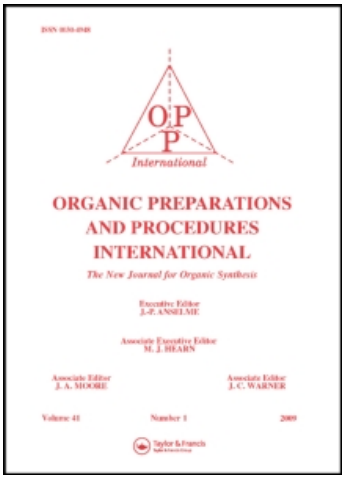

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METHYLATION OF BIDENTATE NITROGEN-CONTAINING HETEROCYCLES WITH METHYL IODIDE AND POTASSIUM HYDROXIDE IN DIMETHYL SULFOXIDE

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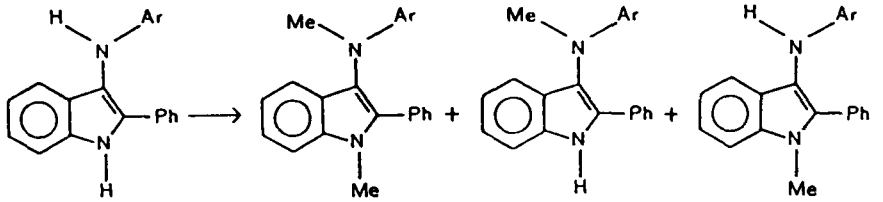
N-Alkylation of indoles, pyrroles and similar compounds has been achieved by several methods using such alkylating agents as alkyl halides and sulfonates,[1] epoxides,[1] dimethyl sulfate[2] and N,N-dimethylformamide dimethyl acetal.[3] Most of these reactions were effected in the presence of bases such as potassium or sodium hydride,[4,5] sodium hydroxide in hexamethylphosphoric triamide[6] or in aqueous solution in the presence of tetraalkylammonium salts,[7] potassium hydroxide under homogeneous[8] and heterogeneous conditions,[9] sodium ethoxide[10] and thallium(I) ethoxide.[11] Although a substantial amount of work has been done on the alkylation of indoles, no investigation of bidentate indole derivatives has been carried out. The present paper reports results obtained from a study of methylation of a number of 3-arylaminoindoles and related compounds with methyl iodide in dimethyl sulfoxide in the presence of base.

When methylated with methyl iodide in EtOH/EtONa under pressure at 140°, compounds 1a and 1c formed only the 3-(N-methyl)arylamino indoles 3a and 3c, respectively, in very low yields.[10] The method

described herein (KOH and DMSO) led to the formation of compounds 2 in nearly quantitative yields; in the case of 1a, some monomethylation at



1 2 3 4

a: Ar = C_6H_5 b: Ar = $C_6H_4Me(p)$ c: Ar = $C_6H_4OMe(p)$
d: Ar = $C_6H_4Cl(p)$ e: Ar = $C_6H_4CN(p)$

exocyclic nitrogen (3a) was observed (15% yield) (Table 1). In order to effect selective methylation, we carried out several experiments on compound 1a with different bases. The results, reported in Table 1, show that tetrabutylammonium hydroxide leads preferentially to monomethylation at the heterocyclic nitrogen atom to afford 4a. In contrast, the use of 4-dimethylaminopyridine resulted in monomethylation at the exocyclic nitrogen atom to afford 3a as the

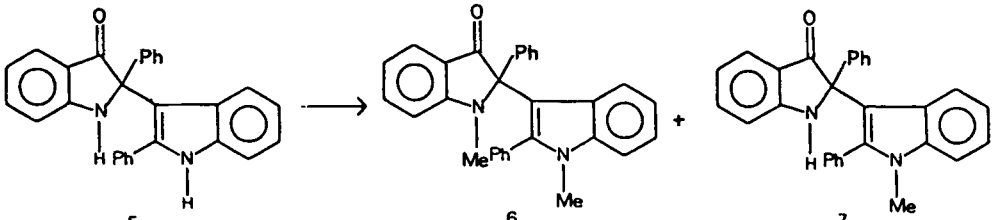
TABLE 1. Yields of Methylation of 1a-e, 5 and 8 in DMSO.

Compd	Base	Products (%)	Compd	Base	Products (%)
1a	KOH	2a (85); 4a (15)	1a[a]	Et_3N	3a (30)
1b	"	2b (100)	1a[a]	Me_3Py[c]	2a (30); 3a (4); 4a (10)
1c	"	2c (100)	1d[a]	Bu_4NOH	2d (26); 4d (40)
1d	"	2d (100)	5	KOH	6 (100)
1e	"	2e (100)	5	Bu_4NOH	6 (75); 7 (25)
1a[a]	Bu_4NOH	2a (19); 3a (5); 4a (35)	8a	KOH	9a (100)
1a[a]	Me_2NPy[b]	2a (8); 3a (55); 4a (3)	8b	"	9b (100)

a) The difference between the total percentage and 100% represents unchanged starting material; b) 4-Dimethylaminopyridine; c) Collidine.

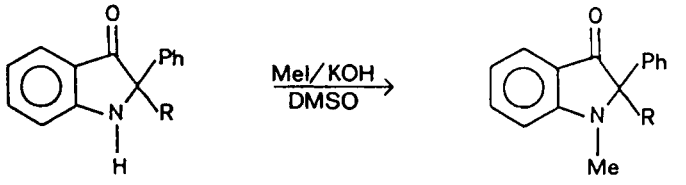
major product. In order to evaluate the effect of an electron-withdrawing substituent at the 4-position of the arylamino group, we methylated 1d in the presence of Bu_4NOH. Comparison of the results with those of 1a under the same conditions suggests that the substituent does not significantly influence the selectivity of the methylation.

Another bidentate system which was investigated was compound 5. The MeI/DMSO/KOH methylation procedure led to the formation of the dimethylated product 6 in nearly quantitative yield. On the other



5 6 7

hand, selective methylation was obtained only with Bu_4NOH as the base and no reaction whatsoever was observed with 4-dimethylaminopyridine. Indolines 8a and 8b, which were previously methylated in very low

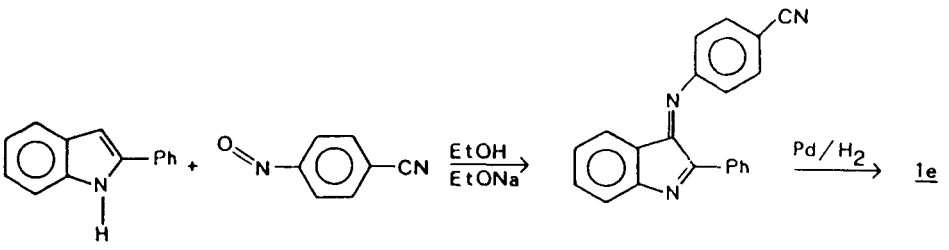


8 9

a: $R = C_6H_5$ b: $R = CH_2Ph$

yield by Berti and coworkers,[12] were methylated with MeI/KOH in DMSO in nearly quantitative yield. Compounds 3a,[13] 6,[14] 7,[15] 9a[12] and 9b[12] were identified by comparison with authentic samples. Compounds 2a-e, 4a and 4d were identified by their analytical and spectroscopic data (Table 2). The ^1H nmr spectra of 2a-e show two singlets, one at δ 3.0 for the NMe group corresponding to the exocyclic nitrogen and the second at δ 3.7 assignable to the NMe of the ring nitrogen. Compounds 4a and 4d show only one of the two singlets reported above. In addition, the infrared spectra of 4a and 4d exhibit peaks for the NH

group at 3425 and 3430 cm^{-1}, respectively (nujol mull). Compound 1e



10 11 12

was prepared by catalytic reduction of 2-phenyl-3-(p-cyanophenylimino) -3H-indole 12, prepared from the reaction of p-cyanonitrosobenzene 11 with 2-phenylindole 10.

TABLE 2. Analytical and Spectral data of 2a-e, 4a and 4b.

Compd	mp.[a] (°C)	Mass m/z (rel. int. %)	^1H NMR (CCl_4)	Elemental Analyses Calcd (Found) C	H	N
2a	145/8	77(65.0); 205(19.2); 219(17.6); 282(39.0); 297(24.7); 312(100.0)	3.05(3H,s, NMe exo);3.72 (3H,s, NMe ring);6.50-7.40(14H,m, aromatic)	84.70 (84.81)	6.41 (6.33)	8.97 (8.85)
2b	108/10	219(16.5); 296(34.7); 311(27.6); 326(100.)	2.20(3H,s, Me);3.02(3H, s, NMe exo);3.70(3H,s, NMe ring);6.40-7.45(13H, m, aromatic)	84.66 (84.77)	6.75 (6.80)	8.59 (8.42)
2c	128/30	219(15.6); 312(30.7); 327(47.4); 342(100.0)	3.03(3H,s, NMe exo);3.66 (3H,s, OMe);3.70(3H,s, NMe ring);6.60-7.35(13H, m, aromatic)	80.71 (80.62)	6.43 (6.48)	8.18 (8.25)
2d	165/7	77(45.2); 219(16.4); 316(31.2); 331(40.1); 346(100.0)	3.04(3H,s, NMe exo);3.70 (3H,s, NMe ring);6.45-7.45(13H,m, aromatic)	76.21 (76.14)	5.48 (5.52)	8.08 (8.15)
2e	110/2	77(50.3); 219(15.8); 307(31.9); 322(35.8); 337(100.0)	3.12(3H,s, NMe exo);3.76 (3H,s, NMe ring);6.52-7.50(13H,m, aromatic)	81.90 (81.72)	5.64 (5.72)	12.46 (12.55)
4a	125/7	77(97.8); 206(15.2); 219(20.9); 222(55.6); 282(54.1); 298(100.0)	3.70(3H,s, NMe ring); 6.50-7.50(15H,m, NH and aromatic)	84.57 (84.66)	6.04 (6.11)	9.39 (9.23)
4d	120/2	77(52.8); 219(17.6); 317(28.9); 332(100.0)	3.71(3H,s, NMe ring); 6.50-7.50(14H,m, NH and aromatic)	75.81 (75.92)	5.11 (5.04)	8.42 (8.53)

a) Benzene/petroleum ether.

EXPERIMENTAL SECTION

IR and NMR spectra were recorded on a Perkin Elmer 298 Infrared Spectrophotometer and on a Perkin Elmer R12 NMR Spectrometer, respectively. Mass spectra were recorded on a Hewlett-Packard mod. 5985 B Spectrometer. Compounds 1a-d,[16] 5,[15] 8a,b[17] were prepared according to the literature. Methyl iodide, dimethyl sulfoxide, potassium hydroxide, tetrabutylammonium hydroxide, 4-dimethylamino pyridine, triethylamine, collidine, carbon tetrachloride were Fluka reagents.

Preparation of p-Cyanonitrosobenzene (11).- This compound was prepared according to the method of Ashley et al.,[18] but with omission of the steam distillation. The mixture, derived from the oxidation of p-cyanoaniline with Caro's Acid, was collected and the solid washed with water until all mineral salts were removed. The resulting water-insoluble solid was dried and crystallized from EtOH to give p-cyanonitrosobenzene in 70% yield, mp. 136°, lit.[18] mp. 136/37°.

Preparation of 2-Phenyl-3-(p-cyanophenylimino)-3H-indole (12).- To a solution of 2-phenylindole (10 mmol, 1.93 g) and p-cyanonitrosobenzene (10 mmol, 1.32 g) in 150 ml of EtOH heated to reflux, was added dropwise a solution of EtONa (3 mmol in 10 ml of EtOH). During the addition, vigorous gas evolution was observed, whereupon the reaction solution became red. After cooling, the expected product precipitated as red needles (1.5 g, 52%), mp. 196° from ligroin (bp. 100-135°).

Anal. Calcd for $C_{21}H_{13}N_3$: C, 82.06; H, 4.26; N, 13.67
Found: C, 82.24; H, 4.26; N, 13.76

Preparation of 2-Phenyl-3-(p-cyanophenylamino)-3H-indole (1e).- Compound 12 (3.3 mmol, 1.06 g in 100 ml of pyridine) was reduced at room temperature and at 3 atm. in the presence of 5% Pd/C (200 mg). When the reduction was complete (1 hr), the catalyst was filtered and the filtrate reduced to 10 ml. This solution was heated to boiling and the product precipitated by adding ligroin (bp. 100-135°) (0.9 g, 85%), mp. 287°.

Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.53; H, 4.88; N, 13.58
Found: C, 81.31; H, 4.94; N, 13.80

Methylation of Compounds 1a-e, 5, 8a,b with KOH as a Catalyst.- The substrate (1 mmol) and methyl iodide (5 mmol), in 5 ml of DMSO and KOH (0.2 mmol), was allow to react at room temperature, with stirring, for 24 hrs and then the red solution was poured in cold water and extracted with benzene (3 x 20 ml). The combined extracts were washed with water (4 x 20 ml) and the organic layer was dried over sodium sulfate. The solution was then evaporated and passed through a silica gel column (Merck; 70-230 mesh ASTM; eluent: cyclohexane/ethyl acetate, 8/2) from which the pure methylated derivatives were recovered.

Methylation of Compounds 1a, 1d and 5 with Other Bases as Catalysts.- The methylations of 1a (with Bu_4NOH, Me_3Py, Et_3N, Me_3Py as catalysts),

and of 1d and 5 (with Bu_4NOH as a catalyst) were carried out under the conditions and in the concentrations above described.
In the case of 1a and 1d, starting materials were also recovered on passing the reaction mixture through a silica gel column (see experimental conditions above) (Table 1).

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