1b",2"}$ = 16.8, 1"-H b)	6.14 (1H, m, 2"-H), 5.24 (1H, d, J_{cis} = 11.5, 3"-H a), 5.20 (1H, d, J_{trans} = 17.7, 3"-H b), 5.01 (2H, m, J_{gem} = 6.0, 1"-H)

* For all compounds $J_{1,2} = J_{10,11} = 7.6$, $J_{2,3} = J_{9,10} = 7.0$, $J_{3,4} = J_{8,9} = 7.9$, $J_{4',5} = 7.9$, $J_{5',6} = 7.2$, $J_{6',7} = 8.3$ Hz.

(12-H). The position of the remaining signals for 2- and 10-H, 3- and 9-H, and 4- and 8-H was then determined by double resonance. The position of the signals for the 5'-H and 6'-H protons was determined by double resonance on the basis of the fact that the signal of 4'-H is upfield from the signal of 7'-H.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Varian VXR-400 spectrometer (400 MHz) with DMSO-d_6 as solvent. The reactions and the purity of the products were monitored by TLC on Merck Kieselgel F_{254} plates in 3:1 petroleum ether–ethyl acetate. Preparative TLC was conducted on 20 × 20 cm glass plates with a 0.5-mm layer of silica gel (Kieselgel 60 F_{254}) in the same system. The electron-impact mass spectra were recorded on a Finnigan SSQ 710 spectrometer.

General Conditions of N-Alkylation. To a suspension of sodium hydride (0.80 mmol) in dry THF (4 ml) we added dropwise a solution of compound **1** (50 mg, 0.135 mmol) in THF (2 ml). After 1 min the alkylating agent was added in a twofold excess for each NH group. In the case of the synthesis of products **4** and **2b** after the formation of the monoallyl derivative **3** a sixfold excess (for each of the two unsubstituted NH groups) of sodium hydride and allyl bromide were added. The reaction mixture was acidified to pH 7, diluted with ethyl acetate, washed three times with water, and dried over sodium sulfate, and the solvent was evaporated. The alkylation products were isolated from the residue by preparative TLC.

5,7-Dimethyl-6-(1'-methyl-3-indolyl)indolo[2,3-*b*]carbazole (2a). The product was a light-gray amorphous powder, yield 53 mg (95%); R_f 0.65. Electron-impact mass spectrum (*m/z*) (I_{rel}, %): 413 $[M]^+$ (100), 398 $[M–Me]^+$ (20), 383 $[M–2Me]^+$ (15), 371 $[M–3Me]^+$ (55). IR spectrum (tablet with potassium bromide), ν, cm^{-1}: 3448.5, 2922.5, 1624.7, 1600.2, 1465.6, 1436.2, 1390.8, 1315.8, 1255.7, 1234.3, 1124.6, 742.3, 726.3, 557.9. Found, %: C 84.35; H 5.72; N 10.29. $C_{29}H_{23}N_3$. Calculated, %: C 84.23; H 5.61; N 10.16.

6-(1'-Allyl-3-indolyl)indolo[2,3-*b*]carbazole (3). The product was an amorphous powder, yield 40 mg (90%); R_f 0.55. Electron-impact mass spectrum, *m/z* (I_{rel}, %): 411 $[M]^+$ (100), 370 $[M–All]^+$ (20). IR spectrum (tablet with potassium bromide), ν, cm^{-1}: 3424.9, 1630.0, 1610.1, 1463.0, 1421.2, 1322.5, 1316.2, 1267.5, 1201.4, 1015.7, 737.1, 576.0. Found, %: C 84.60; H 5.22; N 10.29. $C_{25}H_{21}N_3$. Calculated, %: C 84.64; H 5.14; N 10.21.

5-Allyl-6-(1'-allyl-3-indolyl)indolo[2,3-*b*]carbazole (4) and 5,7-N-Diallyl-6-(1'-allyl-3-indolyl)-indolo[2,3-*b*]carbazole (2b). The product was a yellowish amorphous powder, from which the individual products **4** and **2b** were isolated by preparative TLC. Compound **4**: Yield 8 mg (40%), R_f 0.65. Electron-impact mass spectrum, *m/z* (I_{rel}, %): 451 $[M]^+$ (100), 410 $[M–All]^+$ (25), 369 $[M–2All]^+$ (40). Found, %: C 85.00; H 5.70; N 9.21. $C_{32}H_{25}N_3$. Calculated, %: C 85.11; H 5.58; N 9.31. Compound **2b**: Yield 9 mg (45%), R_f 0.70. Electron-impact mass spectrum, *m/z* (I_{rel}, %): 491 $[M]^+$ (100), 450 $[M–All]^+$ (10), 410 $[M–2All+1H]^+$ (15), 409 $[M–2All]^+$ (20), 369 $[M–3All+1H]^+$ (10), 368 $[M–3All]^+$ (40). Found, %: C 85.66; H 5.89; N 8.43. $C_{35}H_{29}N_3$. Calculated, %: C 85.51; H 5.58; N 8.55.

5,7-Dimethylindolo[2,3-*b*]carbazole (5). A solution of compound **1** (40 mg, 0.11 mmol) in THF (4 ml) was added drop by drop to a suspension of sodium hydride (0.80 mmol) in THF (3 ml). The mixture was stirred at room temperature for 30 min, and dimethyl sulfate (0.8 mmol) was then added. The solvent was evaporated, and the mixture was purified by TLC in 5:1 petroleum ether–ethyl acetate, removing the most polar fluorescent fraction. We obtained 10 mg (36%) of compound **5**. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 8.88 (1H, s, 6-H); 8.19 (2H, d, J_{vic} = 8, 4- and 8-H or 1- and 11-H); 7.62 (1H, s, 12-H); 7.55 (2H, d, J_{vic} = 8, 1- and 11-H or 4- and 8-H); 7.40 (2H, t, J_{vic} = 7.9, 2- and 10-H or 3- and 9-H); 7.20 (2H, t, J_{vic} = 7.9, 3- and 9-H or 2- and 10-H); 3.92 (6H, s, Me). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 141.33; 141.20; 124.53; 122.77; 119.28; 118.51; 116.54; 111.49; 108.47; 87.77; 29.21. Found, %: C 84.48; H 5.67; N 9.85. $C_{20}H_{16}N_2$. Calculated, %: C 84.52; H 5.70; N 9.88.

REFERENCES

1. P. Goekjian and M. Jirousek, *Cur. Med. Chem.*, **6**, 877 (1999).
2. J. Chrisholm and D. Van Vranken, *J. Org. Chem.*, **60**, 6672 (1995).
3. M. Gillner, J. Bergman, C. Cambillau, M. Alexandersson, B. Fernstroem, and J. Gustafsson, *Mol. Pharmacol.*, **44**, 336 (1993).
4. P. Fernandez-Salguero, T. Pineau, D. Hilbert, T. McPhail, S. Lee, Sh. Kimura, D. Nebert, S. Rudikoff, J. Ward, and F. Gonzalez, *Science*, **268**, 722 (1995).
5. Y. Wei, H. Helleberg, U. Rannug, and A. Rannug, *Chem.-Biol. Interact.*, **110**, 39 (1998).
6. N. Hu, S. Xie, Z. Popovic, B. Ong, and A.-M. Hor, *J. Am. Chem. Soc.*, **121**, 5097 (1999).
7. S. Hünig and H.-Chr. Steinmetzer, *Lieb. Ann. Chem.*, 1090 (1976).
8. M. Preobrazhenskaya, A. Korolev, I. Pozhkov, L. Yudina, E. Lazhko, E. Aiello, A.-M. Almerico, and F. Mingoia, *Il Farmaco.*, **54**, 265 (1999).
9. A. M. Korolev, L. N. Yudina, E. I. Lazhko, M. I. Reznikova, and M. N. Preobrazhenskaya, *Khim. Geterotsikl. Soedin.*, 631 (1999).