Simple Dealkylation of Tertiary Amines

By LUIGI BERNARDI* and GERMANO BOSISIO

(*Farmitalia, Laboratori di Milano, Via dei Gracchi,* 35 *Milano, Italy*)

Summary Reaction of tertiary amines with $AgNO_2$ in dimethylformamide yields *N*-dealkyl-*N*-nitroso-amines.

DEALKYLATION, particularly demethylation, of a tertiary amine can be accomplished in various ways,[1] but the conditions are often drastic and the yields moderate. We report here a very mild procedure for the demethylation of tertiary amines *via* conversion into their *N*-demethyl-*N*-nitroso-derivative, from which the secondary amine can be obtained by known methods.[2]

Table

Compound	$AgNO_2$/ mol. equiv.	Time/h	*N*-Demethyl-*N*-nitro-compound[a]	
			M.p.	Yield/%
10,11-Dihydro-*NN*-dimethyl-5*H*-dibenzo[*a,d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine (amitriptyline)	4	6	72—74°	55
2-Diphenylmethoxy-*NN*-dimethylethylamine (diphenhydramine)	4	5	81—82°	52
2-Chloro-10-(3-dimethylaminopropyl)phenothiazine (chlorpromazine)	4	8	115—116°	51
1αH,5αH-Tropan-3α-ol (±)-tropate (atropine)	8	24	65—67°	71
6β,7β-Epoxy-1αH,5αH-tropan-3α-ol (−)-tropate (scopolamine)	8	24	110—112°	82
10-Methoxy-1,6-dimethyl-ergoline-8β-methanol 5-bromonicotinate (nicergoline)	8	24	90—91°	35
8β-[(Carboxyamino)methyl]-1,6-dimethylergoline benzyl ester (methergoline)	8	24	177—179	41
α-(+)-4-Dimethylamino-3-methyl-1,2-diphenylbutan-2-ol propionate (dextropropoxyphene)	4	2	112—113°	73

[a] All reported compounds gave satisfactory elemental analysis (C, H, N).

The Table shows that this simple procedure, which involves treatment of the *N*-methyl derivative with $AgNO_2$ in dimethylformamide (DMF), allows the selective demethylation of a tertiary amine† in fair to good yields; the nitroso-derivative is generally isolated by direct crystallization or, in a few cases, by chromatography on a short silica gel column. The following example is indicative of the method.

A suspension of dextropropoxyphene (1·7 g) and $AgNO_2$ (3·08 g)[3] in DMF (75 ml) was stirred vigorously at 70 °C until the starting material had disappeared (t.l.c.) (2 h). The solution, which was black owing to the presence of metallic silver, was evaporated *in vacuo*; the residue was treated with Na_2CO_3 solution and extracted with $CHCl_3$. The organic layer was washed with dilute HCl and with H_2O and evaporated to dryness. The residue was crystallized from ether–light petroleum to give *N*-demethyl-*N*-nitrosodextropropoxyphene (1·29 g) $[\alpha]_D^{20}$ + 13·5 (*c* 1, $CHCl_3$).

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† Imipramine yielded a complex mixture from which only 10,11-dihydro-5-nitroso-5*H*-dibenz[*b,f*]azepine could be isolated.

[1] F. Moeller in 'Houben-Weyl, Methoden der Organischen Chemie,' Thieme, Stuttgart, 1957, vol. 11/1, pp. 961 ff.
[2] Ref. 1, pp. 957 ff; B. Mühlenbruck and H. J. Roth, *Arch. Pharm.*, 1971, **304**, 823.
[3] N. Kornblum and H. E. Unguade, *Org. Synth.*, 1963; Coll. Vol. IV, 724.