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STERIC EFFECTS IN THE SYSTEM Ph.C(R)<

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Abstract—Increasing size of the group R leads to the formation of a higher proportion of ketone in the methylation of amines of the type, Ph·CH(NH_2)·R, and of a higher proportion of secondary amine in the aluminohydride reduction of oximes of the type, Ph·C(:NOH)·R.

THE production of carbonyl compounds as by-products in the Clarke–Eschweiler methylation of primary amines has from time to time been reported: Gent and McKenna[1] obtained 11% of cholestan-6-one from 6β-aminocholestane, but no ketone from the 6α-epimer. Ketones have also been obtained, in the yields indicated, from the following amines: bornylamine and neobornylamine[2] (15%), *endo*-2-amino-bicyclo-(2,2,1)heptane[3] (20%), *endo*-5-amino-bicyclo(2,2,1)hept-2-ene[3] (24%), 5-aminobicyclo(2,2,2)oct-2-ene[4] (20%), cyclohexylamine[2] (1%), and cyclopentylamine[2] (2·3%). It will be noted that the highest yields of carbonyl compound have been obtained from amines where the amino group is subject to some degree of steric over crowding, and it was pointed out by Gent and McKenna that their results

TABLE 1. CLARKE–ESCHWEILER ALKYLATION OF Ph·CH(NH_2)·R

Group R	% Yield of tertiary amine	% Yield of ketone
CH_3	67	11
Pr^i	51	21
Bu^t	67	20
$(C_2H_5)_2CH$-	57	34
$CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH$-	73	10

suggested that steric compression favoured the production of ketonic by-product. Neobornylamine does indeed give the same amount of ketone as bornylamine, but owing to the *gem*-dimethyl groups on the bridge the environment of the amino group in the former compound is nearly as crowded as in the case of the second. We have investigated a series of amines $C_6H_5CH(NH_2)R$ and the results obtained from methylation experiments are given in Table 1. Two points emerge from these results, first the total yield increases with increasing size of R, and secondly the proportion of ketone also increases with the size of R. If one takes as a measure of the effective size of R the rate of acid catalysed esterification[5] of R.COOH, then with one exception the

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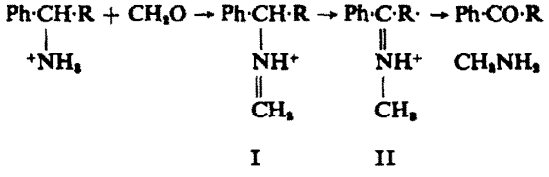
[2] J. McKenna and J. B. Slinger, *J. Chem. Soc.* 2759 (1958).
[3] W. E. Parham, W. T. Hunter, R. Hanson and T. Lahr, *J. Amer. Chem. Soc.* 74, 5646 (1952).
[4] C. A. Grob, H. Kny and A. Gagneux, *Helv. Chim. Acta* 40, 130 (1957).
[5] K. L. Loening, A. B. Garrett and M. S. Newman, *J. Amer. Chem. Soc.* 74, 3929 (1952).

proportional yields of ketone follow the same order. The exception is of course that the yield of isobutyrophenone is too high; the lower yield of cyclobutyl phenyl ketone, which is in line with the rate of esterification[6] of cyclobutane carboxylic acid, may be explained by the "pinning back" of the methylene branches leading to a smaller effective bulk.

Formulating in more general terms the mechanism proposed by Clarke[7] for the production of benzaldehyde from dibenzylamine, the formation of the carbonyl by-product may be represented as follows:



I II

It has been pointed out[8] that formation of tertiary amine can involve only ion I since, for example, optically active 2-amino-1-phenylpropane[8] is methylated without racemization, and the bornylamines and the aminocholestanes are methylated without epimerization; the isomerized ion II must therefore be entirely converted to ketone. The effect of the group R may be rationalized on the basis of this suggested mechanism, since with increasing size of R there will be increasing strain ("back strain"[9]) in ion I which will be relieved in ion II when the carbon atom bonded to R becomes trigonal.

The formation of secondary amine as a by-product in the hydride reduction of acetophenone oxime was first reported by Smith.[10] Lyle and Troscianiec[11] found that electron-releasing substituents in the *para* position of the acetophenone promoted the rearrangement process, and electron-withdrawing substituents inhibited it. Rerick[12] *et al.* extended the work to other ketoximes, benzaldoxime and to hydroxylamines, and Petrarca[13] confirmed the rearrangement for the cases of *syn* and *anti* benzaldoximes. Rerick[12] also demonstrated that a much greater proportion of rearranged product was obtained when a mixture of LAH and $AlCl_3$ was used as reducing agent. With the exceptions of cyclopentanone oxime and cyclodecanone oxime substantial amounts of secondary amine have been obtained only from those oximes which possess an aromatic residue as potential migratory group, and only phenyl migration has been observed. Both the *syn* and *anti* oximes of isobutyrophenone[12,13] gave the same products in the same proportions; a similar lack of stereospecificity was noted in the cases of the benzaldoximes.[13]

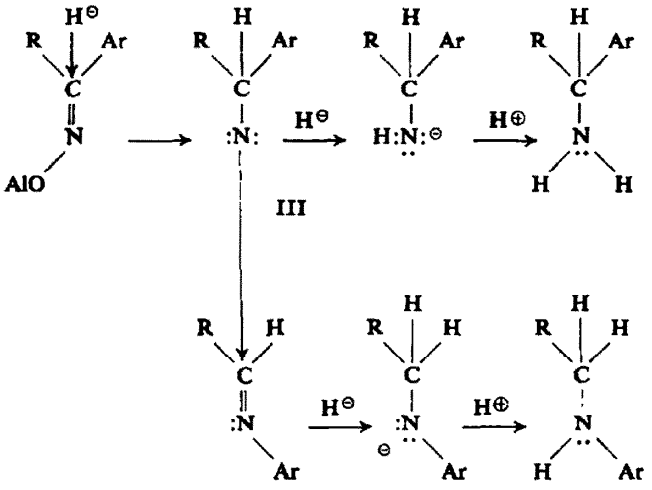
It has been suggested that hydroxylamines are intermediates in the LAH reduction of oximes[12,14] and of tertiary alicyclic nitro[15] compounds, which also leads to mixtures

[6] B. V. Bhide and J. J. Sudborough *J. Ind. Inst. Sci.* **8A**, 89 (1925).
[7] H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *J. Amer. Chem. Soc.* **55**, 4571 (1933).
[8] A. C. Cope, E. Ciganek, L. J. Fleckenstein and M. A. P. Meisinger, *J. Amer. Chem. Soc.* **82**, 4651 (1960).
[9] H. C. Brown, *J. Chem. Soc.* 1261 (1956).
[10] D. R. Smith, M. Maienthall and J. Tipton, *J. Org. Chem.* **17**, 294 (1952).
[11] R. E. Lyle and H. J. Troscianiec, *J. Org. Chem.* **20**, 1757 (1955).
[12] M. N. Rerick, C. H. Trottier, R. A. Daignault and J. D. Defoe, *Tetrahedron Letters* **10**, 629 (1963).
[13] A. E. Petrarca and E. M. Emery, *Tetrahedron Letters* **10**, 635 (1963).
[14] H. K. Hall, *J. Org. Chem.* **29**, 3139 (1964).
[15] H. J. Barber and E. Lunt, *J. Chem. Soc.* 1187 (1960).

of primary and secondary amines though with a much larger proportion of the latter.

We prefer to represent the reduction of hydroxylamines with LAH as proceeding via the complex Ar.CHR.NHOal, from which the aluminate ion is displaced either by attack of hydride ion (formation of primary amine) or by migration of Ar with its electrons (formation of secondary amine). Barber's[15] suggestion that the hydroxylamine is protonated by aluminohydride ion seems fundamentally unsound.

As reduction of hydroxylamines by aluminohydride leads to the same products as the reduction of oximes it is reasonable to regard the hydroxylamines as being intermediates in the latter process, but the reduction of the oximes can also be formulated as proceeding via a Schiff's base type intermediate (IV)



III

IV

The electronic state of the nitrogen atom in the postulated intermediate (III) is similar to that suggested for the intermediate in the Curtius reaction and similar rearrangement processes.[16] Such a mechanism accounts for the formation of $Ph{\cdot}NH{\cdot}CD_2{\cdot}CH_3$ in the reduction of acetophenone oxime with LAD and also for the effects of substituents in the aromatic ring as observed by Lyle[11] and Petrarca.[13]

We examined the reduction of a series of ketoximes of the type

$$Ph{\cdot}C(=NOH){\cdot}R,$$

to see if the nature of R in any way affected the tendency towards rearrangement.

The separation of the geometrical isomers of isobutyrophenone oxime has been described[17] but we were unable to repeat this work; attempted separations by chromatography on alumina, and partition chromatography between benzene and hydrogen phthalate buffer supported on silica were also unsuccessful. Our experiments consequently were conducted with a mixture of *syn* and *anti* isomers, but in view of the results of Rerick this could make no difference. We made an approximate estimation of the composition of the mixture by submitting it to Beckmann rearrangement

[16] E. S. Wallis and J. F. Lane, "*Organic Reactions*" (Editor, R. Adams) Vol. III; p. 273, Chapman and Hall, London.

[17] H. M. Kissman and J. Williams, *J. Amer. Chem. Soc.* **72**, 5323 (1950).

and reducing the resulting mixture of amides with hydride. This gave N-phenylisobutylamine (75%) and N-benzylisopropylamine (25%).

The m.p. reported[18] for cyclobutyl phenyl ketoxime is 91–93°; we obtained the value of 76–77° for material prepared by the method of Lapworth[19] and also in pyridine solution. It consisted largely of *anti*-phenyl oxime as a sample, when treated as described above, gave N-phenylcyclobutylmethylamine (97%) mixed with only 3% of isomeric secondary amine.

The oxime of 3-benzoylpentane has been reported[20–22] to melt at 90°, though Rothstein[23] stated that it had an indefinite m.p. We were able to obtain two sets of crystals melting at 79° and 87° respectively. Both samples could be rearranged exclusively to 3-benzoylaminopentane both by benzene sulphonyl chloride and sodium hydroxide in boiling aqueous acetone and by phosphorus pentachloride at 0°. The isomerization of oximes under the conditions of the Beckmann rearrangement has been observed,[24] but the use of benzenesulphonyl chloride and alkali is regarded as unlikely to cause prior interconversion of the isomeric oximes. Furthermore we observed that the samples of the oxime, m.p. 79°, were transformed, after being kept for some days, into the material m.p. 87°; and it was possible to convert the oxime, m.p. 87°, into material, m.p. 79°, by recrystallization from aqueous methanol. Hence both sets of crystal are regarded as allotropic forms of the *syn*-phenyl oxime; the form, m.p. 79°, being the metastable modification.

The results obtained are tabulated together with relevant results reported by other investigators. The results do suggest a generally increasing tendency towards rearrangement as R becomes larger, but they do not follow any precisely defined progression and strongly suggest that other factors are more important in determining the proportion of secondary amine. In particular, there is a considerable discrepancy between the results for the reduction of isobutyrophenone oxime reported by Rerick[12] and by Petrarca[13] and those obtained by ourselves. Discrepancies, though less marked, also exist between the results of Lyle and Troscianiec[11] and those of Rerick.[12] Also, although we believe that both samples of the oxime of 3-benzoylpentane are of of the *syn*-phenyl isomer, we did not obtain a constant proportion of secondary amine from them as the Table shows. We are not disposed to ascribe the difference in behaviour between these oximes of benzoylpentane to differences in molecular geometry of the starting materials both for the reasons given above, and also in view of the observations of Rerick[12] on the *syn* and *anti* oximes of isobutyrophenone. Pivalophenone oxime (*syn*-phenyl) was not reduced under the standard conditions employed (3 hr at the b.p. of ether). It could be reduced in boiling tetrahydrofuran to give a poor yield of primary amine free of rearranged product, and a large amount of gummy material.

Rerick[12] analysed their mixtures of rearranged and un-rearranged amines by vapour phase chromatography, while we separated them by means of a buffer and solvent extraction as did both Lyle and Troscianiec[11] and Petrarca.[26] The difference in method

[18] W. H. Perkin and W. Sinclair, *J. Chem. Soc.* **61**, 36 (1892).
[19] A. Lapworth and V. Steele, *J. Chem. Soc.* **99**, 1884 (1911).
[20] A. Haller and E. Bauer, *Ann. Chim.* **16**, 340 (1921).
[21] M. Tiffenau and J. Levy, *Bull. Soc. Chim. Fr.* [4], **33**, 745.
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[24] R. F. Brown, N. M. van Gulick and G. H. Schmid, *J. Amer. Chem. Soc.* **77**, 1094 (1955).
[25] E. Graziano, *Gazz. Chim. Ital.* **45 II**, 393 (1915).

of analysis cannot account for the difference between our results and those of Rerick,[12] since the recovery of the separated bases was good, always better than 80% and in some cases 90%.

TABLE 2. REDUCTION OF Ph·C(:NOH)·R WITH LAH

Oxime	% Yield of crude bases	Amine composition		% Recovery of crude bases after separation
		Primary, %	Secondary, %	
Acetophenone		77[10]	23	72
		66[11]	34	75
		80[12]	20	
		62[13]	38	
Propiophenone (*anti*-phenyl)[24]		65	35	81
		*77[10]	23	62
n-Butyrophenone (*anti*-phenyl)[25]		72	28	83
Iso-butyrophenone				
75% *anti*, 25% *syn*	95	61	39	88
80% *anti*, 20% *syn*		30[12]	70	
25% *anti*, 75% *syn*		30[12]	70	
syn			70[12]	
anti			70[12]	
Pivalophenone (*syn*-phenyl)[24]	0	0	0	—
Benzoylcylobutane (97% *anti*-phenyl)	92	56	44	80
2-Benzoylbutane (*anti*-phenyl)	88	36	64	88
3-Benzoylpentane Mixture	90	32	68	94
oxime, m.p. 79°	90	32	68	90
oxime, m.p. 87°	90	45	55	96

* 1·5 mole hydride per mole oxime.

EXPERIMENTAL

Reductive methylation of Ph·CH(NH_2)·R. The following amines were prepared by heating the appropriate ketone (1 mole) with the ammonium formate–formamide reagent,[27] prepared from ammonium carbonate (220 g) and 90% formic acid (225 g), at 180–185° for 6 hr. The reaction mixture was diluted with water, the formyl derivative was extracted into ether and then hydrolysed with 5N HCl (200 ml). The HCl was extracted with ether before isolating the base.

α-Phenylisobutylamine (70%), b.p. 95°/14 mm (lit.,[28] 102–104°/20 mm) [*N-(α-phenylisobutyl)-phthalamic acid*, m.p. 183–184°, flat needles, from aq. EtOH. (Found: C, 72·55; H, 6·6; N, 4·9. $C_{18}H_{15}NO_3$ requires: C, 72·7; H, 6·4; N, 4·7%].

α-Phenylneopentylamine (74%), b.p. 101–102°/11 mm (lit.,[25] 49°/0·5 mm, 115–115·5°/22 mm),[29] benzoyl derivative, m.p. 148–149° (lit.,[29] 149°).

α-Ethyl-n-butyrophenone. α-Ethylbutyryl chloride was prepared from redistilled diethylacetic acid (B.D.H.) (116 g) and $SOCl_2$ (180 g) as previously described[30] and purified by fractional distillation, yield 113 g (84%), b.p. 136–138° (lit.,[30] 138–142°). The acid chloride (105 g) was reacted with benzene

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[28] R. Perez Ossorio and F. Gomez Herrara, *Anales real Soc españa Fis y Quim. Madrid* **50B**, 875 (1954).
[29] A. Brodhag and C. R. Hauser, *J. Amer. Chem. Soc.* **77**, 3028 (1955).
[30] W. H. Miller, A. M. Dessert and G. W. Anderson, *J. Amer. Chem. Soc.* **70**, 502 (1948).

(380 ml) and $AlCl_3$ (125 g) to give, after fractional distillation, the ketone (91·5 g, 66%), b.p. 138°/26 mm (lit.,[28] 117–118°/10 mm) [2,4-dinitrophenylhydrazone, m.p. 129° (orange needles, from EtOH, then from benzene–light petroleum, m.p. unchanged after chromatography on bentonite-kieselguhr) (lit.,[28] 15°). (Found: C, 60·6; H, 5·6; N, 15·8. Calc. for $C_{16}H_{20}N_4O_4$: C, 60·7; H, 5·7; N, 15·7%)].

2-Ethyl-1-phenylbutylamine. α-Ethyl-n-butyrophenone (20 g) was heated at 200° for 8 hr with the formamide–formic acid reagent prepared from ammonium carbonate (26 g) and 90% formic acid (28 g) to give *N-formyl-2-ethyl-1-phenylbutylamine* (23 g), m.p. 71–72° from light petroleum, b.p. 60–80°. (Found: C, 75·6; H, 9·4; N, 6·5. $C_{13}H_{19}NO$ requires: C, 76·0; H, 9·3; N, 6·8%), hydrolysis of which gave *2-ethyl-1-phenylbutylamine* (11 g, 55%), b.p. 127°/15 mm. (Found: C, 81·2; H, 10·8; N, 7·8. $C_{12}H_{19}N$ requires: C, 81·3; H, 10·8; N, 7·9%). This amine (0·35 g) in pyridine (2 ml) at 0° treated with toluene-*p*-sulphonyl chloride (0·42 g) gave *N-toluene-p-sulphonyl-2-ethyl-1-phenylbutylamine* (0·34 g), m.p. 102–103° thick, short needles from aqueous MeOH, then from light petroleum, b.p. 60–80°. (Found: C, 68·5; H, 7·3; N, 4·3. $C_{19}H_{25}NO_2S$ requires: C, 68·8; H, 7·6; N, 4·2%.)

α-Phenylcyclobutylmethylamine (80%), b.p. 70°/0·6 mm,[21] picrate,[21] m.p. 199° dec.

The primary amines were methylated[23] by heating at 100° for 12 hr with 37% formaldehyde (2·2 moles) and 90% formic acid (5 moles) per mole of amine. The product was treated with conc. HCl (1·2 equiv) and extracted with ether before isolating the base. The ether extract was washed with 2N NaOH, water and dried (Na_2SO_4).

TABLE 3. REDUCTIVE METHYLATION OF Ph·CH(NH_2)·R

Amine Ph·CH(NH_2)·R	% Yield of tertiary amine	% Yield of ketone	Derivative of ketone
Me	67[a]	11	2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 241–242°.
Pr^i	51[b]	21	2,4-dinitrophenylhydrazone,[26] m.p. and mixed m.p. 163°
Bu^t	67[c]	20	Oxime, m.p. and mixed m.p. 164–165° (lit.,[29] 165–166°).
Et_2CH	57[d]	34	2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 129°.
$CH_2 \cdot CH_2 \cdot CH_2 \cdot CH$	73[e]	10	2,4-dinitrophenylhydrazone m.p. and mixed[21] m.p. 178–179°.

[a] Picrate, m.p. 137–138° (yellow plates from EtOH and from ethyl acetate–ethanol) (lit.,[28] 140–140·5°, 138–139°,[24] 139·5–140°[25]).

[b] Picrate, m.p. 156° (lit.,[26] 156–157°).

[c] *N,N-Dimethyl-α-phenylneopentylamine*, b.p. 112°/16 mm (Found: C, 81·2; H, 10·9; N, 7·45. $C_{12}H_{21}N$ requires: C, 81·6; H, 11·1; N, 7·3%). *Picrate*, m.p. 140–140·5°, yellow needles, from EtOH. (Found: C, 54·1; H, 5·6; N, 13·3. $C_{18}H_{24}N_4O_7$ requires: C, 54·3; H, 5·8; N, 13·3%.)

[d] *N,N-Dimethyl-2-ethyl-1-phenylbutylamine*, b.p. 132°/20 mm (Found: C, 81·7; H, 11·3; N, 7.2. $C_{14}H_{23}N$ requires: C, 81·9; H, 11·3; N, 6·8%). *Picrate*, m.p. 192–193°, yellow needles, from n-butanol. (Found: C, 54·9; H, 5·8; N, 12·8; $C_{20}H_{26}N_4O_7$ requires: C, 55·3; H, 6·0; N, 12·9%.)

[e] picrate, m.p.[21] 119–120°.

Reduction of oximes with LAH. Results are summarized in Table 4.

Composition of isobutyrophenone oxime, m.p. *and* lit.[19] m.p. 58–60°. A slurry of PCl_5 (6 g) in benzene (50 ml) was added in portions, during 0·5 hr, to the oxime (5 g) in ether (25 ml) at 0°. The

[21] S. H. Graham and A. J. S. Williams, in the press.

[23] M. L. Moore, "*Organic Reactions*" (Editor, R. Adams) Vol. V; p. 323. Chapman and Hall, London.

[24] A. C. Cope, T. T. Foster and P. H. Towle, *J. Amer. Chem. Soc.* **71**, 3929 (1949).

[25] C. G. Overberger, M. A. Klotz and H. Mark, *J. Amer. Chem. Soc.* **75**, 3186 (1953).

[26] A. T. Stewart and C. R. Hauser, *J. Amer. Chem. Soc.* **77**, 1098 (1955).

[28] D. P. Evans, *J. Chem. Soc.* 788 (1936).

mixture was allowed to stand at room temp for 2·5 hr and was then poured onto ice. The usual working up gave brownish crystals (4·7 g, 94%) which were dissolved in ether and added to LAH (1·75 g) in ether (100 ml). The mixture was refluxed for 2 hr and allowed to stand overnight. After adding 10N NaOH (20 ml) the ether was decanted and the residue extracted with ether. The combined ether extract was extracted with 2N HCl. This HCl-extract was separated[36] into N-phenylisobutylamine (1·79 g), toluene-*p*-sulphonyl derivative, m.p. and mixed m.p. 123–124° (lit.[37] 122–123°, 124–126°[38]), and N-benzylisopropylamine[39] (0·61 g), N-*toluene*-p-*sulphonyl*-N-*benzylisopropylamine*, m.p. and mixed m.p. 97–98°, needles from aqueous MeOH, then from petrol. (Found: C, 67·1; N, 6·8; N, 4·7; $C_{17}H_{21}NO_2S$ requires: C, 67·3; H, 7·0; N, 4·6%.)

Benzoylcyclobutane ketoxime. The ketone was prepared by the method of Perkin,[18] b.p. 136°/16 mm (lit.,[40] 122°/10 mm). The ketone (14·6 g), hydroxylamine hydrochloride (9 g) and anhydrous sodium acetate[19] (15 g) were refluxed for 2 hr in absolute EtOH (65 ml). On pouring the mixture into water (600 ml) the oxime crystallized (15·4 g, 90%), m.p. 75–77°. Distillation (b.p. 125°/0·5 mm) or sublimation (100°/0·2 mm), followed by recrystallization from petrol, gave the oxime, m.p. 76° (lit.[18] m.p. 91°). (Found: C, 75·7; H, 7·5; N, 7·9. Calc. for $C_{11}H_{13}NO$: C, 75·4; H, 7·5; N, 8·0%.)

The published method[18] gave oxime (80%) identical with that described above.

To the oxime (5 g) in ether (60 ml) at 0° PCl_5 (6 g) was added, in portions, during 0·75 hr. The mixture was allowed to stand at room temp for 4 hr and then poured onto ice. The ethereal extract was washed with dil NaOHaq, water and dried (Na_2SO_4). Recrystallization of a portion of this material gave N-phenylcyclobutanecarbonamide. This ethereal solution was added to LAH (2 g) in ether (120 ml) and refluxed for 2·5 hr. After stirring for a further 0·5 hr 10N NaOH (20 ml) was added. The ether extract was decanted and the residue washed with ether. The combined ethereal extract was extracted with 2N HCl (25 ml). Water was added to dissolve a sparingly soluble hydrochloride. The aqueous layer contained 2·40 g of bases which were separated[36] into strong base (0·08 g) and N-phenylcyclobutylmethylamine (2·26 g), identified as its toluene-*p*-sulphonyl derivative (crude yield 76%, m.p. 97–100°), recrystallized from benzene–petrol (1:5), m.p. and mixed m.p. 100–101°.

N-*Phenylcyclobutylmethylamine.* N-phenylcyclobutanecarbonamide was prepared from cyclobutane carbonyl chloride, benzene and aniline; it recrystallized as needles from petrol m.p. 113° (lit.[41] 111°).

This anilide (8·5 g) in ether (300 ml) was added to LAH (3 g) in ether (100 ml). The mixture was stirred and refluxed for 2 hr and then allowed to stand overnight. NaOHaq (40 ml) was added, the ethereal solution was decanted and the residue extracted with ether. The combined ether extracts were extracted with 2N HCl (60 ml) giving a sparingly soluble hydrochloride which was dissolved in water. Basification of the aqueous extract, drying and distillation gave N-*phenylcyclobutylmethylamine* (5·1 g, 65%), b.p. 138–139°/15 mm. (Found: C, 81·7; H, 9·3; N, 9·0. $C_{11}H_{13}N$ requires: C, 81·95; H, 9·4; N, 8·7%) [N-*toluene*-p-*sulphonyl*-N-*phenylcyclobutylmethylamine*, m.p. 100–101°, white plates, from EtOH. (Found: C, 68·4; H, 6·8; N, 4·2; $C_{18}H_{21}NO_2S$ requires: C, 68·55; N, 6·7; N, 4·4%.)

α-*Methylbutyrophenone oxime.* The ketone[42] (15 g), b.p. 118°/18 mm (lit.,[43] 114°/12 mm), gave oxime (10·6 g), m.p. 55–65°, after recrystallization from light petroleum (b.p. 60–80°). Further recrystallization from light petroleum gave 9·7 g, m.p. 84–87°, and then from aqueous MeOH, 7 g, m.p. 86–87° (lit.,[44] 82°).

This oxime (m.p. 86–87°; 1·77 g) in acetone (40 ml) and water (10 ml) was refluxed with benzenesulphonyl chloride (1·84 g) and NaOH (0·45 g) for 4 hr. Acetone was distilled from the neutralized mixture and the residue dissolved in ether, which was then washed and dried (Na_2SO_4). Evaporation of ether gave crude anilide (1·5 g), which after dissolving in hot light petroleum (b.p. 60–80°, 3 ml) gave needles (0·85 g), m.p. 105–106°, after softening at 100°. Further recrystallization from benzene–light petroleum (b.p. 60–80°: 12 ml, 1:10) gave needles (0·78 g) m.p. 107–108·5°, m.p. unchanged

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when mixed with authentic α-methylbutyranilide, m.p. 110–111°, needles from light petroleum, b.p. 60–80°. (lit.[45] 110°, 104–105° [46]).

α-Ethyl-n-butyrophenone oxime. The ketone (25 g) in absolute EtOH (100 ml) was refluxed for 1·5 hr with hydroxylamine hydrochloride (15 g) and anhydrous sodium acetate (25 g). On pouring into water oxime (13 g), m.p. 60–80°, was obtained. Two recrystallizations from light petroleum (b.p. 60–80°), then from cyclohexane, followed by recrystallization from MeOH gave Fraction A, m.p. 75–84°.

Dry HCl[47] was passed through a solution of Fraction A (0·5 g) in dry ether (10 ml) at 0°. The white solid which separated was collected and washed with ether (0·4 g), m.p. 101–102°. This solid was stirred with ether and sodium acetate (1·5 g) in water (10 ml). Evaporation of ether and recrystallization from light petroleum (b.p. 60–80°) gave oxime, m.p. 87° (lit.,[20–22] 90°). (Found: C, 75·3; H, 8·7; N, 7·4. Calc. for $C_{11}H_{17}NO$: C, 75·3; H, 9·0; N, 7·3%.) A sample of this oxime melted at 79° after recrystallization from aqueous MeOH, unchanged after recrystallization from light petroleum (b.p. 60–80°).

Evaporation of the petrol mother liquors from which Fraction A was isolated gave oxime, m.p. 79°, needles, from MeOH. (Found: C, 75·25; H, 9·0; N, 7·4%.) A sample of this oxime was found to melt at 86° after storage in the absence of light.

The oxime (m.p. 79°; 0·25 g) in ether (6 ml), treated with HCl at 0°, gave a white solid (0·15 g), m.p. 84°. The ethereal filtrate contained a sticky solid. After treatment with aqueous sodium acetate and recrystallization from light petroleum (b.p. 60–80°) the product melted at 74–79°.

The solid (m.p. 84°) was insoluble in water but rapidly dissolved on addition of ether. Evaporation of ether gave oxime, m.p. 86–87°, before recrystallization: recrystallization from aqueous MeOH, m.p. 79°.

Evaporation of the cyclohexane mother liquors from which Fraction A was isolated gave oxime, m.p. 79–86° (from MeOH). This solid (1·66 g) gave oxime hydrochloride (1·78 g), m.p. 101–102°, which on treatment with aqueous sodium acetate gave oxime (1·1 g), m.p. 87°, after recrystallization from petrol.

Beckmann rearrangement

(a) *With benzenesulphonyl chloride and sodium hydroxide.* The oxime (m.p. 87°; 0·5 g), benzenesulphonyl chloride (0·47 g), NaOH (0·26 g), in acetone (10 ml) and water (1 ml) were refluxed for 4 hr. Removal of acetone and dilution with water gave 3-benzoylaminopentane, m.p. 97–99°, plates, from aqueous EtOH (charcoal): after further recrystallization from light petroleum (b.p. 60–80°), needles, m.p. and mixed m.p. 99–100°.

Under the same conditions the oxime (m.p. 79°) rearranged to the same amide, m.p. and mixed m.p. 97°, the product being more difficult to purify.

(b) *With phosphorus pentachloride.* PCl_5 (0·3 g) was added in portions to the oxime (m.p. 87°; 0·2 g) in ether (15 ml) at 0°. The mixture was allowed to stand at room temp with intermittent shaking. After 1 hr only a trace of chloride remained, ice water was added, and the ether solution worked up to give 3-benzoylaminopentane, m.p. and mixed m.p. 98·5–99·5°, needles, from light petroleum (b.p. 60–80°).

The oxime (m.p. 79°) also rearranged under these conditions to the same amide, m.p. and mixed m.p. 97°, after recrystallization from light petroleum.

3-Benzoylaminopentane. 98% Formic acid (77 g) was added in portions to diethyl ketone (29 g) and formamide (107 g). The mixture was refluxed gently for 20 hr, cooled, diluted with water and extracted with ether. After washing with NaOHaq, water and drying, the ether extract gave a light brown oil (21·6 g) which was refluxed with 5N HCl (66 ml) for 1 hr. The resulting solution was extracted with ether and the ether extract rejected. Basification of the HCl, ether extraction, drying and careful fractional distillation gave 3-aminopentane (2·6 g), b.p. 86° (lit.,[48] 90°), picrate (from EtOH or or ethyl acetate) m.p. 168° (lit.,[49] 168°).

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Benzoyl chloride (1 ml) was added, with cooling, to the amine (0·5 g) in pyridine (2 ml). HCl was added after 1 hr, the product was collected, washed with NaOHaq and recrystallized from aqueous EtOH, then from benzene–petrol to give feathery needles of *3-benzoylaminopentane* (0·6 g), m.p. 99–100°. (Found: C, 75·3; H, 8·75; N, 7·1. $C_{18}H_{17}NO$ requires: C, 75·3; H, 9·0; N, 7·3%.)

The oximes were reduced[11] with LAH (5·5 moles per mol oxime) in boiling ether for 3 hr and the mixture bases separated as described by Petrarca.[26]

Microanalyses were carried out by Drs. Weiler and Strauss, Oxford.

TABLE 4. YIELDS OF BASES FROM HYDRIDE REDUCTIONS OF Ph·C(:NOH)·R

Ph·C(:NOH)·R	Recovered oxime	Yield of mixed bases	R·CH(NH$_2$)·Ph	R·CH$_2$·NH·Ph
Et (3 g, 0·02 mole)				
m.p. and lit.[50] m.p. 53°	0·1 g (3·3%)	2·13 g (81%)	1·38 g[a]	0·75 g[b]
Pr^n(3·26 g, 0·02 mole)				
m.p. and lit.[51] m.p. 49–50°	0·2 g (6·2%)	2·34 g (83%)	1·62 g[c]	0·62 g[d]
Pr^i (3·26 g, 0·02 mole)	—	2·85 g (95%)	0·98 g[e]	1·54 g[f]
$\overbrace{CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH}$ (3·5 g, 0·02 mole)	—	3 g (92%)	1·35 g[h]	1·05 g[i]
Bu^n (3·54 g, 0·02 mole)	0·25 g (7%)	2·5 g (88%)	0·80 g[j]	1·42 g[k]
Bu^t (5 g)‡				
m.p. and lit.[52] m.p. 165–166°	gum		0·68 g[l]	—
Et$_2$CH				
2·86 g, m.p. 60–80°*	0·97 g (84%)	1·56 g (90%)	0·39 g[m]	0·81 g[n]
2·58 g, m.p. 87°	0·71 g (40%)	1·65 g (90%)	0·67 g[m]	0·84 g[n]
2·86 g, m.p. 79°	1·20 g (42%)	1·36 g (87%)	0·39 g[m]	0·81 g[n]

* Reaction time, 9 hr.

‡ Failed to reduce in ether. Boiling THF, 6 hr.

[a] Benzenesulphonyl† deriv. (94%), m.p. 79–80° (lit.,[53] 81°).

[b] Benzenesulphonyl deriv. (96%). m.p. 52–53° (lit.,[53] 54°).

[c] Benzoyl deriv., m.p. 127–127·5° (lit.,[54] 128°).

[d] Toluene-*p*-sulphonyl deriv., softens 47°, m.p. 54°. Authentic sample, m.p. 54°. Mixed m.p. 54° after softening at 47°. (lit.,[55] 54°, 52°[56] 47°[57]).

[e] N-(α-Phenylisobutyl)phthalamic (60%), m.p. and mixed m.p. 183–184°. N-Benzylisopropylamine[58] absent.

[f] Toluene-*p*-sulphonyl deriv., (90%) m.p. 124° (lit., 122–123°,[27] 124–126°[59]).

[h] Toluene-*p*-sulphonyl deriv.† (98%), m.p. and mixed[31] m.p. 171–172°.

[i] Toluene-*p*-sulphonyl deriv. (98%), m.p. and mixed m.p. 101°.

[j] Homogeneous by g.l.c. N-Toluene-*p*-sulphonyl-2-methyl-1-phenylbutylamine,† m.p. and mixed m.p. 108–109°.

α-Methylbutyrophenone (4·3 g) was heated for 6 hr at 180° with the formamide–formic acid reagent prepared from ammonium carbonate (11·5 g) and 90% formic acid (12 ml). Hydrolysis with 5N HCl (10 ml) and the usual working up gave 2-methyl-1-phenylbutylamine (2·9 g, 67%), b.p. 118°/17 mm (lit.,[59] 130–135°/15 mm). (Found: C, 81·15; H, 10·55; N, 8·35. Calc. for $C_{11}H_{17}N$: C, 80·9; H, 10·5; N, 8·6%.) *N-toluene-*p*-sulphonyl-2-methyl-1-phenylbutylamine*, m.p. 108–109°, needles, from aqueous MeOH, then from benzene–petrol. (Found: C, 68·1; H, 7·6; N, 4·3; $C_{18}H_{23}NO_2S$ requires: C, 68·1; H, 7·3; N, 4·4%.)

[k] Homogeneous by g.l.c. Toluene-*p*-sulphonyl deriv. (91%), m.p. and mixed m.p. 86–86·5°.

Reduction of α-methylbutyranilide (8 g; m.p. 110–11°, lit,[41] 110–111°) in ether (175 ml) with LAH (3 g) in ether (100 ml) was 70% complete after 3 hr and gave N-phenyl-2-methylbutylamine (4·1 g, 55%), b.p. 132°/20 mm (lit.,[60] 142°/25 mm), toluene-*p*-sulphonyl deriv., m.p. 86–86·5° (lit.,[59] 85°).

[l] N-Benzoyl deriv. m.p. and mixed m.p. 149° (lit.,[59] 149°).

[m] Toluene-*p*-sulphonyl deriv.† (22% after recrystallization from aqueous MeOH (charcoal), then recrystallization from petrol), m.p. and mixed m.p. 102–103°.

‡ N-Toluene-*p*-sulphonyl-N-phenyl-2-ethylbutylamine (95%), m.p. and mixed m.p. 114–115°.

α-Ethyl-n-butyranilide (m.p. 126°, lit.,[61] 124°; 8·8 g) in ether (300 ml) and tetrahydrofuran (35 ml) refluxed for 4 hr with LAH (3·3 g) in ether (100 ml) gave crude base (2·4 g) and anilide (5·8 g).

The unreacted anilide was then refluxed for 6 hr with LAH (3 g) in tetrahydrofuran (125 ml). After evaporation of solvent *in vacuo*, ether (100 ml) was added, followed by 6N NaOH (40 ml). The ether was decanted and the residue washed with ether (50 ml). After extracting the ether extract with 2N HCl (2 × 50 ml) the ether layer gave a brown oil (1 g) which was rejected. Basification of the HCl-extract gave a dark brown oil (3·7 g). Distillation gave a pale yellow oil (5·1 g, 70%). Redistillation from Zn dust in an atmosphere of N_2 gave a pale yellow distillate of N-*phenyl-2-ethylbutylamine*, b.p. 131°/11 mm. (Found: C, 80·9; H, 10·85; N, 8·15. $C_{12}H_{19}N$ requires: C, 81·3; H, 10·8; N, 7·9%.) N-*toluene*-p-*sulphonyl*-N-*phenyl*-2-*ethylbutylamine* (93%), after recrystallization from EtOH, then from benzene–petrol (1:12), m.p. 114–115°. (Found: C, 69·1; H, 7·7; N, 4·3. $C_{19}H_{25}NO_2S$ requires: C, 68·8; H, 7·6; N, 4·2%.)

† Insoluble in 2N NaOH (cf. Carothers[58]).

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