Chemistry of Heterocyclic Compounds, Vol. 41, No. 11, 2005

INTERACTION OF 3-SUBSTITUTED INDOLES WITH PHENYLGLYOXAL

S. P. Ivonin and A. V. Lapandin

The interaction of 3-substituted indoles with phenylglyoxal has been studied. It was shown that a methyl group directs attack to the nitrogen atom, but hydrazonomethyl to position 2 of the indole. The reasons for the difference in regioselectivity are discussed.

Keywords: arylhydroxals, hydrazones, indoles, electrophilic substitution.

Investigations into indole chemistry have been and remain one of the most important areas of heterocyclic chemistry [1-3]. The indole fragment is met in nature in the most diverse structures, many of which possess biological activity [4-10]. Electrophilic substitution in position 3 of indole has been studied widely. For indoles already containing a substituent in this position reaction with electrophilic reagents bears a more complex character. In this case substitution may be directed to the benzene ring, to the nitrogen atom [11], to position 2 of the indole as a result of a 1,2-shift in the intermediate cation [12, 13], and to the methyl group in skatole [14], depending on the nature of the electrophile and the reaction conditions.

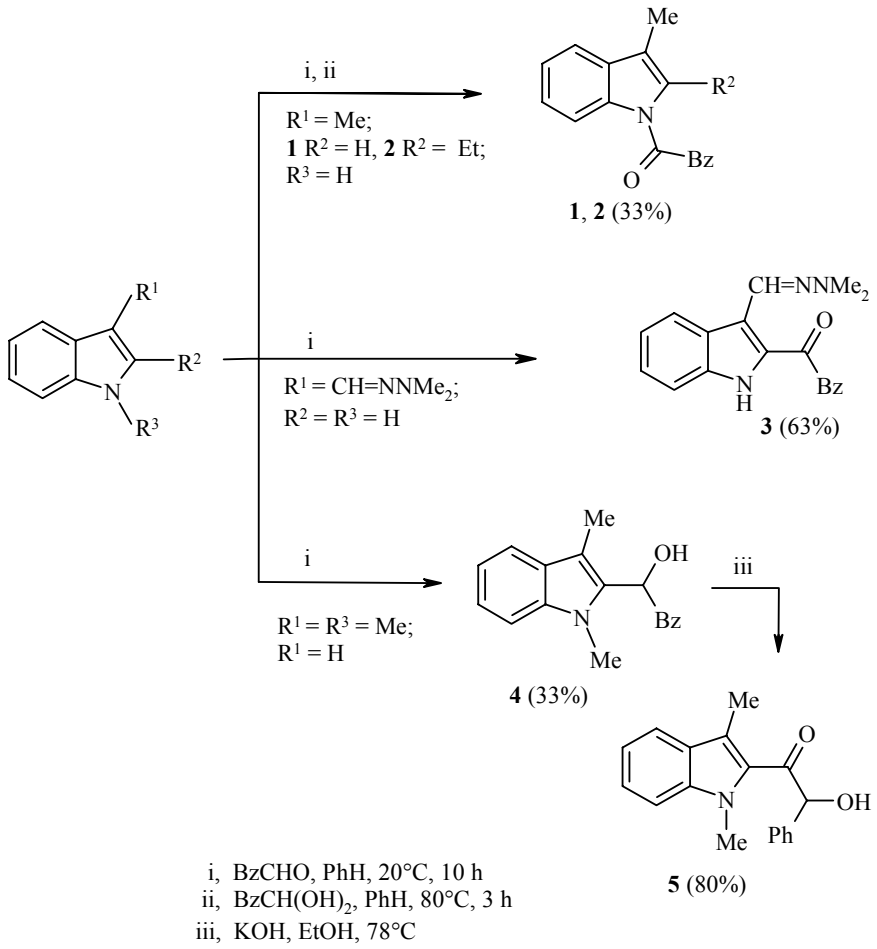
Previously we studied hydroxymethylation with arylglyoxals of π-excessive heterocycles, including 2-substituted indoles [15]. The aim of the present work is the study of the interaction of phenylglyoxal with 3-substituted indoles.

We found that skatole at room temperature in benzene forms a substitution product at the nitrogen atom, diketone **1**. 2-Ethylskatole forms diketone **2** analogously. On using the less reactive phenylglyoxal hydrate the regioselectivity and yield were unchanged.

Replacement of the methyl group in skatole by the more electron-donating dimethylhydrazonomethyl group changes the direction of hydroxymethylation and leads to the formation of the product of substitution at position 2 of the heterocycle, diketone **3**. In this case the reaction probably proceeds as an electrophilic substitution in the N,N-disubstituted hydrazones of the aldehydes at the most remote atom of the conjugated system in accord with the "azoenamine" concept [17]. It should be mentioned that the introduction of an acceptor into position 3 (indole-3-carbaldehyde) completely deactivates the latter in the reaction with phenylglyoxal.

On introducing a methyl group onto the nitrogen atom in skatole the reaction proceeds at position 2 of the indole with the formation of benzoin **4**. Owing to the low nucleophilicity of this position in indole the reaction proceeds only with anhydrous phenylglyoxal in low yield. Introduction of methyl groups into positions 1 and 2 of skatole (1,2,3-trimethylindole) leads to complete loss of reactivity in relation to phenylglyoxal.

Dnepropetrovsk National University, Dnepropetrovsk 49050, Ukraine; e-mail: ivonin@dp.ukrtel.net.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1653-1656, November, 2005. Original article submitted June 7, 2004.



The results of the reactions indicate, in our opinion, that the interaction of phenylglyoxal with indoles has orbital control and occurs by an electrophilic substitution mechanism [11].

It was shown previously by us that α→β isomerism of hetaryl analogs of unsymmetrical benzoins proceeds smoothly under the action of triethylamine [18]. Unlike 3-substituted indoles, α-benzoin **4** isomerizes to the β-isomer **5** only in the presence of a stronger base, potassium hydroxide, which is linked with the significantly lower electron-donating ability of position 2 of the indole and with steric hindrance created by the methyl groups.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained in DMSO-d_6 on a Varian VXR-300 (300 MHz) instrument, internal standard was TMS. The IR spectra were obtained on a UR-20 instrument in KBr disks. A check on the progress of reactions and the purity of the compounds obtained was effected by TLC on Silufol UV-254 plates in the system benzene–acetone, 5:1.

Electrophilic Substitution (General Procedure). A solution of phenylglyoxal (5.00 mmol) or its hydrate and the 3-substituted indole (5.00 mmol) in benzene (8 ml) was kept at room temperature or boiled (see Scheme). The benzene was evaporated in vacuum. The residue was crystallized from the solvent indicated.

1-(3-Methylindol-1-yl)-2-phenylethane-1,2-dione (1). White needles; mp 93-94°C (hexane). IR spectrum, ν, cm^{-1}: 3115, 3080, 2950, 1695, 1615, 1475, 1400, 1360, 1285, 1205, 1120, 980. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, 3-CH_3 Ind); 7.04 (1H, t, *J* = 7.5, H-5 Ind); 7.05-7.15 (3H, m, H-2,4,7 Ind); 7.18 (1H, t, *J* = 7.5, H-6 Ind); 7.45 (2H, t, *J* = 7.5, H-3,5 Ph); 7.60 (1H, d, *J* = 7.5, H-4 Ph); 7.98 (2H, d, *J* = 7.5, H-2,6 Ph). Found, %: C 77.53; H 4.95. $C_{17}H_{13}NO_2$. Calculated, %: C 77.55; H 4.98.

1-(2-Ethyl-3-methylindol-1-yl)-2-phenylethane-1,2-dione (2). Yellow needles; mp 135-136°C (hexane). IR spectrum, ν, cm^{-1}: 3080, 2987, 2961, 2893, 1705, 1610, 1480, 1408, 1345, 1286, 1239, 1190, 1110, 1055, 990. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.8, $CH_2C\underline{H}_3$); 2.18 (3H, s, CH_3 Ind); 2.89 (2H, q, *J* = 7.8, $C\underline{H}_2CH_3$); 6.98 (1H, t, *J* = 6.9, H-5 Ind); 7.11 (1H, t, *J* = 6.9, H-6 Ind); 7.32 (1H, d, *J* = 6.9, H-4 Ind); 7.35 (1H, d, *J* = 6.9, H-7 Ind); 7.41 (2H, t, *J* = 7.5, H-3,5 Ph); 7.54 (1H, d, *J* = 7.5, H-4 Ph); 7.84 (2H, d, *J* = 7.5, H-2,6 Ph). Found, %: C 78.27; H 5.79. $C_{19}H_{17}NO_2$. Calculated, %: C 78.33; H 5.88.

1-[3-(Dimethylhydrazonomethyl)-1H-indol-2-yl]-2-phenylethane-1,2-dione (3). Red powder; mp 140-141°C (hexane). IR spectrum, ν, cm^{-1}: 3344, 2970, 2890, 1694, 1550, 1482, 1355, 1315, 1234, 1188, 1077. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.82 (6H, s, $N(CH_3)_2$); 7.07 (1H, t, *J* = 6.9, H-5 Ind); 7.32 (1H, t, *J* = 6.9, H-6 Ind); 7.43 (1H, d, *J* = 6.9, H-4 Ind); 7.60 (2H, t, *J* = 7.2, H-3,5 Ph); 7.74 (1H, d, *J* = 7.2, H-4 Ph); 7.96 (2H, d, *J* = 7.2, H-2,6 Ph); 8.27 (1H, d, *J* = 6.9, H-7 Ind); 11.79 (1H, s, NH). Found, %: C 71.35; H 5.30. $C_{19}H_{17}N_3O_2$. Calculated, %: C 71.46; H 5.37.

2-(1,3-Dimethyl-1H-indol-2-yl)-2-hydroxy-1-phenylethanone (4). Yellow powder; mp 142-143°C (ethanol). IR spectrum, ν, cm^{-1}: 3450, 3115, 3080, 2960, 2885, 1695, 1617, 1474, 1400, 1360, 1285, 1205, 1110, 1052, 983. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24 (3H, s, 3-CH_3 Ind); 3.70 (3H, s, 1-CH_3 Ind); 5.95 (1H, d, *J* = 5.5, CHO$\underline{H}$); 6.45 (1H, d, *J* = 5.5, C$\underline{H}$OH); 6.98 (1H, t, *J* = 5.1, H-5 Ind); 7.12 (1H, t, *J* = 5.1, H-6 Ind); 7.33 (1H, d, *J* = 5.1, H-4 Ind); 7.40-7.50 (3H, m, H-3,5 Ph, H-7 Ind); 7.52 (1H, d, *J* = 6.9, H-4 Ph); 7.86 (2H, d, *J* = 6.9, H-2,6 Ph). Found, %: C 77.33; H 6.11. $C_{18}H_{17}NO_2$. Calculated, %: C 77.40; H 6.13.

1-(1,3-Dimethyl-1H-indol-2-yl)-2-hydroxy-2-phenylethanone (5). A solution of α-benzoin **4** (1.50 mmol) and potassium hydroxide (1.80 mmol) in ethanol (6 ml) was boiled. The solvent was evaporated in vacuum, and the residue was crystallized from aqueous ethanol. Light-orange powder; mp 145-146°C. IR spectrum, ν, cm^{-1}: 3480, 3090, 2970, 1700, 1620, 1510, 1465, 1445, 1365, 1220, 950. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.34 (3H, s, 3-CH_3 Ind); 3.87 (3H, s, 1-CH_3 Ind); 6.05 (1H, d, *J* = 5.5, CHO$\underline{H}$); 6.42 (1H, d, *J* = 5.5, C$\underline{H}$OH); 7.22 (1H, t, *J* = 7.8, H-5 Ind); 7.27 (1H, t, *J* = 7.8, H-6 Ind); 7.28 (1H, d, *J* = 7.8, H-4 Ind); 7.30 (1H, d, *J* = 7.8, H-7 Ind); 7.38 (2H, t, *J* = 8.7, H-3,5 Ph); 7.49 (1H, d, *J* = 8.7, H-4 Ph); 7.63 (2H, d, *J* = 8.7, H-2,6 Ph). Found, %: C 77.36; H 6.09. $C_{18}H_{17}NO_2$. Calculated, %: C 77.40; H 6.13.

The work was carried out with the financial support of the Ministry of Education and Science of Ukraine (State Registration No. 0104U000476).

REFERENCES

1. J. A. Joule, in: E. J. Thomas (editor), *Hetarenes and Related Ring Systems: Fused Five-Membered Hetarenes with One Heteroatom,* Vol. 10, Georg Thieme Verlag, Stuttgart, New York (2000), p. 361.
2. R. J. Sundberg, *Indoles*, Academic Press, San Diego (1996).
3. H. Düpp, D. Düpp, U. Langer, and B. Gerding, in: R. P. Kreher (editor), *Heteroarenes I, Pt 2*, E6b, Georg Thieme Verlag, Stuttgart (1994), p. 546.
4. A. M. Lobo and S. Prabhakar, *J. Heterocycl. Chem.*, **39**, 429 (2002).
5. S. Hibino and T. Choshi, *Natur. Prod. Rep.*, **19**, 148 (2002).
6. U. Pindur and T. Lemster, *Curr. Med. Chem.*, **8**, 1681 (2001).
7. J. Bonjoch and D. Sole, *Chem. Rev.*, **100**, 3455 (2000).

8. M. Lounasmaa, P. Hanhinen, and M. Westersund, in: G. A. Cordell (editor), *Alkaloids: Chemistry and Biology*, Vol. 52, Academic Press, New York (1999), p. 103.
9. J. W. Huffman, *Curr. Med. Chem.*, **6**, 705 (1999).
10. A.-U. Rahman and A. Basha, *Indole Alkaloids*, Harwood Academic Press, Amsterdam (1998).
11. V. A. Budylin, L. G. Yudin, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 1181 (1980).
12. A. H. Jackson and P. Smith, *Tetrahedron*, **24**, 2227 (1968).
13. A. H. Jackson, B. Naidoo, A. E. Smith, A. S. Bailey, and A. S. Vandrevala, *J. Chem. Soc., Chem. Commun.*, 779 (1978).
14. M. Pal, R. Dakarapu, and S. Radakanti, *J. Org. Chem.*, **69**, 2913 (2004).
15. S. P. Ivonin, A. V. Lapandin, A. A. Anishchenko, and V. G. Shtamburg, *Synth. Commun.*, **34**, 451 (2004).
16. A. A. Tolmachev, S. P. Ivonin, A. A. Anishchenko, and A. M. Pinchuk, *Heteroatom Chem.*, **9**, 461 (1998).
17. R. Fernandez and J. M. Lassaletta, *Synlett.*, 1228 (2000).
18. S. P. Ivonin, A. V. Lapandin, and V. G. Shtamburg, *Khim. Geterotsikl. Soedin.*, 187 (2004).