Deamination of Primary Amines with Dinitrogen Tetraoxide at Low Temperatures: Formation of Nitrates

By **Derek H. R. Barton** * and **Subhash C. Narang**, Department of Chemistry, Imperial College, London SW7 2AY

Treatment of a primary or secondary alkyl primary amine at −78 °C with dinitrogen tetraoxide in the presence of excess of an amidine base gives an improved yield of nitrate ester or of nitrate ester plus alcohol. Use of these conditions significantly reduces the formation of olefins. Reactions of 3α- and 3β-aminocholestane proceed mainly with retention of configuration.

DEAMINATION of amines [1,2] has been the subject of intensive investigation for a long time. Work has been mainly concentrated on the use of nitrous acid. Little attention has been paid to the utilisation of other nitrosating agents. Nitrosation of amines is often not useful in synthesis, because of the multitude of side reactions like elimination and of structural rearrangements involving carbocation intermediates.

Besides nitrous acid, one can carry out nitrosations with nitrosyl halides [1,3] and dinitrogen tetraoxide.[4,5] We conceived that the denitrosation of a primary amine by dinitrogen tetraoxide in the presence of an organic tertiary base (of greater basic strength than the amine) should lead to nitrates. We also argued that at temperatures (−80 °C) much lower than normally used the carbocations generated would be ' cooler ' than usual and

[1] For a review, see E. H. White and D. J. Woodcock, ' The Chemistry of the Amino Group,' ed. S. Patai, Interscience, New York, 1968, p. 407.
[2] J. H. Ridd, *Quart. Rev.*, 1961, **15**, 418.
[3] J. Bakke, *Acta Chem. Scand.*, 1967, **21**, 1007.
[4] E. H. White and W. R. Feldman, *J. Amer. Chem. Soc.*, 1957, **79**, 5832.
[5] F. Wudl and T. B. K. Lee, *J. Amer. Chem. Soc.*, 1971, **93**, 271.

therefore less prone to undergo elimination and rearrangement.

Our results are summarised in the Table, with appropriate results from the literature for comparison.

Nitrate esters [6] are useful intermediates in synthesis, since the hydroxy-group is protected but can be regenerated quantitatively on reduction under mild conditions.

The deamination was studied in detail with cyclohexylamine. Nitrosation of cyclohexylamine in ether at −78 °C, in the absence of any other base, gave a oxide under the usual conditions. The reaction proceeded predominantly with retention of configuration. Cholestan-3α- and -3β-yl nitrates were characterised by comparison with authentic samples.[7] The composition of the product mixture was again dependent on the reaction temperature. At 0 °C, 3β-aminocholestane gave cholest-2-ene in 11% yield, whereas at −78 °C no cholest-2-ene was detected. In the nitrosation of 3α-aminocholestane at −78 °C, elimination occurred to the extent of 35%. Lowering the reaction temperature to −150 °C decreased the yield of elimination product to only 20%.

Amine	Product *	Yield (%)	Product †	Yield (%)
Cyclohexylamine [a]	Cyclohexanol	68	Cyclohexyl nitrate Cyclohexanol	81—89
	Cyclohexene	~20	Cyclohexene	Trace
n-Octylamine [b]	n-Octanol	44	n-Octyl nitrate	81
t-Butylamine [c]	Olefin	64	t-Butyl nitrate	5
			2-Methylpropene	30
3β-Aminochestane [d]	3β-Cholestanol Cholestan-3β-yl acetate	66.4	3β-Cholestanol Cholestan-3β-yl nitrate	87
	3α-Cholestanol Cholestan-3α-yl acetate	24.6	3α-Cholestanol Cholestan-3α-yl nitrate	11
	Cholestene	9	Cholestene	0 ‡
3α-Aminocholestane [d]	3α-Cholestanol Cholestan-3α-yl acetate	39.6	3α-Cholestanol Cholestan-3α-yl nitrate	57
	3β-Cholestanol Cholestan-3β-yl acetate	3.4	3β-Cholestanol Cholestan-3β-yl nitrate	8
	Cholestene	57	Cholest-2-ene	35 20 §

* Literature work. † Present work; all reactions at −78 °C (unless specified otherwise) in the presence of an excess of amidine ‡ 11% at 0 °C. § At −150 °C.

[a] W. Hückel and E. Wilip, *J. prakt. Chem.*, 1941, **158**, 21. [b] D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 1934, 838. [c] B. E. Weller, ref. 1, p. 481. [d] C. W. Shoppee, R. E. Lack, and P. Ram, *J. Chem. Soc.* (*C*), 1966, 1018.

mixture of cyclohexyl nitrate, cyclohexanol, and other products in *ca.* 50% yield. However, nitrosation under identical conditions but, in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) gave a much improved yield of the nitrate (75%). Owing to solubility problems, it was preferable to use DBU (1,5-diazabicyclo[5.4.0]-undec-5-ene) or DBN (1,5-diazabicyclo[4.3.0]non-5-ene) instead. Both amidines proved equally effective, giving, after reduction, yields greater than 80% of cyclohexanol. Pyridine and triethylamine were not basic enough to neutralise preferentially the acid produced during the reaction.

Varying the molar ratio of cyclohexylamine to DBU from 1 : 2 to 1 : 6 did not produce any significant increase in yield. The change in molar ratio of cyclohexylamine to dinitrogen tetraoxide from 1 : 2.5 to 1 : 10 did not alter the yield or the nature of the products. On the other hand, an increase in reaction temperature from −78 to 0 °C made elimination more competitive with normal substitution. The yield of cyclohexene increased from a trace at −78 °C to 16%. A decrease in reaction temperature from −78 to −150 °C slowed the nitrosation significantly. The reaction took much longer but there was no improvement in the yield of cyclohexyl nitrate.

To study the stereochemistry of this reaction, 3β- and 3α-aminocholestane were treated with dinitrogen tetra-

Nitrosation was also successful with normal alkyl primary amines. The reaction of n-octylamine provided n-octyl nitrate in 81% yield. However, the reaction was not applicable to tertiary alkyl primary amines. The major product from the nitrosation of t-butylamine was 2-methylpropene.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded for neat compounds or for Nujol mulls. N.m.r. spectra were measured for solution in deuteriochloroform with tetramethylsilane as internal standard. $[\alpha]_D$ Values were measured for solutions in chloroform (*c* 1—2%). Reactions were followed by t.l.c. on silica GF_{254} plates. Organic solvent extracts were dried over anhydrous magnesium sulphate. Light petroleum refers to the fraction with b.p. 40—60 °C.

Nitrosation of Cyclohexylamine.—Cyclohexylamine (1 g) and DBU (2.5 g) in ether (10 ml) were added dropwise over 30 min to stirred dinitrogen tetraoxide (4.5 g) in ether (50 ml) at −78 °C. The mixture was stirred overnight at −78 °C and quenched with brine, then extracted with ether. The extract was washed with concentrated hydrochloric acid, brine, and saturated aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was chromatographed on silica. Elution with light petroleum furnished cyclohexyl nitrate (1.09 g, 75%), b.p. 68° at 10 mmHg (lit.,[8] 70—72° at

[6] F. Hodosan, I. Jude, N. Serban, and A. Balogh, *Chem. Ber.*, 1962, **95**, 1094; D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *J.C.S. Perkin I*, 1975, 2252.

[7] G. Snatzke, H. Laurent, and R. Wiechert, *Tetrahedron*, 1969, **25**, 761.

[8] Fr. Fichter and A. Petrovich, *Helv. Chim. Acta*, 1941, **24**, 253.

12 mmHg), $\nu_{max.}$ 2 940, 1 625, 1 460, 1 280, 1 010, 950, and 870 cm^{-1}. Further elution with light petroleum–ether (3 : 1) provided cyclohexanol (138 mg, 14%).

The combined aqueous extracts were neutralised with sodium carbonate and extracted with ether. The extract was dried and evaporated. The residue was taken up in pyridine and treated with benzoyl chloride (500 mg) at room temperature overnight. The mixture was taken up in ether and the solution washed successively with dilute hydrochloric acid and aqueous 5% sodium hydrogen carbonate, dried and evaporated to yield *N*-cyclohexylbenzamide (135 mg, 7%), m.p. and mixed m.p. 146—147° (from ethanol).

The same procedure was followed for nitrosation of cyclohexylamine at other temperatures and in the presence of other tertiary amines.

For reductive work-up, acetic acid (10 ml) was added to the dried ethereal extract containing cyclohexyl nitrate and cyclohexanol. Zinc dust (8 g) was added in portions (1 g) with stirring till the reduction was complete (8 h). The excess of acetic acid was neutralised with solid sodium carbonate. The mixture was filtered and the solid residue washed with ether (3 × 15 ml). The combined extract was distilled to yield cyclohexanol (772 mg, 77%).

Traces of cyclohexanone were isolated by extraction of the crude product with aqueous sodium hydrogen sulphite. The n.m.r. spectrum of the crude product showed the presence of only traces of cyclohexene.

Nitrosation of n-Octylamine.—Nitrosation of n-octylamine (1 g) by the usual procedure at −78 °C (see above) provided, on chromatography, n-octyl nitrate (1.21 g, 81%), b.p. 93—94° at 10 mmHg (lit.,[9] 109—111° at 19 mmHg), identical (t.l.c.) with an authentic sample, $\nu_{max.}$ 2 920, 1 630, 1 460, 1 380, 1 280, and 860 cm^{-1}.

Nitrosation of t-Butylamine.—t-Butylamine (1 g) was nitrosated at −78 °C as described for cyclohexylamine. Distillation of the ethereal extract provided 2-methylpropene (240 mg, 30%), spectroscopically identical with an authentic sample. Careful distillation of the resulting ethereal solution left a residue, which on distillation gave t-butyl nitrate (82 mg, 5%), b.p. 24° at 10 mmHg (lit.,[10] b.p. 23—24° at 4—5 mmHg), identical with an authentic sample, $\nu_{max.}$ 2 920, 1 625, 1 375, 1 280, and 860 cm^{-1}.

Nitrosation of 3β-Aminocholestane.—3β-Aminocholestane (120 mg) and DBU (500 mg) in methylene chloride (10 ml) were nitrosated at −78 °C by dinitrogen tetraoxide (1.5 g) in ether (50 ml). After the usual work-up, the crude product was chromatographed on silica gel. Elution with benzene provided the following products in order of increasing polarity: cholestan-3α-yl nitrate (3.5 mg, 3%), m.p. 103°, mixed m.p. 103—104°, $[\alpha]_D$ +24.8° (lit.,[7] +24°), $\nu_{max.}$ 2 980, 1 640, 1 480, 1 390, 1 290, 945, and 870 cm^{-1} (Found: C, 74.7; H, 10.7; N, 3.15. Calc. for $C_{27}H_{47}NO_3$: C, 74.8; H, 10.9; N, 3.25%); cholestan-3β-yl nitrate (79.5 mg, 59%), m.p. 117—119.5°, mixed m.p. 118—119.5°, $[\alpha]_D$ +16.9° (lit.,[7] +17°), $\nu_{max.}$ 2 910, 1 635, 1 460, 1 380, 1 280, and 860 cm^{-1} (Found: C, 74.35; H, 10.65; N, 3.3%); and cholestan-3α-ol (10 mg, 8%), m.p. 183—185°. Elution with ether gave cholestan-3β-ol (33 mg, 28%), m.p. 139—140°.

Nitrosation of 3α-Aminocholestane.—3α-Aminocholestane (110 mg) was nitrosated by the usual procedure. Elution with light petroleum from a silica column gave cholest-2-ene (37 mg, 35%), m.p. 72.5—74°. Further elution with benzene–light petroleum (1 : 1) gave cholestan-3α-yl nitrate (67 mg, 54%), cholestan-3β-yl nitrate (7 mg, 6%), and cholestan-3α-ol (*ca.* 3 mg, 3%). Further elution with ether gave cholestan-3β-ol (2 mg, 2%).

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