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AMINE-N-OXIDE REARRANGEMENTS

MECHANISM AND PRODUCTS OF THERMOLYSIS*

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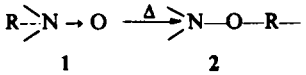
Abstract—The thermolysis of a series of structurally similar amine-N-oxides has been examined individually and as mixtures. Product analysis shows that in addition to the expected N-alkoxylamines, smaller amounts of t-amines, aldehydes, and bibenzyls are formed. Thermolysis of mixtures produces intermolecular rearrangement products thus challenging the previously favored intramolecular mechanism as the exclusive process for the Meisenheimer rearrangement. The data are consistent with a mechanism involving homolytic fission to intermediates which recombine to produce the N-alkoxylamines.

THE chemistry of t-amine-N-oxides **1** has received considerable attention, in part because of the role these compounds serve in the microsomal[1] and plant[2] metabolism of t-amines and in part because of the interesting thermal rearrangement they undergo[3] to the corresponding N-alkoxylamines **2**. In order to better define the nature of this reaction, we have studied the thermally induced N → O rearrangements (Meisenheimer rearrangement) of a series of t-amine-N-oxides.



1 **2**

Studies on the mechanism of the Meisenheimer rearrangement have supported both a concerted cyclic intramolecular process[4, 5] and free radical process.[6, 7] Both in terms of product analysis[8] and EPR data,[9] the related nitrone, **3**, is proposed to undergo a homolytic dissociation to the iminoxy and the benzhydryl radicals **4** and **5**, followed by recombination of the radical intermediates to afford the products, **6** and **7**. Implicit in this proposal is the intermolecular recombination of radicals to effect product formation. Should the Meisenheimer rearrangement of N-benzyl-t-amine-N-oxides proceed by an analogous process, nitroxide and benzyl radicals would be generated by homolytic fission and the benzyloxyamine formed by their recombination. Such an intermolecular process has been disfavoured since thermolysis of the mixture of N-oxides **8** and **9** gave high yields of the "intramolecular" trisubstituted hydroxylamines **10** and **11** with no crossover products detected. However, as pointed out by the authors,[5] compound **8** rearranged 100 times faster than **9** making their conclusions uncertain.

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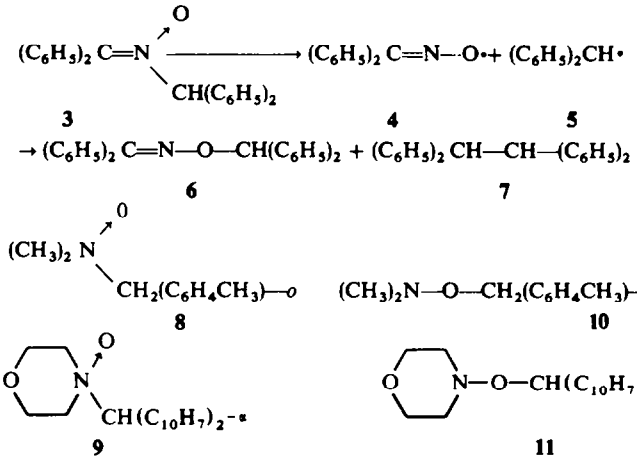
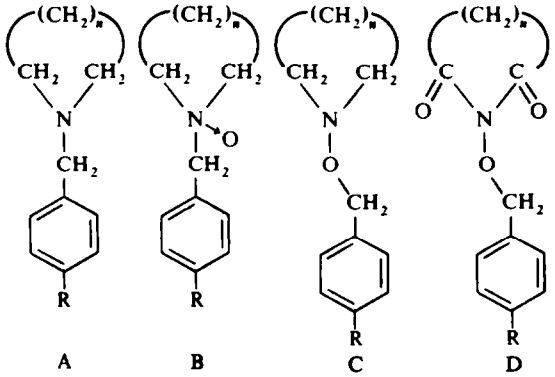


With the availability of more sensitive analytical methods we have undertaken a re-examination of the intramolecular *vs* intermolecular nature of the Meisenheimer rearrangement. The four closely related t-amine-N-oxides, **16–19**, were prepared by *m*-chloroperbenzoic acid oxidation of the corresponding t-amines, **12–15**. Because of their hygroscopic nature, the N-oxides were characterized as their picrates. As has been reported previously with related systems,[6] rearrangement of these compounds took place readily in the flash heater of the GLPC apparatus. Previous heating, either neat or in solution (xylene or dimethylformamide), did not alter the qualitative nature of the products formed.

Pyrolysis of the individual N-oxides, **16–19**, in each case produced three components which separated cleanly from the solvent peak.* Thus, GLPC analysis of an acetone solution of 1-benzylpiperidine-1-oxide (**16**) gave rise to three peaks in the ratio of 1 : 3 : 30 (Table 1) which were identified as benzaldehyde (**28**) by retention time and isolation of its 2,4-DNP derivative, 1-benzylpiperidine (**12**) by retention time, and 1-benzyloxypiperidine (**20**) by retention time and isolation of its picrate salt, respectively. There was no indication of the presence of Cope elimination products.

	A	B	C	D
n = 3, R = H	**12**	**16**	**20**	**24**
n = 2, R = CH_3	**13**	**17**	**21**	**25**
n = 3, R = CH_3	**14**	**18**	**22**	**26**
n = 2, R = H	**15**	**19**	**23**	**27**

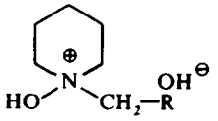


* When a highly volatile solvent such as acetone was used, additional peaks near the solvent peak were also detected. Since these components are not directly concerned with the present problem, they have not been further investigated at this time.

The structures of the N-alkoxylamines, **20–23**, were confirmed by independent syntheses of these compounds, using aluminum hydride reduction of the corresponding N-substituted cyclic imides, **24–27**. The NMR, IR spectra, retention times of the synthetic alkoxylamines, and the melting points of their picrates were identical with those of the compounds resulting from N-oxide rearrangements.

The difference in the retention times of all ten compounds [**12–15**, **20–23**, **28** and *p*-tolualdehyde (**29**)] resulting from the pyrolysis of the four individual t-amine-N-oxides **16–19** permitted the identification of each component in the presence of the others should cross-over products be produced during the pyrolysis of mixtures. When a mixture of **16** and **17** in acetone was injected into the flash heater, the resulting GLPC tracing did indeed show ten peaks, all of which could be clearly identified by retention times as the t-amines **12–15**, the alkoxylamines **20–23**, and the aldehydes **28** and **29** (Fig 1A) in the ratios shown in Table 1. In order to substantiate further the number and identity of the products, this result was confirmed by obtaining the *same* products, with identical retention times, but with the expected difference in the ratios (Table 1) by employing the opposite mixture, **18** and **19** (Fig 1B). The large amounts produced of the crossover alkoxylamines (Table 1) clearly establishes that intermolecular processes occur as part of the reaction.

The presence of protons which exchange with D_2O in the NMR spectra of the N-oxides **16–19** showed these compounds to exist as hydrates. It was important to determine if this water was in any way influencing the thermolysis reaction. Anhydrous N-oxides (no exchangeable protons by NMR) could be obtained by removing water azeotropically with toluene. The GLPC tracings obtained with the anhydrous N-oxides were in no way different from those with the hydrated compounds, thus ruling out any special contributions of structure **30** to the reaction mechanism.



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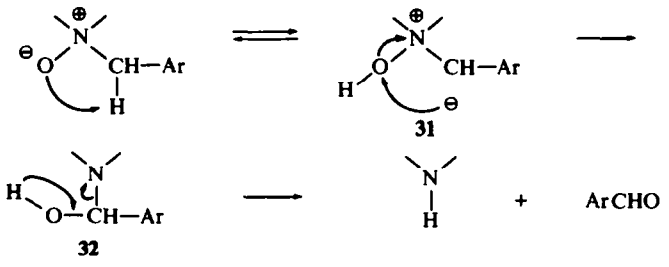
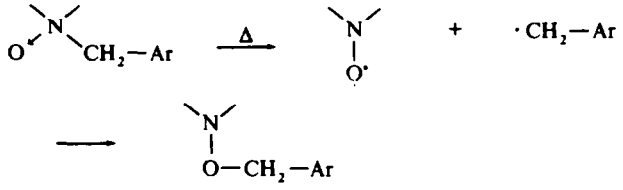
In order to determine the influence of solvent and prolonged heating on the mixed reaction, N-oxide mixtures in xylene and DMF were analyzed by GLPC after heating for various periods. The GLPC tracings remained qualitatively unchanged after heating, and showed the same ten products with identical retention times. The main quantitative change with prolonged heating was an increase in the relative amounts of the two aldehydes (Table 1).

The origins of the t-amines **12–15**, and of the aldehydes **28** and **29** are obscure. Pyrolytic deoxygenation of t-amine-N-oxides to the corresponding t-amines has been previously reported,[10] although no explanations as to the mechanism of formation have been offered. Aldehydes have not been reported from pyrolytic reactions although the N-oxides are known to yield aldehydes and the corresponding sec-amines when treated with reagents such as sulfur dioxide[11] or acetic anhydride.[12] As model reactions for metabolic oxidative N-dealkylation, t-amine-N-oxides have been shown to yield sec-amines and aldehydes in aqueous solutions of iron salts and complexing agents such as tartaric acid.[13] Furthermore, N-benzyloxyamines are known to cleave under acid conditions to give benzaldehyde and the corresponding amine.[14]

In an attempt to determine if the pure alkoxylamines **20–23** are thermally unstable, they were analyzed by GLPC at flash heater temperatures ranging from 160 to 250°. However, no aldehyde could be detected when the alkoxylamine was subjected to pyrolysis either alone or in the presence of varying amounts of t-amine. Prolonged heating of the alkoxylamines in xylene, with or without t-amines, also did not effect aldehyde formation. It would therefore appear that the alkoxylamines do not contribute to the formation of the aldehydes in these studies, thus leaving the N-oxides as their most likely source. A possible mechanism leading to aldehydes from the corresponding N-oxides would involve proton transfer from carbon to oxygen to form the ylid **31** followed by rearrangement to the carbinolamine **32** which would be expected to cleave thermally to the aldehyde and the amine. Studies directed to this question will be reported separately.



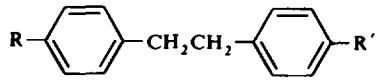
The formation of the same ten products from both the mixtures of **16** + **17** and **18** + **19** clearly demonstrates that migration of the benzyl and tolyl groups is not a strictly intramolecular process, since intermolecular products account for a significant percentage of the overall reaction product. An explanation for these observations is consistent with the radical mechanism proposed by others[6, 7] in which thermolysis leads to homolytic dissociation of the N-oxides to benzyl and nitroxide radical intermediates, which can then combine to form the major products. The observed predominance of the "intramolecular" products can be accounted for in terms of paired radicals.



The proposed intermediary role of the benzyl radical in this mechanism receives strong support by the demonstration of the presence of the radical coupling products bibenzyl (**33**) and bitolyl (**34**). By increasing the recorder sensitivity it was possible to detect **33** as a pyrolysis product of N-oxides **16** and **19**, and **34** as a pyrolysis product of N-oxides **17** and **18**. Furthermore, the pyrolysis of any mixture of N-oxides consisting of both the N-benzyl and N-tolyl types (as shown in Fig 2) produced all three expected radical coupling products, namely **33**, **34** and the cross product 1-phenyl-2-*p*-tolylethane (**35**). The retention times of the bibenzyls **33**, **34** and **35** were identical with those of authentic samples[22, 23] on two different GLPC columns.

Independent experiments (GLPC analyses) established that the alkoxylamines **20**

to **23** were not the source of these coupling products. This evidence therefore establishes that the N-oxides do pyrolyze to benzyl radicals and strongly supports the proposed radical mechanism.



33, R = R′ = H; **34**, R = R′ = CH_3; **35**, R = H, R′ = CH_3

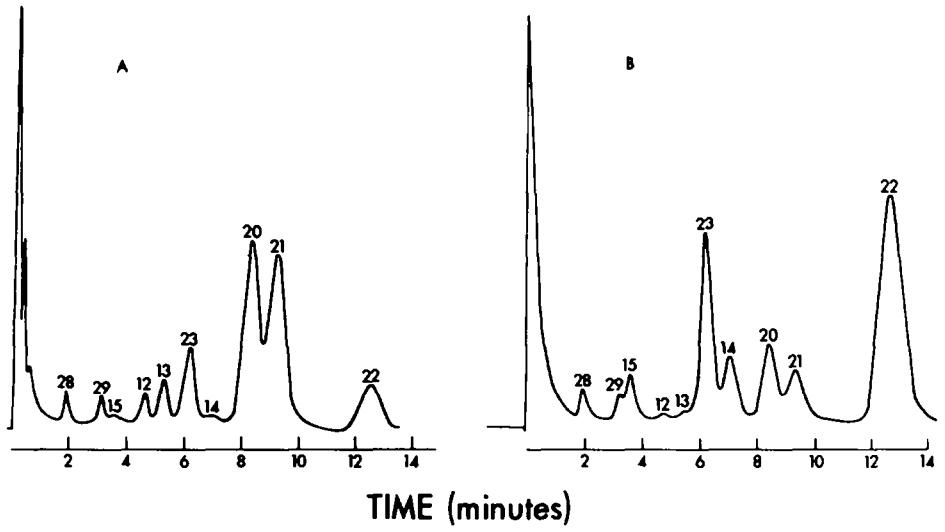


FIG 1. A. Glpc behavior of an acetone solution of compounds **16** and **17**.
B. Glpc behavior of an acetone solution of compounds **18** and **19**. In the above, numbers refer to structures given in text; column 2m × 5mm, 5·6% P.E.G. 20,000 on Firebrick; flash heater temp. 200°; column temp. 160°; pressure 25 lb. p.s.i.

TABLE 1. RELATIVE YIELDS OF N-OXIDE THERMOLYSIS PRODUCTS[a]

	Products (Retention times in min)									
	28 (1·85)	**29** (3·06)	**15** (3·46)	**12** (4·56)	**13** (5·20)	**23** (6·08)	**14** (6·93)	**20** (8·18)	**21** (8·97)	**22** (12·30)
Reactant(s)	Relative yields (Percentage of total)									
16	2·8	—	—	8·6	—	—	—	88·6	—	—
17	—	4·6	—	—	9·8	—	—	—	85·6	—
18	—	3·2	—	—	—	—	7·8	—	—	89·0
19	8·9	—	14·7	—	—	76·4	—	—	—	—
16 + **17**	1·8	2·4	<1·0	2·9	4·2	10·9	<1·0	33·3	33·3	10·9
18 + **19**	2·3	2·1	4·5	<1·0	<1·0	20·3	9·4	10·5	7·8	43·4
16 + **17**[b]	*d*	2·2	2·9	7·8	7·2	10·5	2·7	28·0	27·8	10·8
16 + **17**[c]	11·5	7·5	1·5	10·0	13·7	6·5	<1·0	25·3	21·5	3·5

[a] Determined by GLPC analysis of acetone solns, and excluding bibenzyls. Values are reproducible within 5%.
[b] In DMF.
[c] After 14 hr in DMF at 100°.
[d] Benzaldehyde peak hidden under solvent peak; detectable after 90 min at 100°.

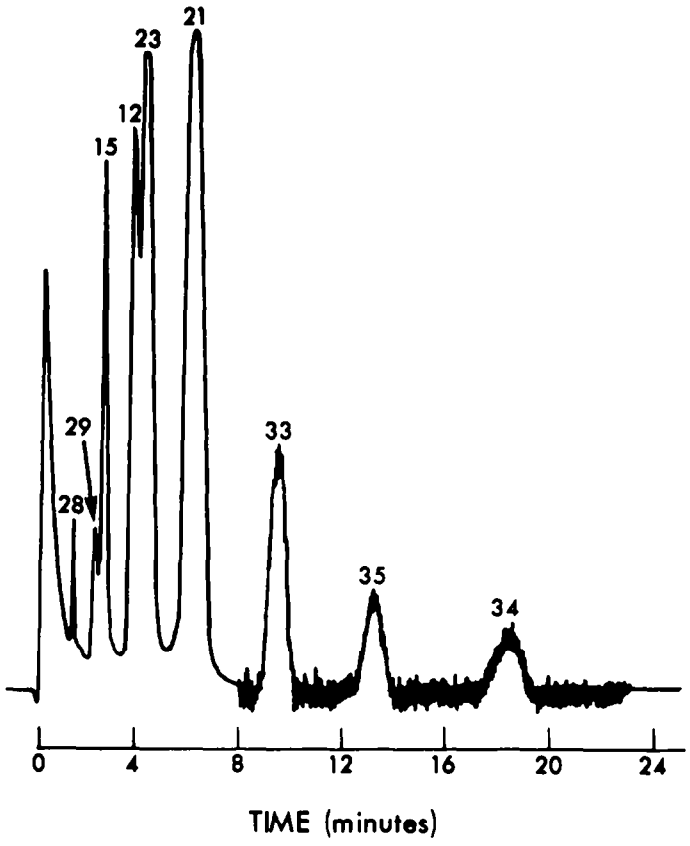


FIG 2. GLPC behavior of an acetone solution of compounds **17** and **19**. Sensitivity increased 100 × at 8 min. Numbers refer to structures given in text; column 2m × 5mm 5·6% P.E.G. 20,000 on Firebrick; flash heater temp. 214°; column temp. 179°; 20 lb. p.s.i.

TABLE 2. ANALYTICAL DATA

No.	m.p.[a]	Formula	Calc % C	Calc % H	Calc % N	Found % C	Found % H	Found % N
14	—	$C_{13}H_{19}N$	82·48	10·12	7·40	82·33	9·96	7·66
20	—	$C_{12}H_{17}NO$	75·35	8·96	7·32	75·27	8·94	7·09
21	—	$C_{12}H_{17}NO$	75·35	8·96	7·32	75·27	8·94	7·09
22	—	$C_{13}H_{19}NO$	76·06	9·33	6·82	76·07	9·23	6·91
23	—	$C_{11}H_{15}NO$	74·54	8·53	7·90	74·68	8·52	7·57
24[b]	141–142	$C_{12}H_{13}NO_3$	65·74	5·98	6·93	65·68	6·01	6·88
25	191–192	$C_{12}H_{13}NO_3$	65·74	5·98	6·93	65·79	5·79	6·87
26	139–140	$C_{13}H_{15}NO_3$	66·94	6·48	6·00	68·03	6·49	6·01
27[c]	139–140	$C_{11}H_{11}NO_3$	—	—	6·83	—	—	6·88

[a] See Experimental for boiling ranges.
[b] Lit.[20] m.p. 140–141°.
[c] Lit.[20] m.p. 140–141°.

TABLE 3. PICRATES

No.	m.p. (°C)	Formula	Calc % C	Calc % H	Calc % N	Found % C	Found % H	Found % N
14	149–150	$C_{19}H_{22}N_4O_7$	54·54	5·30	13·39	54·29	5·10	13·41
16	131–132	$C_{18}H_{20}N_4O_8$	51·42	4·80	13·32	51·42	4·80	13·13
17	127–128	$C_{18}H_{20}N_4O_8$	51·42	4·80	13·32	51·67	5·04	13·61
18	151–152	$C_{19}H_{22}N_4O_8$	52·53	5·10	12·90	52·30	4·89	12·70
19	129–131	$C_{17}H_{18}N_4O_8$	50·24	4·47	13·79	50·15	4·54	13·64
20	138–139	$C_{18}H_{20}N_4O_8$	51·42	4·80	13·32	51·60	4·81	13·33
21	131–132	$C_{18}N_{20}N_4O_8$	51·42	4·80	13·32	51·64	4·88	13·49
22	132–133	$C_{19}H_{22}N_4O_8$	52·53	5·10	12·90	52·21	5·16	12·94
23	118–119	$C_{17}H_{18}N_4O_8$	50·24	4·47	13·79	50·52	4·52	13·86

EXPERIMENTAL

Unless otherwise indicated, all reactions were performed under N_2 and solvents were concentrated on a rotary evaporator under vacuum. M.ps were taken on a Thomas–Hoover apparatus and are uncorrected. IR spectra were measured in $CHCl_3$ soln with a Perkin–Elmer Model 337 spectrophotometer. NMR spectra were recorded in the Model A-60A Varian Associates spectrometer using $CDCl_3$ as solvent and TMS as an internal standard (TMS = 0·0 ppm). Abbreviations: b = broad; s = singlet; p = pentuplet; m = multiplet. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

Procedure A

t-Amines **12–15**. To a stirred soln of pyrrolidine or piperidine (0·4 mol) in anhyd benzene maintained at reflux was added dropwise a soln of α-bromotoluene or α-bromo-*p*-xylene in anhyd benzene. After an additional hr at reflux, the cooled heterogeneous mixture was added to water and the benzene layer separated and washed once with $NaHCO_3$ aq and once with water. The dried ($MgSO_4$) organic layer was then distilled at 120–130°/15 mm to give the products in 90% yield: b.ps **12** 75°/2 mm (lit.[15] b.p. 120–122°/20 mm), picrate m.p. 166–167° (lit.[24] m.p. 166°) **13** 78°/2 mm (lit.[16] b.p. 107–108°/7 mm), picrate m.p. 125–126° (lit.[16] m.p. 130–131°), **14** 82°/2 mm, **15** 60°/2 mm (lit.[17] 116–122°/22 mm), picrate m.p. 128–129° (lit.[25] m.p. 128°); NMR 3·4–3·5 ppm s ($ArCH_2$), 2·4 m (pyrrolidine NCH_2CH_2), 1·7 m (pyrrolidine NCH_2CH_2), 2·3 m (piperidine NCH_2CH_2), 1·5 m (piperidine $CH_2CH_2CH_2$), 2·30 s (CH_3).

Procedure B

t-*Amine*-N-*oxides* **16–19**. To a vigorously stirred ice-cold soln of the t-amine (0·1 mol) in CH_2Cl_2 was added portion-wise 85% *m*-chloroperoxybenzoic acid (0·1 mol). The soln was allowed to warm to room temp and the next day was chromatographed on alkaline alumina (100 g). Any unreacted t-amine was eluted with CH_2Cl_2 after which the N-oxide was obtained with CH_2Cl_2–MeOH (4:1). Removal of solvent followed by crystallization of the residue from MeOH–ether gave 93–98% of the N-oxides: m.ps **16** 152–154° (lit.[21] m.p. 144°) and 160–161° after sublimation at 83°/0·008 mm, **17** 166–168°, **18** 157–159°, **19** 152–154° (see Table 3 for picrates); NMR 4·3–4·5 s ($Ar\text{-}CH_2$), 3·3 m (pyrrolidine NCH_2CH_2), 2·2 m (pyrrolidine NCH_2CH_2), 3·1 m (piperidine NCH_2CH_2), 2·9 m, b (piperidine $CH_2CH_2CH_2$) 2·3 s (CH_3), 4·1–4·6 s (H_2O, exchanges with D_2O).

Procedure C

Thermal rearrangement of t-*amine*-N-*oxides—isolation of alkoxylamines* **20–23**. The amine oxide (5 mmol) was heated slowly to 160°/30 mm in a short path distillation apparatus and maintained at this temp for 3 hr. The distillate (80% of original wt) was dissolved in ether and filtered from any ether insoluble N-oxide which sublimed during the reaction. The filtrate was then added to an ethereal soln of picric acid (2·3 g, 10 mmol) and the crystalline picrate purified by recrystallization from EtOH (Table 3). The yield of the alkoxylamine (isolated as its pure picrate salt) was 45–50%.

Procedure D

1-*Benzyloxypiperidine* **20**. The picrate of compound **20** (220 mg, 0·53 mmol) in a mixture of chloroform (20 ml) and acetone (5 ml) was chromatographed of 5 g alkaline alumina. The free base was eluted with chloroform (200 ml) and after short path distillation at 110°/5 mm pure **20** (72 mg, 0·37 mmol, 72%) was obtained (Table 2).

Procedure E

N-*Alkoxyimides* **24–27**. A suspension of N-hydroxysuccinimide[19] or N-hydroxyglutarimide[20] (0·1 mol) in 250 ml anhyd benzene containing Et_3N (10·1 g, 0·1 mol) was treated with freshly distilled α-bromotoluene or α-bromo-*p*-xylene (0·1 mol). The resulting mixture was stirred under reflux for 6 hr, and after cooling, diluted with 250 ml CH_2Cl_2. Successive washings with water, 10% $NaHCO_3$ aq, 10% HCl and water, followed by drying ($MgSO_4$) removal of solvent and crystallization of the residue from benzene gave the products (55–70% yield) which were sublimed at 60°/0·5 mm for analysis (Table 2): IR, 1730–1740 cm^{-1} (carbonyl); NMR 5·0–5·1 ppm s (OCH_2), 2·62 s (succinimide CH_2), 2·68 t J = 6 Hz (glutarimide O ‖ CCH_2), 1·85 m (glutarimide $CH_2CH_2CH_2$), 2·30 s (CH_3).

Procedure F

Aluminum hydride reduction of imides—preparation of N-*alkoxylamines* **20–23**. To a stirred soln of aluminum hydride prepared from LAH (1·57 g, 37·5 mmol) and 100% H_2SO_4 (2·0 g, 1·1 ml, 18·8 mmol) in 75 ml anhyd THF the imide (12·5 mmol) in 75 ml anhyd THF was added dropwise. After 4 hr at room temp, the mixture was treated with 15 ml THF–water (1 : 1) and then filtered free from salts. The concentrated filtrate was extracted with 6 × 25 ml CH_2Cl_2, the latter dried ($MgSO_4$) and after removing solvent, the residue was subjected to short path distillation to yield pure compounds in 62–74%: b.ps, **20** 64°/2 mm; **21** 70°/2 mm; **22** 84°/1·5 mm; **23** 75°/4 mm; IR, absence of carbonyl stretch; NMR, 4·6–4·7 ppm s (OCH_2), 3·95 m (pyrrolidine NCH_2), 1·72 p J = 3 Hz (pyrrolidine NCH_2CH_2), 5·8 b (piperidine NCH_2), 1·55 b (piperidine $\overline{C}H_2\overline{C}H_2\overline{C}H_2$), 2·30 s ($\overline{C}H_3$). The picrates were identical with those described in Procedure C.

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