higher (and possibly sometimes of the opposite sense) had crystalline MPCA been used instead of crude extract. To check upon the generality of this hypothesis, several previously reported MPCA asymmetric oxidations were repeated using crystalline **1**. The results of these comparisons and of the asymmetric synthesis of several other oxaziridines, again using different compositions of the MPCA isomers, appear in Table III. In general, the use of crystalline **1**, rather than the crude extract, increases optical yield by 50–100%. In some instances, optical yields are still fairly low. However, the 60% optical yield obtained in the case of oxaziridine **4** (Table II) demonstrates that crystalline **1** sometimes functions as quite an efficient chiral oxidant.

Acknowledgment. This work has been partially supported by grants from the National Institutes of Health and the National Science Foundation.

Registry No.—**1**, 16211-85-1; **2**, 62058-73-5; **3**, 39923-07-4; (−)-**4**, 62058-74-6; (±)-**4**, 62058-75-7; camphoric acid, 5394-83-2; *p*-bromobenzylidene-*N*-*tert*-butylamine, 62058-76-8.

References and Notes

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(2) U. Folli, D. Iarossi, and F. Montanari, *J. Chem. Soc. C*, 1372 (1968).
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(4) R. C. Ewins, H. B. Henbest, and M. A. McKervey, *Chem. Commun.*, 1085 (1967).
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(8) (a) F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 1694 (1968); (b) *Gazz. Chim. Ital.*, **103**, 681 (1973).
(9) C. Belzecki and D. Mostowicz, *J. Chem. Soc., Chem. Commun.*, 244 (1975).
(10) N. A. Milas and A. McAlevy, *J. Am. Chem. Soc.*, **55**, 349 (1933).
(11) The originally reported melting point of 49–50 °C may indicate that Milas and McAlevy had in hand a mixture of **1** and **2**.
(12) A sample of this material with 39.6% ee had $[\alpha]^{23}_{D}$ −29.7° (tentatively assigned the 2*S*,3*R* configuration).[13]
(13) An NMR method for the determination of absolute configuration and enantiomeric composition of oxaziridines is being reported elsewhere.

Reduction of Amides and Lactams to Amines by Reactions with Phosphorus Oxychloride and Sodium Borohydride[1]

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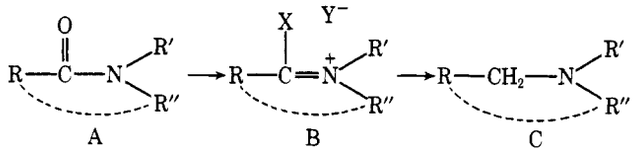
Received November 16, 1976

Practical and convenient procedures were developed for the reduction of carboxamides and lactams to corresponding secondary and tertiary amines by reactions with $POCl_3$ and $NaBH_4$. Optimum conditions for formation of *O*-phosphoryl (or chloroimonium) intermediates and their reductions are structure dependent. Selective reductions of amide esters and amide nitriles to amino esters and amino nitriles were obtained.

The reduction of amides and lactams to amines with lithium aluminum hydride[2] sometimes proceeds with difficulty, particularly where secondary amines are to be generated, due to NH proton acidity and formation of insoluble complexes. The use of forcing reaction conditions such as reduction in refluxing *N*-ethylmorpholine[3] does not always overcome this barrier. Alternatively, diborane may be used for such reductions but other susceptible groups, such as double bonds, can then also react. Selective reduction of amido esters to amino esters[4] with diborane usually requires a deactivated pentachlorophenyl or an aromatic acid ester. The recently developed reduction of amides to amines by a sodium borohydride–carboxylic acid complex[6] could also not be used for selective reduction of the lactam ester **18**, with both carbonyl groups lost in the reduction product. However, selective reduction of lactams in the presence of ester functions can be achieved by conversion to thiolactams and desulfurization with Raney nickel[7,8] or by formation of alkoxyimonium intermediates with triethyloxonium fluoroborate and subsequent reduction with sodium borohydride.[9,10]

Since the latter procedures suffer from being either cumbersome, experimentally difficult, or costly, a more practical preparative method for reduction of N-mono- and disubstituted amides and lactams was required, preferably with selectivity for these functional groups. This was found in the reactions of lactams and amides with $POCl_3$ followed by $NaBH_4$.[11] While a previous report of the reaction of *N*-benzylpiperidone with $POCl_3$ and subsequent borohydride reduction had indicated only dimeric amine products,[12] we found that good yields of the monomeric amine could be obtained from this lactam as well as from other examples listed in Table I.

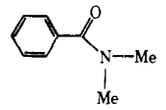
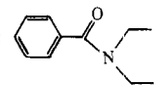
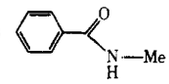
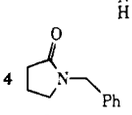
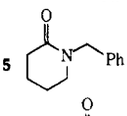
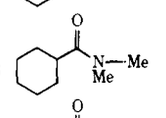
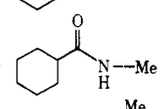
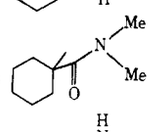
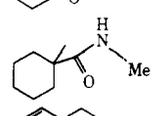
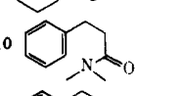
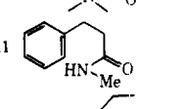
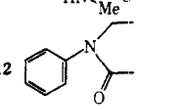
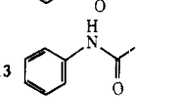
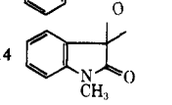
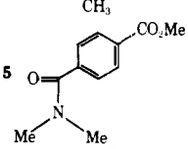
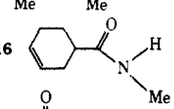
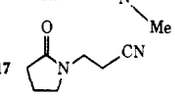
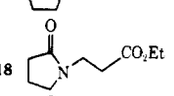
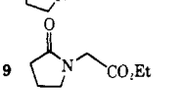
The reaction sequence proceeds from an amide or lactam A to an imino derivative B where X and/or Y can be $OPOCl_2$



and/or Cl. While an *O*-phosphoryl derivative may be favored over the corresponding imino chloride, in analogy to observations in related studies,[13–16] either or both types of derivatives may be produced in the reaction medium. Formation of the imonium derivatives was followed by NMR spectra which showed a downfield shift of 0.8–1.0 ppm for protons α to nitrogen in tertiary amides and 0.4–0.6 ppm in secondary amides. It was also noted that alkyl groups in *N*,*N*-dialkylamides, usually nonequivalent in $CDCl_3$ solutions, became equivalent in $POCl_3$ solutions (owing to amide protonation by HCl, which could be suppressed by addition of pyridine). This equivalence was lost as the amide A was converted to the imino derivative B in *N*,*N*-dimethyl- and -diethylbenzamide and in *N*,*N*-dimethylcyclohexanecarboxamide, but not in the other examples shown in Table I. Observation of these conversions provided minimal reaction times for the first step of the reaction sequence.

Table I lists the times necessary for complete reaction of amides with $POCl_3$, plus 20–30%. A dependence of the reaction rate on steric and electronic structural parameters may be

Table I

	Conditions for complexation[a]		Conditions for reduction[b]		
Amide	Time, h	Amide concn, M	Equiv of $NaBH_4$	Time, h	Yield,[c] %
1 	3	0.5	2.7	1	89
2 	2	0.5	3.2	1.25	88
3 	4.5	0.5	3.2	1	87
4 	0.25 0.33	1.0 1.0	3.2[d] 2.8[d]	1.0 0.25	84 72[e,f]
5 	0.25	1.0	3.0[d]	1.0	70[e]
6 	3.5	1.0	3.1	1.5	86
7 	0.5	1.0	3.1	1.0	83
8 	5.0[g]	1.1	3.0[d]	1.0	80
9 	2.5[h]	1.0	3.9	1.25	85
10 	0.33 0.33 1.0[g]	1.0 1.0 1.0	3.0[d] 2.0[d] 2.0[d]	1.0 0.25 0.25	78[e] 71[e,f] 38[e,f]
11 	0.25 0.33 2.0[g]	1.0 1.0 1.0	3.0[d] 2.0[d] 2.0[d]	1.0 0.25 0.25	72[e] 74[e,f] 51[e,f]
12 	6.0	1.0	3.1	1.0	41[m]
13 	10.0	1.0	3.0	1.0	68[f]
14 	24.0[i]	1.0			
15 	3.0[j]	1.0	3.0	1.0	75[k]
16 	0.75	1.0	2.0[d,l]	0.25	76
17 	0.33	1.0	2.0[d,l]	0.25	66
18 	0.33 0.33	1.0 1.0	2.0[d,l] 1.5[d,l]	0.25 0.25	71 59
19 	0.33	1.0	2.0[d,l]	0.25	50

[a] Reaction at room temperature. [b] Reaction at room temperature, about 0.25 M in glyme. [c] Determined by gas chromatographic analysis. [d] Recrystallized $NaBH_4$ used. [e] Dimer also isolated; see text. [f] Isolated yield. [g] At 69–72 °C. [h] At 50–55 °C. [i] Reaction at reflux with no substantial complexation being observed. [j] At 45–40 °C. [k] This selective reduction could be carried out in glyme. The amine–borane complex is difficult to decompose; refluxing in methanolic HCl for 8 h was required. [l] Reaction with about 0.7 M $NaBH_4$ in ethanol. [m] Transalkylation–dealkylation products also isolated.

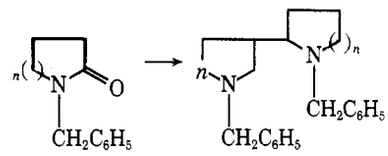
noted. Increasing substitution α to the carbonyl group decreases the reaction rate and secondary amides generally react faster than corresponding tertiary amides (**6** vs. **7**; **8** vs **9**). Aliphatic amides react faster than benzamides, which in turn react more rapidly than anilides. Addition of pyridine increased the rates of imonium derivative formation considerably over those shown in Table I (see Table II). This is of particular value for systems lacking protons α to the carbonyl group which generally react slowly (i.e,, **1–3, 8**) but pyridine addition should be chosen with caution for others owing to the possibility of increased dimerization reactions (see below).

Evaporation of excess phosphorus oxychloride and addition of glyme and sodium borohydride resulted in reduction of the imino derivatives B to amines C. This reduction could also be achieved with diborane. Since it was found in a control experiment that diborane is generated by addition of sodium borohydride to phosphorus oxychloride and the crude imonium derivatives were suspect of containing residual $POCl_3$, or of generating HCl, reduction of the imino intermediates by diborane had to be considered as a possible general reaction course in the amide reduction sequence.

Diborane was also generated from excess sodium borohydride on workup of the reduction reactions with aqueous hydrochloric acid and resulted in formation of amine borane adducts. These adducts, which are stable in aqueous solution, were readily decomposed by heating for 20 min in aqueous acid.[17,18] In order to establish direct reduction of the imino derivatives by sodium borohydride and to optimize selective reductions of amides and lactams with preservation of ester, nitrile, and olefinic groups, it was desirable to avoid the presence of diborane. This was achieved by addition of sodium borohydride, as an ethanolic solution, to the imino derivatives in glyme. Examples **16–19,** Table I, showed no reduction of the second functional group and only traces of aminoboranes when this procedure was used. It may also be noted that reduction of the imonium derivative of *N,N*-dimethylbenzamide in glyme by a limited amount of diborane was not affected by a severalfold excess of cyclopentene (a 92% yield of amine was obtained), but that no reduction of the corresponding amide was found under those conditions, owing to exclusive hydroboration of the olefin.

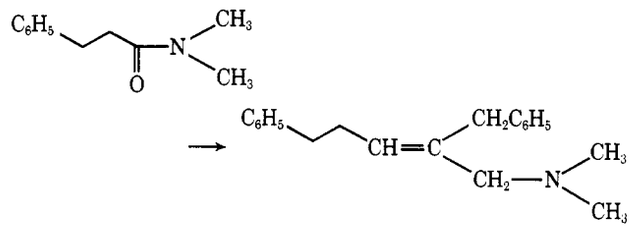
Amides or lactams with protons α to the carbonyl carbon can be expected to show equilibrium of an initially generated imonium intermediate B with a corresponding heterosubstituted enamine D[19] or imine E. Formation of enamines D is increased by addition of pyridine and can then be readily seen in NMR spectra (see Table II, $6^{b,f}$). The enamines D and imines E are subject to electrophilic alkylation by the imonium intermediate B, thus giving rise to dimeric products F–H[20] which are then subject to reduction by sodium borohydride. While addition of pyridine was found to increase the rate of imonium derivative formation, such addition may thus also lead to lower yields of monomeric amines, depending on the structure of the amide or lactam.

Even without pyridine this initial dimerization accounts for a decreased yield of some monomeric amines. Thus *N*-benzylpyrrolidone gave 7% of the dimeric amine **20a,** *N*-benzylpiperidone gave 8% of the homologue **20b,** *N,N*-dimethyl-3-phenylpropionamide gave 9% of the three dimers **21–23** in ratios of 81:17:2, and *N*-methyl-3-phenylpropionamide gave a 7% yield of amine **24.**

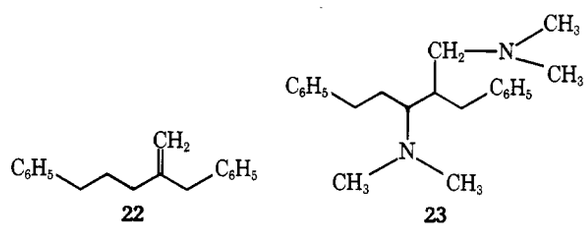


20a, $n = 1$

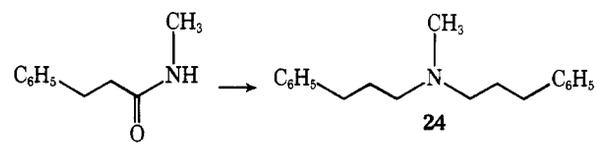
b, $n = 2$



21



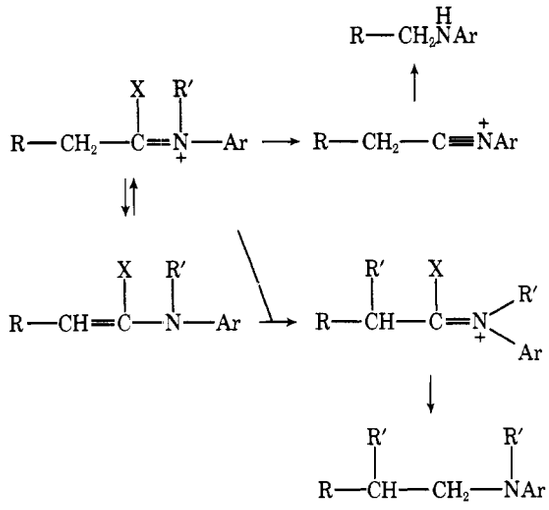
22 **23**



24

The dimerization can be observed during reaction of the amides with $POCl_3$ by the increased complexity of NMR spectra of the crude imonium intermediates B and by isolation of N,N^1-dibenzyl-3-(4-aminovaleryl)-2-piperidone[12] when the *N*-benzylpiperidone reaction is quenched with water rather than reduced with sodium borohydride. Heating *N,N*-dimethylphenylpropionamide in $POCl_3$ for 1 h and subsequent reduction changed the ratio of monomeric to dimeric products (**21–23**) from 70:9% to 39:40%. Dimerization may also take place during the reduction, i.e., following the known reaction of piperideins[21] in the piperidone reduction. In any event dimerization is inhibited by a second substituent α to the carbonyl group (e.g., in cyclohexanecarboxamides).

A further limit to the $POCl_3$–$NaBH_4$ reduction sequence is found in amides with *N*-aryl substituents. Stabilization of charge on nitrogen promotes dealkylation[22–24] and transalkylation reactions. Thus *N*-ethylacetanilide (**12**) gave only 39% of *N,N*-diethylaniline, 52% of *N*-ethylaniline, and 6% of *N*-butyl *N*-ethylaniline.



Experimental Section

Imonium Derivative Formation. The conditions necessary for imonium derivative formation were determined in separate experiments. In most cases room temperature gave practical reaction rates. The most notable feature observed with the NMR spectra was a downfield shift of protons α to nitrogen upon complexation. Table II lists the observed NMR data for several amides and lactams and their imonium derivatives, from which one can judge the progress of the reaction.[25] As seen in Table II, addition of pyridine gave a large increase in reaction rates. The following procedure for the complexation of *N,N*-dimethylcyclohexanecarboxamide (**6**) is representative. To 2 mL of phosphoryl chloride was added 304 mg (2 mmol) of amide **6**. The reaction mixture was sealed and stirred at room temperature. At appropriate intervals aliquots were withdrawn for NMR spectra.

Reduction of *N*-Benzylpyrrolidone (4). The following procedure for the reduction of *N*-benzylpyrrolidone (**4**) is representative of the general procedure followed for reduction of amides and lactams in *glyme*.

A. *N*-Benzylpyrrolidone (0.81 g, 4.7 mmol) was added to 5 mL of phosphoryl chloride at room temperature. The solution was stirred for 15 min and excess phosphoryl chloride then removed at 20 °C (10 mm). The resultant oil was placed under high vacuum for 20 min to remove residual phosphoryl chloride and then dissolved in 20 mL of glyme. The solution was cooled in ice and sodium borohydride[26] (0.56 g, 15 mmol) was added with vigorous stirring. The reaction mixture was warmed to 20 °C, stirred for 1 h, and cooled in ice and 10 mL of 10% hydrochloric acid was added dropwise. The glyme was evaporated, water added to bring the volume to 30 mL, and the mixture refluxed for 20 min. After extraction with ether, sodium hydroxide (3.0 g) was added to the aqueous solution followed by extraction with ether. The basic extracts were dried over potassium carbonate and concentrated. Addition of benzene and a measured amount of dimethylaniline (internal standard) allowed for determination of the yield by GC analysis. One component corresponding to an 84% yield of *N*-benzylpyrrolidine was found.

B. In a similar experiment starting with 0.91 g (5.2 mmol) of *N*-benzylpyrrolidone the basic extract was distilled to 70 °C (0.005 mm) to give 0.61 g (72%) of *N*-benzylpyrrolidine. A residual 0.13 g of oil was tube distilled (160–200 °C block temperature, 0.005 mm) to give 0.10 g of colorless oil. Preparative TLC of the oil on alumina (chloroform–ethyl acetate, 7:2) and elution of the first major band (R_f 0.7) gave 0.06 g of oil which displayed the spectral characteristics of **20a**: IR 2785 cm^{-1}, no carbonyl; NMR δ 7.30 (m, 10 H), 4.1–3.1 (m, 4 H), 3.0–1.5 (m, 14 H); mass spectrum *m/e* (rel intensity) 320 M^+ (72), 229 (100), 186 (81), 172 (62), 160 (94), 91 (90). Picrate (ethanol) mp 151–153 °C.

Anal. Calcd for $C_{34}H_{34}N_8O_{14}$: C, 52.44; H, 4.40; N, 14.39. Found: C, 52.30; H, 4.47; N, 14.26.

Reduction of *N*-Ethyl-β-carboethoxypyrrolidone (18). The following procedure is representative of the general procedure followed to effect selective reductions using *ethanolic* sodium borohydride solution. The imonium derivative prepared from 1.03 g (5.50 mmol) of lactam ester and 5 mL of phosphoryl chloride, as described in the general procedure, was taken up in 3 mL of glyme at room temperature and cooled to 0 °C. To the glyme solution was added 16 mL of 0.7 M sodium borohydride in ethanol (11.0 mmol) at such a rate as to maintain a vigorous reaction. After stirring for 15 min at room temperature 10 mL of 2% hydrochloric acid was added. The ethanol was evaporated, water added, and the solution extracted with ether. The ether extracts were dried over magnesium sulfate and concentrated to give 0.37 g of oil: IR 2360, 2250, 1735 cm^{-1}; weak bands indicative of the presence of small quantities of amine borane adduct. Most of the extract consisted of ethyl esters of phosphoric acid: IR 3500–3200, 1000–1100 cm^{-1}; NMR strong quartets δ 4.3–4.0. The aqueous acidic solution was brought to pH 10.5–11.0 by addition of 30 mL of 20% potassium carbonate while cooling in an ice–salt bath at 0 °C. The cold aqueous solution was extracted with ether and the extracts dried over magnesium sulfate and concentrated at 1 atm. Addition of toluene and *N*-ethylaniline (internal standard) allowed determination of the yield by GC analysis. One component corresponding to a 71% yield of *N*-ethyl-β-carboethoxypyrrolidine was found. GC comparison of the reaction mixture with the corresponding amino alcohol indicated that negligible reduction of the ester had occurred. The determination of dimerization products was not undertaken in this case.

Reduction of *N*-Benzylpiperidone (5). Reduction of 0.95 g (5.0 mmol) of *N*-benzylpiperidone using the general procedure described above gave a 70% yield of *N*-benzylpiperidine by GC analysis. No other volatile products were evident. Distillation of the reaction mixture under high vacuum left a residual solid, 0.13 g, which was recrystallized from ethanol to give 0.07 g of dimeric amine **20b**: mp 116–118 °C (lit. 117–118 °C);[12] IR (KBr) 2790, 2750 cm^{-1}; NMR δ 7.26 (m, 10 H), 4.20, 3.98, 3.22, 3.0 (dd, 2 H), 3.50 (s, 2 H), 3.2–2.6 (m, 4 H), 2.2–1.3 (m, 14 H); mass spectrum *m/e* (rel intensity) 348 M^+ (23), 257 (43), 186 (17), 174 (100). Picrate (ethanol) mp 194–195 °C (lit. mp 194–195 °C).[12]

Reduction of *N,N*-Dimethyl-β-phenylpropionamide (10). A. The amide (1.85 g, 10.5 mmol) was added to 10 mL of phosphoryl chloride and heated to 69–72 °C for 1 h. Excess phosphoryl chloride was removed as described in the general procedure. The imonium derivative was taken up in 20 mL of glyme and cooled to 0 °C, and 0.79

Table II. NMR Signals of Protons α to Nitrogen during Imonium Derivative Formation

Compd	Chemical shift, ppm: Amide	Chemical shift, ppm: Imonium derivative	$\Delta\delta$, ppm	Reaction time, h[a]
1	(s) 3.14	(bd) 4.0	0.86	2.25
1[b]	(s) 3.0	(s) 3.94	0.94	0.5
1[c]	(s) 3.0	(bs) 3.92	0.92	0.8
2	(q) 3.4	(d/q) 4.3	0.90	1.5
3	(s) 3.16	(s) 3.68	0.52	2.0
3[b]	(d) 3.02	(s) 3.52	0.50	0.25
4[d]	(s) 4.5[e]	(s) 5.48	0.98	0.2
5[d,f]	(s) 4.6[e]	(s) 5.60	1.0	0.2
6	(s) 3.0	(d) 3.92	0.92	2.0
6[b,f]	(d) 3.14	(s) 2.84	−0.30	2.0
7	(s) 3.02	(s) 3.42	0.40	0.5
8[g]	(s) 2.96	(s) 3.92	0.96	4.0
8	(s) 2.98	(s) 3.94	0.96	24.0[h]
8[b]	(s) 3.0	(s) 4.08	1.08	25.0
9	(s) 3.0	(s) 3.40	0.40	9.0
9[i]	(s) 3.0	(s) 3.40	0.40	2.0
9[b]	(d) 2.94	(s) 3.52	0.58	0.15
10[f]	(s) 3.0	(s) 3.92	0.92	0.3
11	(d) 2.8[e]	(s) 3.35	0.55	<0.25
12[f]	(q) 3.82	(q) 4.58	0.76	~3.5
13[f]	(s) 2.38	(s) 2.68	0.30	~4–5
13[b]	(s) 2.12	(s) 2.52	0.40	0.2
14	(s) 3.26			24.0[j]
14[b]	(s) 3.26			15.0[j]
15	(bs) 2.92	(s) 3.80	0.88	4.5
15[i]	(bs) 3.00	(s) 3.90	0.90	2.0
16	(s) 2.90	(s) 3.30	0.40	0.5

[a] For completion of complexation at room temperature. [b] 1 equiv of pyridine added. [c] 0.1 equiv of pyridine added. [d] Value for benzyl protons. [e] Taken from NMR spectra of sample run in $CDCl_3$. [f] Spectra became more complex over extended period. [g] Run at 69–72 °C. [h] 30% completion by integration. [i] At 45–50 °C. [j] Run at reflux with no substantial complexation observed.

g (21.0 mmol) of sodium borohydride was added. After the mixture was stirred at room temperature for 15 min it was worked up as described in the general procedure. Tube distillation of the basic extract up to 70 °C (0.1 mm), with the collector cooled to −78 °C, gave 0.64 g (38%) of monomeric amine. The residue was distilled at 140–160 °C (0.01 mm) to give 0.57 g of distillate. This distillate was chromatographed on a 20 g silica gel column. Elution with 60 mL of ethyl acetate gave 0.04 g (3.3%) of **22:** IR no carbonyl, N–H, or O–H stretch; NMR δ 7.30 (m, 10 H), 4.88 (d, 2 H), 3.40 (s, 2 H), 2.60 (t, 2 H), 2.1–1.5 (m, 4 H); mass spectrum *m/e* (rel intensity) 236 M^+ (44), 145 (85), 132 (57), 117 (92), 105 (74), 104 (100), 92 (40), 91 (85).

Elution with 90 mL of ethyl acetate–ethanol (10:1) gave 0.51 g (35%) of **21:** IR 3090, 3060, 2820, 2765, 1600 cm^{-1}; NMR δ 7.30 (m, 10 H), 5.60 (t, 1 H), 3.44 (bs, 2 H), 2.8–2.4 (m, 6 H), 2.1 (bs, 6 H); mass spectrum *m/e* (rel intensity) 279 M^+ (100), 188 (86), 174 (45), 143 (83), 128 (48), 91 (67), 58 (65); picrate (ethanol) mp 105–106 °C.

Anal. Calcd for $C_{26}H_{28}N_4O_7$: C, 61.4; H, 5.5; N, 11.0. Found: C, 61.2; H, 5.5; N, 10.8.

Further elution with ethyl acetate–ethanol (10:1) gave 0.03 g of oil consisting of a mixture of **21** and **23.** Ethyl acetate–ethanol (10:2) gave 0.02 g of the third product **23:** mass spectrum *m/e* (rel intensity) 324 M^+ (3), 279 (8), 188 (90), 163 (62), 162 (100), 91 (72), 58 (64). Elution with ethyl acetate–ethanol (1:1) gave 15 mg of a mixture of third product **23** and a fourth product. Preparative TLC of this mixture (ethyl acetate–ethanol, 1:1) gave 8 mg of the fourth component. Identical mass spectra for the third and fourth reaction products indicate stereoisomeric structures **23.**

B. The imonium derivative was prepared from 1.81 g (10.2 mmol) of amide at room temperature as described in the general procedure. It was reduced under the conditions described in part A. Distillation gave 1.19 g (71%) of monomeric amine. The residue, upon distillation, gave 0.13 g of oil, which upon chromatography as described in part A gave 20 mg of **22,** 96 mg of **21,** and 2 g of **23,** as a mixture of isomers.

Reduction of *N*-Methyl-β-phenylpropionamide (11). A. The imonium derivative was prepared from 1.62 g (9.9 mmol) of amide by the general procedure. Its reduction in glyme with 0.75 g (19.8 mmol) of sodium borohydride for 15 min at room temperature was followed by normal workup. Tube distillation of the basic extract (up to 80 °C, 0.1 mm) with cooling of the collector to −78 °C gave 1.10 g (74%) of monomeric amine. Tube distillation of the residue (130–155 °C, 0.1 mm) gave 0.13 g of oil consisting of one major component by TLC. Preparative TLC (ethyl acetate–ethanol, 10:1.5) gave 96 mg (7.2%) of **24:** IR 2750–2800 cm^{-1}; NMR δ 7.48 (m, 10 H), 2.72 (t, 4 H), 2.42 (t, 4 H), 2.28 (s, 3 H), 1.84 (m, 4 H); mass spectrum *m/e* (rel intensity) 267 M^+ (50), 162 (100), 91 (77), 58 (77), metastable ion at ~20.5 and 98.3. Spectra obtained with a sample of **24** prepared by lithium aluminum hydride reduction of *N*-methyl *N*-3-phenylpropyl-β-phenylpropionamide were found to be identical with those described above.

B. The amide (1.63 g, 10.0 mmol) was added to 10 mL of phosphoryl chloride and heated to 60–72 °C for 1 h. Excess phosphoryl chloride was removed as described in the general procedure. The imonium derivative was reduced as described in part A. Distillation gave 0.76 g (51%) of monomeric amine. Tube distillation of the residue gave 0.18 g of oil which upon chromatography gave 0.14 g (10%) of **24.**

Reduction of *N*-Ethylacetanilide (12). Reduction of 0.80 g (4.9 mmol) of amide was carried out as described in the general procedure. GC analysis of the crude product on a Carbowax 20M column at 150 °C indicated two volatile components, one of which corresponded to *N,N*-diethylaniline. The basic mixture was chromatographed on a 15-g silica gel column. Elution with 60 mL of petroleum ether (bp 60–90 °C)–chloroform (10:2) gave 0.28 g of oil, which was a mixture of two components. The oil was applied to three preparative TLC plates and developed four times in petroleum ether–chloroform (10:1). Elution of the topmost band afforded 0.04 g of *N*-butyl-*N*-ethylaniline: NMR δ 7.5–6.5 (m, 5 H), 3.57–3.10 (m, 4 H), 1.75–0.90 (m, 10 H); mass spectrum *m/e* (rel intensity) 177 M^+ (90), 135 (60), 134 (100), 106 (89), 77 (73), metastable ion at 101.5. The second component of the mixture was *N,N*-diethylaniline. Elution with 30 mL of petroleum ether–chloroform (10:2) gave 0.12 g of a mixture of *N,N*-diethylaniline and a third component. Elution with another 120 mL of the same solvent mixture provided 0.25 g of the third component, which was found to be identical with *N*-ethylaniline by comparison of NMR spectra and GC retention times.

Reduction of *N,N*-Dimethyl-*p*-carbomethoxybenzamide (15). The amido ester (0.62 g, 3.0 mmol) was added to 3 mL of phosphoryl chloride and heated to 45–50 °C for 3 h. Excess phosphoryl chloride was removed and the imonium derivative reduced as described in the general procedure. The reduction was stopped by addition of 5 mL of methanolic hydrogen chloride, concentration of the solution, addition of a further 20 mL of methanolic hydrogen chloride, and heating to reflux for 8 h. Further workup as described in the general procedure gave methyl *p*-(*N,N*-dimethylaminomethyl)benzoate in 75% yield, as determined by GC analysis. A trace of the amino alcohol could be detected by TLC.

Imonium Derivative Reduction in Presence of Cyclopentene. *N,N*-Dimethylbenzamide (0.76 g, 5.0 mmol) was treated with phosphoryl chloride in the usual manner. A solution containing the imonium derivative, 20 mL of tetrahydrofuran, and 2.20 g (32.3 mmol) of cyclopentene was cooled in an ice bath. Borane (10 mL, 1.0 M) solution in tetrahydrofuran was added over 2 min. The mixture was warmed to room temperature and allowed to stir for 1 h. Workup according to the general procedure and GC analysis of the extract indicated a 92% yield of *N,N*-dimethylbenzylamine. Borane and *N,N*-dimethylbenzamide under the same conditions, and without initial reaction with phosphoryl chloride, gave no amine.

Borane Adduct of *N,N*-Dimethylbenzylamine. A. To *N,N*-dimethylbenzylamine (1.74 g, 12.9 mmol) in 30 mL of glyme was added 13 mL of 1 M borane solution in tetrahydrofuran at 0 °C. The mixture was allowed to stir for 20 min at room temperature, followed by addition of 10 mL of 2% hydrochloric acid, and evaporation of the ethereal solvents. The aqueous solution was extracted three times with ether. The ether extracts were washed with brine, dried over magnesium sulfate, and concentrated to give 1.93 g of amine borane adduct: IR 2460, 2410, 2365 cm^{-1}; NMR δ 7.26 (m, 5 H), 3.94 (s, 2 H), 2.50 (s, 6 H); mp 101–102 °C (lit. mp 104–105 °C).[28]

B. To a solution of *N,N*-dimethylbenzylamine (0.80 g, 5.9 mmol) 20 mL of glyme, and 0.57 g (15 mmol) of sodium borohydride cooled in an ice bath was added dropwise 10 mL of 10% hydrochloric acid. The mixture was worked up as described in part A to give 0.62 g of amine borane adduct.

***N*,1-Dimethylcyclohexanecarboxamide (9).** To 275 mL of benzene saturated with methylamine at 0 °C was added dropwise a solution of 22.6 g (0.14 mmol) of 1-methylcyclohexanecarbonyl chloride[29] in 25 mL of benzene. The mixture was stirred for 2 h at room temperature. Water was added and the layers separated. The benzene layer was washed with brine, dried over magnesium sulfate, and concentrated to give a colorless oil which crystallized upon standing. The solid was recrystallized from ether–hexane to give 20.0 g (92%) of **9:** mp 74–75 °C; IR 3456, 1645 cm^{-1}; NMR δ 5.98 (b, 1 H), 2.82 (d, 3 H), 1.90 (m, 2 H), 1.6–1.2 (m, 8 H), 1.14 (s, 3 H).

Anal. Calcd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.8; H, 11.3; N, 9.1.

***N*-methyl-1-methylcyclohexylmethylamine.** To 7.3 g (0.19 mol) of lithium aluminum hydride in 300 mL of ether was dropped a suspension of 15.0 g (0.1 mol) of *N*,1-dimethylcyclohexanecarboxamide (**9**) in 50 mL of ether. The mixture was refluxed for 20 h. Excess lithium aluminum hydride was destroyed by consecutive addition of 7 mL of water, 7 mL of 15% sodium hydroxide, and 21 mL of water with vigorous stirring. The white suspension was filtered and washed with ether. The ether solution was concentrated, taken up in 70 mL of 10% hydrochloric acid, and extracted with ether. The aqueous solution was basified with 12.0 g of sodium hydroxide and extracted four times with ether. The latter ether extracts were dried over potassium carbonate, concentrated, and distilled to give 12.0 g (88%) of oil: bp 76–78 °C (17 mm); IR 2790 cm^{-1}; NMR δ 2.56 (s, 3 H), 2.48 (s, 2 H), 1.7–1.2 (m, 10 H), 1.08 (bs, 1 H), 0.96 (s, 3 H). Benzoyl derivative, mp 75–76 °C.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.3; H, 9.5; N, 5.7. Found: C, 78.5; H, 9.5; N, 5.5.

Formation of *N,N*-Dimethyl-*p*-carbomethoxybenzamide (15). To 200 mL of benzene saturated with dimethylamine at 0 °C was added dropwise a solution of 30 mL of benzene and *p*-carbomethoxybenzenecarbonyl chloride prepared from 21.8 g (0.1 mol) of potassium methyl terephthalate.[30] The mixture was stirred for 1 h at 0 °C followed by addition of 5% hydrochloric acid. The benzene layer was washed with water, 5% sodium carbonate, and brine, dried over magnesium sulfate, and concentrated to give 20 g of solid. Recrystallization from ether–methanol gave 12.6 g (61%) of **15:**[31] IR 1712, 1625 cm^{-1}; NMR δ 8.0–7.4 (dd, 4 H), 3.90 (s, 3 H), 3.1–2.9 (bd, 6 H).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8. Found: C, 63.7; H, 6.4; N, 6.6.

***N*-Methyl-*N*-3-phenylpropyl-β-phenylpropionamide.** A solution of 3.0 g (20 mmol) of β-phenylpropionic acid in 40 mL of benzene was cooled to 0 °C, and 2.8 g (22 mmol) of oxalyl chloride was added slowly with stirring. After 10 h at room temperature the benzene and excess oxalyl chloride were evaporated. The crude acid chloride in 10 mL of toluene was added slowly with stirring to a solution of 3.0 g (20 mmol) of *N*-methyl-3-phenylpropylamine, 2.0 g (20

mmol) of triethylamine, and 70 mL of toluene, cooled to 0 °C. After 12 h at room temperature water was added and the layers separated. The toluene layer was washed with 2% hydrochloric acid, 5% sodium hydroxide, and brine, dried over magnesium sulfate, and concentrated to give 5.4 g (96%) of yellow oil. This oil was used without further purification in the preparation of *N*-methyl-*N*-3-phenylpropyl-3-phenylpropylamine (**24**). An analytical sample was prepared by tube distillation (0.003 mm, 175–185 °C): IR 1640 cm^{-1}; NMR δ 7.24 (m, 10 H), 3.44 (t), 3.20 (t), 2.90 (d) (7 H total), 2.7–2.40 (m, 4 H), 1.90 (m, 2 H).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.83; H, 8.33; N, 4.72.

Reduction of Acetanilide (13). Acetanilide (1.35 g, 10 mmol) was reduced according to the general procedure. Tube distillation of the basic extracts (up to 70 °C, 0.005 mm) gave 0.81 g (68%) of monomeric amine. GC analysis (Carbowax 20M, 150 °C) indicated the presence of a trace of diethylaniline and another unidentified component. Tube distillation of the residue (160–180 °C, 0.005 mm) gave 0.15 g of oil. Preparative TLC of the oil on alumina (hexane–chloroform–ethyl acetate, 10:2:1) gave 0.10 g (8.2%) of 2,3-di-*N*-phenylaminobutane (R_f 0.5): IR 3390, 1600 cm^{-1}; NMR δ 7.2 (m, 4 H), 6.7 (m, 6 H), 3.8–3.4 (m, 4 H), 1.12 (dd, 6 H), two protons in the 3.8–3.4 region would be exchanged with deuterium oxide; mass spectrum *m/e* (rel intensity) 240 M^+ (50), 121 (92), 120 (100), 77 (69). Benzamide, mp 254–255 °C.

Anal. Calcd for $C_{30}H_{28}N_2O_2$: C, 80.32; H, 6.29; N, 6.24. Found: C, 79.95; H, 6.38; N, 6.04.

A second component (R_f 0.2), 7 mg (<1%), had spectral data identical with that of *N*,*N*^{1}-diphenylacetamidine: IR (KBr) 3275–3200, 1630, 1585 cm^{-1}; mass spectrum *m/e* (rel intensity) 210 M^+ (92), 118 (100), 77 (84), 51 (92); mp 131–132 °C (lit. mp 134–135 °C).[32]

Registry No.—**1**, 611-74-5; **2**, 1696-17-9; **3**, 613-93-4; **4**, 5291-77-0; **5**, 4783-65-7; **6**, 17566-51-7; **7**, 6830-84-8; **8**, 61930-85-6; **9**, 61930-86-7; **10**, 5830-31-9; **11**, 940-43-2; **12**, 529-65-7; **13**, 103-84-4; **14**, 20200-86-6; **15**, 21928-11-0; **16**, 54385-24-9; **17**, 7663-76-5; **18**, 61930-87-8; **19**, 61516-73-2; **20a**, 61930-88-9; **20a** picrate, 61930-89-0; **20b**, 24333-47-9; **20b** picrate, 61930-90-3; **21**, 61930-91-4; **21** picrate, 61930-92-5; **22**, 61930-93-6; *R**,*R**-**23**, 61930-94-7; *R**,*S**-**23**, 61930-95-8; **24**, 61930-96-9; phosphoryl chloride, 10025-87-3; *N*-butyl-*N*-ethylaniline, 13206-64-9; *N*,*N*-dimethylbenzylamine, 121-69-7; borane, 13283-31-3; *N*,*N*-dimethylbenzylamine borane adduct, 61967-06-4; 1-methylcyclohexanecarbonyl chloride, 2890-61-1; *N*-methyl-1-methylcyclohexylmethylamine, 61930-97-0; *N*-methyl-1-methylcyclohexylmethylamine benzoyl derivative, 61930-98-1; *p*-carbomethoxybenzenecarbonyl chloride, 7377-26-6; *N*-methyl-*N*-3-phenylpropyl-β-phenylpropionamide, 61930-99-2; β-phenylpropionic acid, 501-52-0; *N*-methyl-3-phenylpropylamine, 23580-89-4; 2,3-di-*N*-phenylaminobutane, 59540-56-6; 2,3-di-*N*-phenylaminobutane benzamide derivative, 61931-00-8; *N*,*N*′-diphenylacetamidine, 621-09-0.

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