Chemistry of Heterocyclic Compounds, Vol. 30, No. 9, 1994

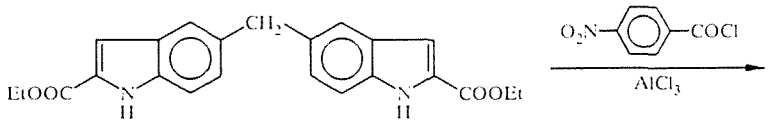
SYNTHESIS OF NOVEL BENZOYLATED INDOLES

Sh. A. Samsoniya, I. Sh. Chikvaidze, É. O. Gogrichiani, N. Sh. Lomadze, and N. L. Targamadze

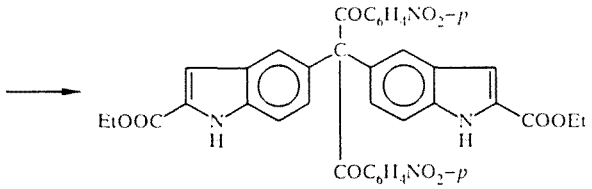
It has been shown that Friedel–Crafts p-nitrobenzoylation of 2,2'-dicarbethoxybis(5-indolyl)methane occurs at the bridging group. From the products of p-nitrobenzoylation of 2-carbethoxy-5-methylindole, 2-carbethoxy-5-hydroxy-indole and 2,7-dicarbethoxy-1H,6H-pyrrolo[2,3-e]indole there were obtained corresponding amines and an oxime.

It is known that electrophilic substitution in indole is principally directed to the pyrrole ring 3 position [1]. However, it has been shown [2] that Friedel–Crafts p=nitrobenzoylation of 2-carbethoxyindole gives a mixture of 3-, 5-, and 7- mono substituted compounds with a predominance of 5-acylation. Thus the 2-carbethoxy group hinders electrophilic substitution in the pyrrole ring. We have previously shown [3] that p-nitro-benzoylation of 2-carbethoxy-5-methylindole occurs at positions 4 and 7 but 2-carbethoxy-5-methoxyindole reacts only at 4. This direction of electrophilic substitution to 4 is unexpected and unprecedented in the chemistry of indole.

With the aim of further investigating p-nitrobenzoylation by method [3] we have studied the reactions of 2,2'-dicarbethoxy-bis(5-indolyl)methane (I) and 2,7-dicarbethoxy-1H,6H-pyrrolo-[2,3-e]indole (III) [4].



I

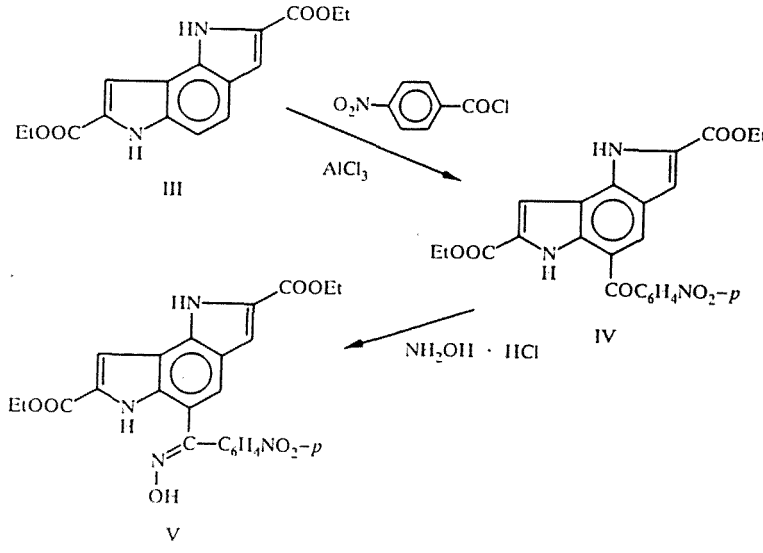


II

p-Nitrobenzoylation of I at 15-20°C gives a mixture of three compounds from which only the product of disubstitution at the methylene group (II) could be isolated. This substitution was proved by comparison of the PMR spectra of II and the starting bisindolylmethane I. In the PMR spectrum of II the aromatic region signals agree in chemical shift and the multiplicity with those of I but the signal for the CH_2 group (4.02 ppm in I) is absent. The PMR spectrum of II also shows A–H and B–H doublet signals at 7.94 and 8.38 ppm for the two p-nitrobenzoyl groups which are absent in I.

Iv. Dzhavakhishvili State University, Tbilisi 380028. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1202-1205, September, 1994. Original article submitted September 15, 1994.

0009-3122/94/3009-1039$12.50



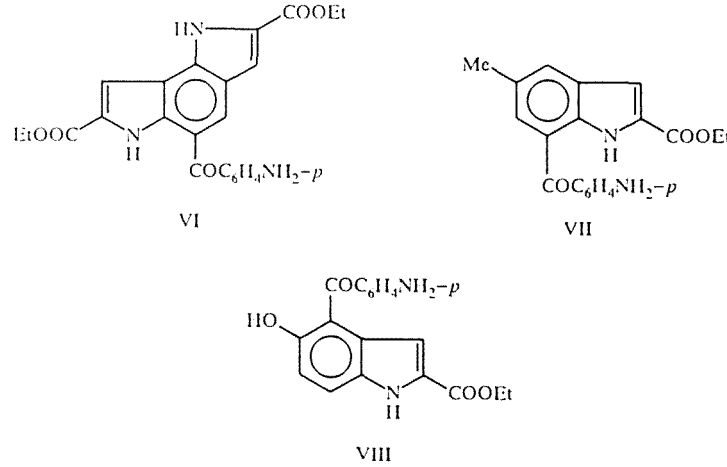
III

IV

V

p-Nitrobenzoylation of III gives only the mono 5-acylated product IV which was converted to the corresponding oxime V.

Reduction of the p-nitrobenzoylation products (compound IV and the previously obtained 2-carbethoxy-5-methyl-7-(p-nitrobenzoyl)indole and 2-carbethoxy-5-methyl-7-(p-nitrobenzoyl)indole and 2-carbethoxy-4-(p-nitrobenzoyl)-5-hydroxyindole [3]) is significantly complicated by the presence of the carbonyl group. A method was successfully developed for reduction and separation of three amines: 2,7-dicarbethoxy-5-(p-aminobenzoyl)-1H,6H-pyrrolo[2,3-e]indole (VI), 2-carbethoxy-5-methyl-7-(p-aminobenzoyl)indole (VII), and 2-carbethoxy-4-(p-aminobenzoyl)-5-hydroxyindole (VIII):



VI

VII

VIII

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for vaseline mulls, UV spectra on a Specord using ethanol solvent, and PMR spectra on WP-200 SY and Bruker-300 spectrometers with DMSO-D_6 solvent and TMS internal standard. Mass spectra were recorded on a Ribermag 10-10-B instrument with an ionization energy of 70 eV.

Reaction monitoring, compound purity and product R_f were measured on Silufol UV-254 TLC plates. Silica gel (100-250 microns) was used as sorbent for column chromatography.

Elemental analytical data for C, H, and N for VIII, XI-XIV agreed with those calculated.

TABLE 1. Parameters for the Synthesized Compounds VIII, XI-XIV

Compound	Empirical formula	mp, °C	R_f	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum		Yield, %
						Chemical shifts, δ, ppm	spin–spin coupling, J, Hz	
II	$C_{37}H_{28}N_4O_{10}$	218...220	0,53*	3310 (NH), 1690 (CO ester), 1650 (C=O), 1320, 1520 (NO_2)	205 (4,76), 258 (4,83), 278 (4,73) sh	12,42 (1H, s, 1-H), 7,33 (1H, s, 3-H), 8,13 (1H, s, 4-H), 7,62 (1H, d, 6-H), 7,79 (1H, d, 7-H), 4,36 (2H, q, $\underline{CH_2}CH_3$), 1,35 (3H, t, $\underline{CH_3}CH_2$), 7,94 (2H, d, A–H), 8,38 (2H, d, B–H)	J_o = 8,7, J_{AB} = 8,4	8
III		292...294	0,48*2, 0,47*2	3340 (NH), 3300 (OH), 1690 (CO ester), 1630 (C=N), 1330, 1510 (NO_2)	203 (4,46), 291 (4,45), 324 (3,99) sh., 350 (3,84)	11,95 (1H, s, 1-H), 7,71 (1H, s, 4-H), 11,73 (1H, s, 6-H), 7,30 (1H, d, 8-H), 12,46 (1H, s, OH), 4,35, 4,30 (4H, q., 2-$\underline{CH_2}CH_3$, 7-$\underline{CH_2}CH_3$), 1,37, 1,32 (6H, t, 2-$\underline{CH_3}CH_2$), 7,69 (2H, d, A–H), 8,21 (2H, d, B–H)	J_{AB} = 8,9	67
VI	$C_{23}H_{21}N_3O_5$	219...220	0,54*	3400 (NH), 3210 (NH_2), 1720 (CO ester), 1700 (C=O)	–	–	–	48
VII	$C_{19}H_{18}N_2O_3$	120...122	0,48*3	3460 (NH), 3245 (NH_2), 1715 (CO ester), 1600 (C=O)	207 (4,53), 229 (4,31) sh, 280 (4,11)	10,89 (1H, s, 1-H), 7,21 (1H, d, 3-H), 7,70 (1H, s, 4-H), 7,37 (1H, s, 6-H), 2,42 (3H, s, 5-CH_3), 4,35 (2H, q, $\underline{CH_2}CH_3$), 1,34 (3H, t, $\underline{CH_3}CH_2$), 6,15 (2H, s, NH_2), 7,59 (1H, d, A–H), 6,64 (1H, d, B–H)	J_{13} = 1,4	23
VIII	$C_{18}H_{16}N_2O_4$	203...204	0,33*3	3380 (NH), 3190 (NH_2), 1710 (CO ester), 1610 (C=O)	208 (4,56), 229 (4,44) sh, 277 (4,21), 344 (4,29)	11,82 (1H, s, 1-H), 6,57 (1H, s, 3-H), 6,96 (1H, d, 6-H), 7,41 (1H, d d, 7-H), 9,40 (1H, s, OH), 4,27 (2H, q, $\underline{CH_2}CH_3$), 1,28 (3H, t, $\underline{CH_3}CH_2$), 6,08 (2H, br.s, NH_2), 7,47 (2H, d, A–H), 6,54 (2H, d, B–H)	J_o = 8,9, J_{AB} = 8,8	17

*Benzene–ether, 4:1.

*2Benzene–ether, 5:1.

*3Benzene–ether, 2:1.

Di(p-nitrobenzoyl)-[2,2′-dicarbethoxybis(5-indolyl)]methane (II). To a solution of $AlCl_3$ (13.4 g, 100 mmole) in 1,2-dichloroethane (150 ml) there were added with cooling a solution of p-nitrobenzoyl chloride (9.27 g, 50 mmole) in dichloroethane (60 ml) and then 2,2′-dicarbethoxybis(5-indolyl)methane (I, 5 g, 13 mmole) in dichloroethane (100 ml). The product was stirred for 3 h at 15-17°C and poured into iced water (1 liter). It was acidified with HCl to pH 1 and extracted with chloroform. The extract was washed with water, sodium hydroxide solution (2%), water again, and then dried with anhydrous $CaCl_2$. Solvent was evaporated off and the residue chromatographed on a column using toluene to give orange crystals (0.74 g). Found: M^+ 688. Calculated for $C_{37}H_{28}N_4O_{10}$: M 688.

2,7-Dicarbethoxy-5-(p-nitrobenzoyl)-1H,6H-pyrrolo[2,3-e]-indole (IV). Obtained by the above method, mp 278-279°C. Lit. data [4] 278-279°C.

2,7-Dicarbethoxy-5-(p-nitrobenzoyl)-1H,6H-pyrrolo[2,3-e]-indole Oxime (V). Pyridine (50 ml) and hydroxylamine hydrochloride (0.076 g, 1.1 mmole) were added to a solution of IV (0.45 g, 1 mmole) in ethanol (20 ml) and the product was refluxed for 1 h. The solution was evaporated to one-third volume and the precipitate filtered, washed with water, and dried to give a mixture of syn and anti somers of oxime V as a light yellow solid (0.31 g). Found: M^+ 464. Calculated for $C_{23}H_{20}N_4O_7$: M 464.

2,7-Dicarbethoxy-5-(p-aminobenzoyl)-1H,6H-pyrrolo[2,3-e]-indole (VI). Freshly prepared sodium polysulfide (3 g) was added with stirring to a solution of IV (0.45 g, 1 mmole) in water (30 ml) at 60°C and the product was refluxed for 4 h. The yellow crystalline precipitate was filtered, washed with water, and dried to give VI (0.2 g).

2-Carbethoxy-5-methyl-7-(p-aminobenzoyl)indole (VII). Obtained similarly to VI from the corresponding nitro compound (0.93 g, 2.6 mmole) giving yellow crystals (0.19 g). Found M^+ 322. Calculated for $C_{19}H_{18}N_2O_3$: M 322.

2-Carbethoxy-4-(p-aminobenzoyl)-5-hydroxyindole (VIII). Obtained similarly to VI from the corresponding nitro compound (0.5 g, 1.4 mmole) giving yellow crystals (0.076 g).

The authors thank the director of the department of organic chemistry of Saarbrücken University (Prof. H. Dürr) for giving permission to record the PMR spectra of certain compounds.

REFERENCES

1. J. Joule and G. Smith, Fundamental Chemistry of Heterocyclic Compounds [Russian translation], Mir, Moscow (1975), p. 286.
2. Y. Murakami, M. Tani, K. Tanaka, and Y. Yokayama, Heterocycles, **22**, 241 (1984).
3. I. Sh. Chikvaidze, É. O. Gogrichiana, L. N. Kurkovskaya, L. V. Baramidze, Sh. A. Samsoniya, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 8, 1055 (1983).
4. N. Sh. Lomadze, I. Sh. Chikvaidze, N. L. Targamadze, L. N. Kurkovskaya, and Sh. A. Samsoniya, Khim. Geterotsikl. Soedin., No. 9, 1197 (1994).