Reactions of NN-Dialkylanilines with Diethyl Azodicarboxylate and with Ozone †

By **Geoffrey H. Kerr, Otto Meth-Cohn,** * **Ernest B. Mullock,** and **Hans Suschitzky,** * The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, Lancashire

Thermolysis of the adduct formed from N-phenylpyrrolidine and diethyl azodicarboxylate leads to a mixture of isomeric dimers whose structures and mechanisms of formation have been elucidated. The same dimers are formed by ozonation of N-phenylpyrrolidine. Other NN-dialkylanilines and their reactions with the azodicarboxylate as well as with ozone are described.

KENNER and STEDMAN [1] have shown that diethyl azo-dicarboxylate (DEAD) (1) reacts with NN-dimethyl-aniline to give the hydrazine (2), a reaction which was corroborated and rationalised by Huisgen [2] according to Scheme 1. The structure of the product was confirmed by us from its n.m.r. spectrum (see Experimental section). As part of a general investigation into the chemistry of tertiary anilines,[3] we undertook a study of this reaction with homologues of NN-dimethylaniline.

We found that N-phenylpyrrolidine reacts readily with DEAD to give an analogous adduct (3a) in high yield. In accord with the postulated mechanism, the weaker base, N-phenylmorpholine, reacts more slowly to give the appropriate adduct (3b). These adducts are thermally labile as indicated by their mass spectra which, at temperatures above 200°, show little or no

† Part II in the series 'Ozonation of Tertiary Aromatic Amines.' For Part I, see ref. 7.

[1] G. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 1952, 2089.
[2] R. Huisgen and F. Jacob, *Annalen*, 1954, **590**, 37.
[3] O. Meth-Cohn and H. Suschitzky, *Adv. Heterocyclic Chem.*, 1972, **14**, 211.

parent ion but large peaks corresponding to diethyl hydrazodicarboxylate and fragments derived from the tertiary aniline group. This thermal lability is significant with the phenylpyrrolidine adduct, since on heating in xylene it eliminates diethyl hydrazodicarboxylate

(1)

(2)
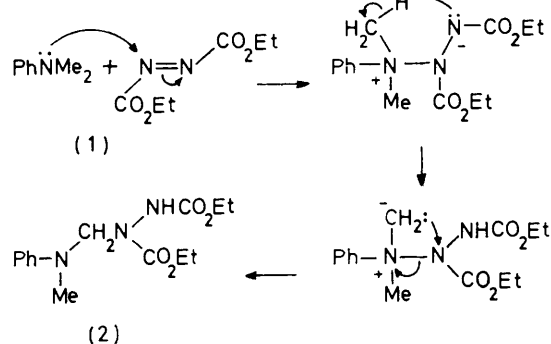
SCHEME 1

to form two isomers. These analyse for $C_{10}H_{11}N$ and one has the same m.p. as that reported[4] for N-phenyl-2-pyrroline (4). This latter product was reported to be

$(3)a; X = [CH_2]_2$
$b; X = CH_2OCH_2$
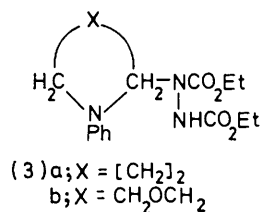
formed by lithium aluminium hydride reduction of N-phenyl-2-pyrrolidone (5) and its structure was inferred on the basis of analytical data and a reasonable molecular weight by the Rast method. We were able, by careful chromatography, to isolate the foregoing two isomeric products from the reported reduction of (5). The i.r. spectra of the two isomers are very similar. Their mass spectra above 200° show the highest ion at m/e 145 ($C_{10}H_{11}N$), while below this temperature, both isomers show a molecular ion at m/e 290, indicative of a dimer. The dimeric nature of the products is further borne out by their n.m.r. spectra, each of which is similar, and which show a one-proton doublet at τ 4·98 and 5·65 respectively, with nine aromatic protons and twelve other aliphatic protons in each case. On the basis of this and other evidence, we assign to the dimers structure (6), which is composed of configurational isomers [(A) and (B)] dependent upon the disposition of H-3b. Their formation is best rationalised as a Diels–Alder reaction as shown in Scheme 2. A good analogy exists for this type of ' heterocyclic ' diene addition in the interaction of vinyl ethers with N-benzylideneaniline to give tetrahydroquinolines (7)[5] (Scheme 3) and with dimethylaniline in the presence of benzoyl peroxide to give similar products.[6] The regiospecificity indicated in
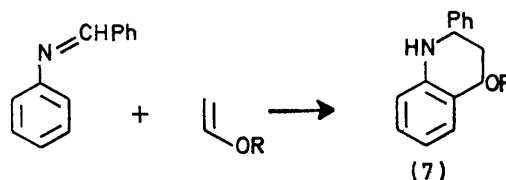
[4] G. Wittig and H. Sommer, *Annalen*, 1955, **594**, 1.
[5] L. S. Povarov and B. M. Mikhailov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1963, 955.

Scheme 2 is in accord with the expected reactivity of the pyrroline (4) behaving as an enamine. The alternative structure (8) from such a Diels–Alder reaction is ruled
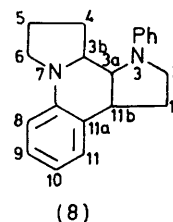

(5)

(4)

(6) Isomers (A) and (B)

SCHEME 2

(7)
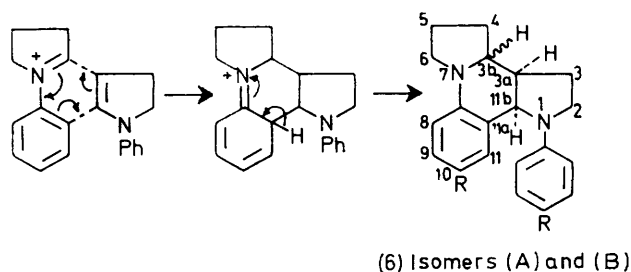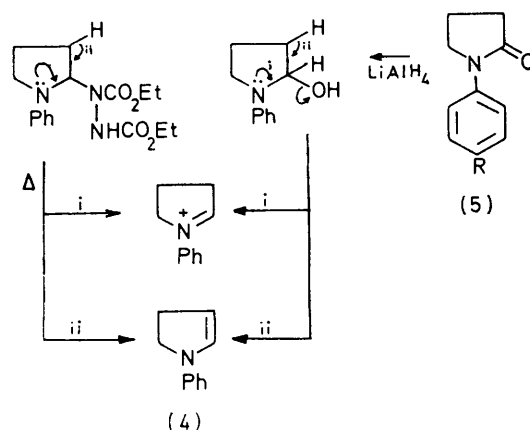
SCHEME 3

out since protons 3a, 3b, and 11b in this structure would all appear as multiplets. It is significant that in this and in a variety of related reactions only two isomers were formed with one, (A), always in higher proportion

(8)

[the two types of isomers, (A) and (B), are readily identified from the chemical shift and coupling constant of the proton doublet at τ 4—6]. This fact speaks for a concerted reaction resulting in *cisoid* geometry at the site of ring fusion and suggests tentatively that isomer (A) has *endo* configuration in accord with the known preference of the Diels–Alder reaction for *endo* addition.

[6] G. A. Swan, *Chem. Comm.*, 1969, 20; R. B. Roy and G. A. Swan, *ibid.*, 1968, 1446; *J. Chem. Soc.* (C), 1969, 1886, 2015.

Attempts to trap the diene and dienophile systems by conducting the reduction of N-phenylpyrrolidone in the presence of anthracene, isoprene, or acenaphthene were unsuccessful, the trapping agent and dimers (6) being isolated as the sole products.

The mass spectra of the isomers (6) are very similar, the major differences being in peak intensity. However, because of the temperature sensitivity, it is difficult to make comparative assignments on the basis of peak intensities. Nevertheless, the breakdown strongly favours the proposed structures. Thus the base peak is at m/e 170 with other significant fragment ions at m/e 185, 184, 171, 170, 157, 156, 143, 142, 106, 105, and 77. A rational breakdown pattern is shown in Scheme 4.
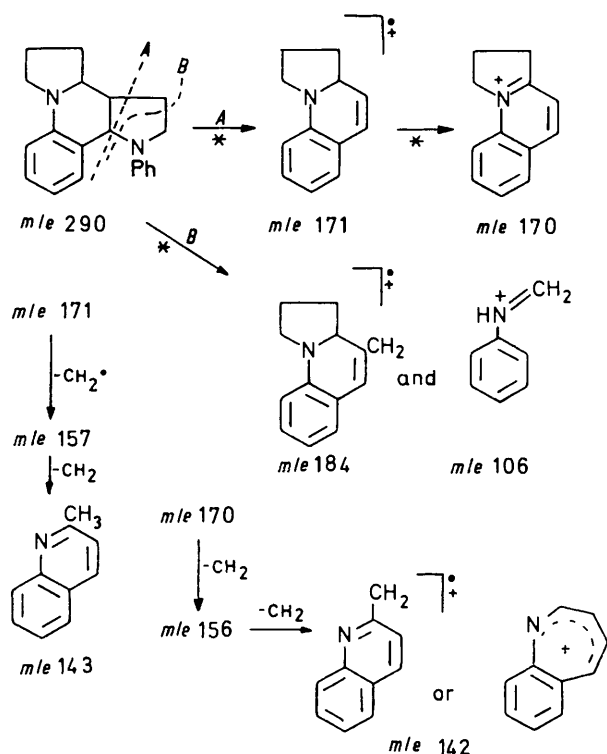
SCHEME 4 * Denotes metastable.

The n.m.r. spectra of these two isomers at 60 and 100 MHz are extremely complex. Attempts to simplify the spectra using shift reagents were without success, probably for steric reasons. However, the 220 MHz spectra were sufficiently resolved to allow some assignments to be made and confirmed by double resonance at 100 or 220 MHz. Thus, commencing with the doublet signal for H-11b we were able, by successive double resonance experiments, to locate the signals due to H-11b, 3e, and 3b, and thereby extract all the coupling constants for these protons (Table 1). From these data the approximate geometry of these protons should be derivable by the Karplus equation. However, considerable difficulty is found in measuring the appropriate angles from Dreiding models of the dimers since (a) the two nitrogen atoms may have their lone pair of electrons

arranged in four possible dispositions for each isomer, and (b) some of these arrangements also allow considerable flexibility.
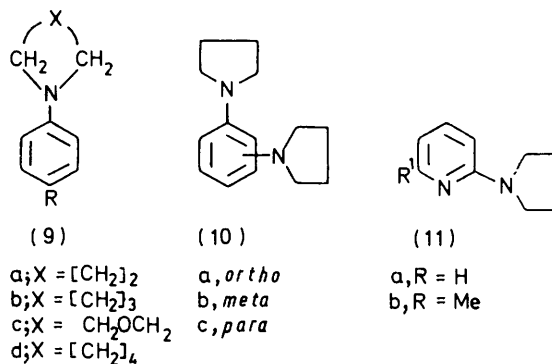

(9)   (10)   (11)

a;X =[CH₂]₂   a,ortho   a,R = H
b;X =[CH₂]₃   b,meta   b,R = Me
c;X = CH₂OCH₂ c,para
d;X =[CH₂]₄

TABLE 1

N.m.r. data for the dimers (6A) and (6B) in CDCl₃

Compound	Proton	Chemical shift (τ)	Coupling constants $J_{x,y}$	Hz
(6A)	11b	4·93	3a, 11b	6·75
	3a	7·50	3, 3a	12·0
			3′, 3a	6·0
			3a, 3b	3·25
	3b	6·27	3b, 4	10·0
			3b, 4′	4·5
(6B)	11b	5·58	3a, 11b	8·5
	3a	7·33	3, 3a	7·0
			3′, 3a	7·0
			3a, 3b	9·5
	3b	6·74	3b, 4	9·5
			3b, 4′	6·5

From previous experience,[7] iminium ions, such as those invoked in Scheme 2, can be generated by ozonation of tertiary anilines. To this end, we ozonised N-phenyl pyrrolidine and observed the formation of the dimers (6) together with N-phenyl-2-pyrrolidone (5). The formation of these products is in accord with the related results from ozonation of NN-dimethylaniline and with the above observations, involving initial formation of an N-ozonide as shown in Scheme 5.
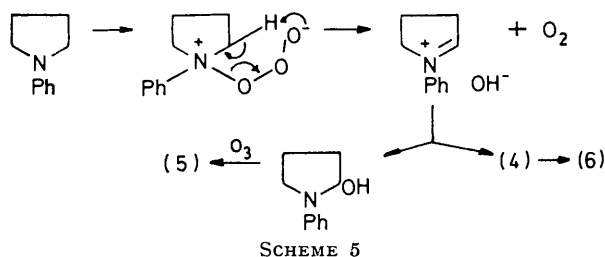
SCHEME 5

In order to examine the effects of structure, solvent, and temperature on the course of ozonation, a series of tertiary anilines was prepared. N-Phenylpyrrolidines and N-phenylpiperidines are conveniently prepared by passing a suitably substituted aniline, together with a cyclic ether (tetrahydrofuran or tetrahydropyran) down a heated tube containing activated alumina.[8]   A variety

[7] G. H. Kerr and O. Meth-Cohn, J. Chem. Soc. (C), 1971, 1369.
[8] A. N. Bourns, H. E. Embleton, and M. K. Hansuld, Org. Synth., Coll. Vol. IV, 1963, p. 795.

of pyrrolidines [(9a), (10), and (11)] were prepared by this route in good yield.

TABLE 2

Products from the ozonation of anilines (9a)

Aniline (9a) R	Solvent *	Temp. (°C)	Products (%)		
			(5)	(6)	(9a)
H	A	0	18·5	41	0
F	A	0	20	19	1
Cl	A	0	15	24	0
OMe	A	0	0 †	0 †	0 †
H	A	−45	24	31·5	0
F	A	−45	18	19	4
OMe	A	−45	1 †	1 †	1 †
H	B	0	20	25	24
F	B	0	24	13	10·5
Cl	B	0	15	21	6
NO₂	B	0	10	50	14
OMe	B	0	0 †	0 †	0 †
H	B	−45	11	40	6·5
F	B	−45	13	22	4
Cl	B	−45	38	23	6
OMe	B	−45	0 †	0 †	0 †
H	C	0	16	13	33
F	C	0	29	11	8
Cl	C	0	22	19	0
OMe	C	0	0 †	0 †	0 †
H	C	−45	19	20	1
F	C	−45	19	6	12·5
Cl	C	−45	18	5	14·5
OMe	C	−45	0 †	1 †	1 †

* A = n-hexane, B = methylene chloride, and C = methanol. † Almost all products water-soluble.

Ozonation of p-substituted N-phenylpyrrolidines (9a; R = F, Cl, or NO₂) gave both the dimers (6), with

side reactions, while at low temperatures in hexane anomalies probably arise because of the precipitation of intermediates such as the primary N-ozonide or of products during the course of the ozonation. The results are difficult to rationalise. Pyrrolidone formation appears to be largely independent of temperature, solvent, or substituent effects.

The dipyrrolidin-1-ylbenzenes (10) gave complex mixtures on ozonation, the meta- and para-analogues (10b and c) giving some polymeric products which could be extended analogues of the dimers (6). The pyridines (11) gave no dimer analogous to (6), the products being intractable. Furthermore, from the N-p-nitrophenyl-piperidine, -morpholine, and -perhydroazepine (9b, c, and d respectively; R = NO₂), complex mixtures were obtained yielding very small amounts of the dimers analogous to (6) as evidenced by mass spectroscopy. It would appear that the enamine [cf. (4)] formed in these cases is less reactive as a dienophile and suffers further ozonation.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer, n.m.r. on a Varian A60A, HA100, or 220 instrument, and mass spectra on an A.E.I. MS12 or MS902S. Ozonations were conducted using a B.O.C. Mk. II ozoniser, the carrier gas being dried through a column of B.D.H. 4A molecular sieve at a flow rate of 400 ml min⁻¹. Column chromatography employed either B.D.H. silica gel (M.F.C.)

TABLE 3

Properties of the anilines (9) and (10) and pyridines (11)

Compound No.	R	M.p. (°C) or [b.p. (°C)/mmHg]	Yield (%)	Found (%)			Formula	Required (%)		
				C	H	N		C	H	N
(9a)	H	[110—116/9] ᵃ	65							
(9a)	Cl	92 ᵇ	70	65·3	6·5	7·7	C₁₀H₁₂ClN	65·3	6·5	7·7
(9a)	F	[246]	95	72·8	7·3	8·4	C₁₀H₁₂FN	72·7	7·3	8·5
(9a)	OMe	55—57	10	74·2	8·4	7·8	C₁₁H₁₅NO	74·5	8·5	7·9
(10a)		[165/14]	30	77·2	8·9	12·85	C₁₁H₂₀N₂	77·6	9·25	13·0
(10b)		93—94	50	77·7	9·5	12·5	C₁₄H₂₀N₂	77·6	9·25	13·0
(10c)		158—159	55	77·9	8·9	12·6	C₁₄H₂₀N₂	77·6	9·25	13·0
(11a)		[252]	35	73·0	8·0	18·8	C₉H₁₂N₂	73·0	8·1	18·9
(11b)		[262]	55	74·5	8·9	17·15	C₁₀H₁₄N₂	74·1	8·6	17·2
(9a)	NO₂	170 ᶜ								
(9b)	NO₂	102 ᵈ								
(9c)	NO₂	150 ᵉ								
(9d)	NO₂	80—81 ᶠ								
(9c)	H	57 ᵍ	70							

ᵃ Lit.,⁸ b.p. 126° at 12·5 mmHg. ᵇ B. Berger, G.P. 812,552 (Chem. Abs., 1953, 47, 3351) quotes 85°. ᶜ J. E. Luvalle, D. B. Glass, and A. Weissberger, J. Amer. Chem. Soc., 1948, 70, 2223, quote 167—168°. ᵈ The authors in footnote e quote 103—105°. ᵉ R. H. Harradence and F. Lions, J. Proc. Roy. Soc. N.S.W., 1937, 70, 406, quote 149—150°. ᶠ M. S. Raasch, U.S.P. 2,612,500/1952, quotes 74—76°. ᵍ R. E. Rindfusz and V. L. Harnack, J. Amer. Chem. Soc., 1930, 42, 1725, quotes 52°.

dimer (A) always predominant, and the appropriate N-phenylpyrrolidone (5). However, N-p-methoxy-phenylpyrrolidine (9a; R = OMe) gave intractable, water-soluble products, as has been observed with the ozonation of p-methoxy-NN-dimethylaniline.⁷ Attack of the highly activated aromatic ring was proposed to account for this result. The effect of ozonation in solvents of different dielectric constant and at two different temperatures is summarised in Table 2. In methanol, tar formation is considerable, indicative of

or Laporte Industries' Alumina 'H.' Light petroleum refers to b.p. 60—80°, unless stated otherwise.

Preparation of the Tertiary Anilines.—(a) The equipment and method described previously ⁸ were employed, using tetrahydrofuran with aniline, p-chloroaniline, p-fluoroaniline, and p-methoxyaniline. The crude product so obtained was freed from tetrahydrofuran by evaporation and chromatographed on silica gel with light petroleum as eluant. The resultant product was further purified by distillation in the case of liquids, or recrystallisation from light petroleum in the case of solids (Table 3).

(b) p-Chloronitrobenzene (1 mol. equiv.) and the appropriate base (2·2 mol. equiv.) were heated on a steam-bath for 5 h, water was added, and the yellow solid was filtered, washed well with water, and recrystallised from ethanol to give the p-nitrophenyl derivatives (9) in very high yield (Table 3).

(c) Bis-(2-chloroethyl) ether (1 mol. equiv.) and aniline (3 mol. equiv.) were heated under reflux for 2 h. Addition of benzene caused precipitation of aniline hydrochloride which was removed by filtration, and the filtrate was evaporated and purified as in (a) to give N-phenyl-morpholine (Table 3).

N-Phenyl-2-pyrrolidone (5; R = H).—A mixture of γ-butyrolactone (1 mol. equiv.) and aniline (1 mol. equiv.) was heated at 200° for 15 h in an autoclave. The product was extracted with ether and washed successively with dilute hydrochloric acid, water, and sodium carbonate solution, then dried and evaporated. The residue (78%) was recrystallised from light petroleum to give the title product, m.p. 67—68° (lit.,[9] 67—69°).

Diethyl Azodicarboxylate (DEAD) Adducts of Tertiary Anilines.—A mixture of DEAD (1 mol. equiv.) and the

12 h reflux) (Found: C, 56·7; H, 7·0; N, 12·5. $C_{16}H_{23}N_3O_5$ requires C, 56·9; H, 6·9; N, 12·5%), τ (CDCl$_3$) 2·67 (m, 2 × ArH), 3·03 (m, 3 × ArH), 3·80br (NH), 4·20 (m, CH), 5·7 (two overlapping t, 2 × CO$_2$CH$_2$), 5·9 (m, CH$_2$OCH$_2$), 6·38 (m, NCH$_2$), 8·72 (t, J 7·0 Hz, NCO$_2$CH$_2$CH$_3$), and 8·78 (t, J 7·0 Hz, NHCO$_2$CH$_2$CH$_3$).

Thermal Decomposition of the Adduct (3a).—A solution of the adduct (3a) (4 g) in xylene (500 ml) was heated under reflux for 15 h. Evaporation of the solvent gave a pale brown residue which on repeated trituration with hot light petroleum left diethyl hydrazine-NN'-dicarboxylate (2·0 g, 91%). The petroleum extracts were evaporated to dryness to give a solid (1·9 g) which was chromatographed on silica gel. Elution with light petroleum (b.p. 80—100°)-benzene (3 : 2) gave a white solid (1·0 g) of the dimer (6B) (1-phenyl-cis-2,3,3a,3bξ,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a:3',2'-c]-quinoline) which crystallised from ethanol, m.p. 159° (Found: C, 82·9; H, 7·85; N, 9·4. $C_{20}H_{22}N_2$ requires C, 82·7; H, 7·65; N, 9·65%), λ$_{max.}$ (hexane) 249 (log ε 4·33) and 292 nm (3·71). Further elution with light petroleum (b.p. 80—100°)-benzene (2 : 3) gave a white solid of the 3b-epimer (6A) (0·8 g) as needles from ethanol, m.p. 171°

TABLE 4

Properties of the products from ozonation of anilines (9)

Product		M.p. (°C)	Found (%)			Formula	Required (%)			N.m.r. (CDCl$_3$) of (6); H-IIb	
No.	R		C	H	N		C	H	N	τ	$J_{3a,11b}$ (Hz)
(5)	H	67—68°									
(5)	F	66	67·05	5·6	7·8	$C_{10}H_{10}FNO$	67·0	5·8	7·8		
(5)	Cl	75	61·2	5·1	7·2	$C_{10}H_{10}ClNO$	61·4	5·1	7·2		
(5)	NO$_2$	89	57·8	4·8	13·6	$C_{10}H_{10}N_2O_3$	58·25	4·85	13·6		
(6A)	H	171 ‡								4·93	6·75
(6B)	H	159 ‡								5·58	8·5
(6A)	F	195	73·2	6·1	8·5	$C_{20}H_{20}F_2N_2$	73·6	6·2	8·6	4·97	7·0
(6B)	F *									5·65	9·0
(6A)	Cl	228	66·8	5·5	7·9	$C_{20}H_{30}Cl_2N_2$	66·9	5·6	7·8	4·95	7·0
(6B)	Cl *									5·62	8·5
(6A)	NO$_2$	255	63·0	5·4	14·6	$C_{20}H_{20}N_4O_4$	63·2	5·3	14·7	†	
(6B)	NO$_2$	245	62·9	5·3	14·8	$C_{20}H_{20}N_4O_4$	63·2	5·3	14·7	⊥	

* Not separated.　† Insoluble.　‡ See text.

aniline (1 mol. equiv.) was heated in cyclohexane solution for an appropriate time. Evaporation of the solvent gave a red oil which precipitated the required adduct (2) or (3) on trituration with light petroleum. Recrystallisation from light petroleum gave the following pure compounds which all showed absorptions at 3280 (NH), 1750 and 1680 (C=O), and 755 and 695 cm^{-1} (mono- and ortho-di-substituted (a) diethyl N-(N-methylanilinomethyl)hydrazine-NN'-dicarboxylate (2), m.p. 72° (lit.,[2] 73—75°) (90% after 2 h reflux), τ (CDCl$_3$) 2·78br (NH), 2·78 (m, 2 × ArH), 3·20 (m, 3 × ArH), 4·90br (s, NCH$_2$), 5·83 (q, J 7·0 Hz, NHCO$_2$CH$_2$), 5·89 (q, J 7·0 Hz, NCO$_2$CH$_2$), 7·01 (s, NMe), 8·76 (t, J 7·0 Hz, NCO$_2$CH$_2$CH$_3$), and 8·83 (t, J 7·0 Hz, NHCO$_2$CH$_2$CH$_3$); (b) diethyl N-(1-phenylpyrrolidin-2-yl)-hydrazine-NN'-dicarboxylate (3a), m.p. 109° (80% after 2 h reflux) (Found: C, 59·8; H, 7·2; N, 13·5. $C_{16}H_{23}N_3O_4$ requires C, 59·8; H, 7·2; N, 13·1%), τ (CDCl$_3$) 2·81br (NH), 2·81 (m, 2 × ArH), 3·32 (m, 3 × ArH), 4·05 (m, CH), 5·78 (q, J 7·0 Hz, NHCO$_2$CH$_2$), 5·88 (q, J 7·0 Hz, NCO$_2$CH$_2$), 6·62 (m, α-CH$_2$), 7·35 (m, 4β-CH$_2$), 8·73 (t, J 7·0 Hz, NCO$_2$CH$_2$CH$_3$), and 8·80 (t, J 7·0 Hz, NHCO$_2$CH$_2$CH$_3$); (c) diethyl N-(N-phenylmorpholin-3-yl)-hydrazine-NN'-dicarboxylate (3b), m.p. 118° (36% after

(Found: C, 82·8; H, 7·65; N, 9·4%), λ$_{max.}$ (hexane) 251 (log ε 4·38) and 308 nm (3·85).

Reduction of N-Phenyl-2-pyrrolidone.—A suspension of lithium aluminium hydride (2·5 g) in ether (25 ml) was slowly added with stirring to a solution of N-phenyl-2-pyrrolidone (20 g) in ether (400 ml) at 0°. After a further 5 h at 0° the mixture was treated with aqueous sodium hydroxide solution and the ethereal layer separated, dried, and evaporated. The residue was chromatographed as above on silica gel to give the dimers (6A) and (6B) identical with those reported above.

Ozonation of the Anilines (9), (10), and (11).—The aniline (2·0 g) in an appropriate solvent (150 ml) at the required temperature was treated with ozonised oxygen (4 mole ozone per mole of amine). In the case of water-immiscible solvents the reaction mixture was washed with water, dried, and evaporated. When methanol was used, the solvent was removed and the residue dissolved in chloroform and treated as before. The crude products were chromatographed on silica gel, eluting first with light petroleum to give unchanged material, and then successively

[9] P. L. Julian and H. C. Printz, J. Amer. Chem. Soc., 1949. 71, 3206.

with light petroleum–benzene to give the dimers (6A) and (6B), with benzene or benzene–chloroform to give the pyrrolidone (5), and finally with ethyl acetate to remove any other products. The results are summarised in Table 4.