47. *Preparation and Properties of Some Long-chain Aliphatic Amines.*

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A series of primary, secondary, and tertiary aliphatic amines containing between 8 and 30 carbon atoms were prepared and tested for antibacterial activity. Those with from 17 to 20 carbon atoms proved to be highly active *in vitro* against *Streptococcus hæmolyticus* and *Staphylococcus aureus*, and several inhibited the growth of *Mycobacterium tuberculosis*. The dissociation constants of 17 secondary and tertiary amines were measured by an electrometric method, but there appeared to be no correlation between these constants and antibacterial activities of the compounds.

Adams and Stanley (*J. Pharmacol.*, 1932, **45**, 121) found that a number of long-chain fatty acids had a marked inhibitory effect on the growth of the tubercle bacillus, the maximum effect being produced with compounds containing 16 or 17 carbon atoms. The activity increased, too, as the carboxyl group was displaced towards the centre of the molecule. Active compounds also resulted when the carboxyl group was replaced by a dialkylaminomethyl group. Robinson (*J.*, 1940, 508) reported the preparation of branched-chain fatty acids even more potent than those of Adams and Stanley, the most effective being 3-methyl-3-*n*-octyl-*n*-undecoic acid. Following a suggestion by Mr. G. Newbery, of May & Baker, Ltd., it was decided to prepare a number of long-chain amines analogous to the fatty acids of Adams and Stanley, and test their activity on the tubercle bacillus and other micro-organisms. Fuller (*Biochem. J.*, 1942, **36**, 548) reported that primary aliphatic amines containing 9 to 18 carbon atoms inhibited the growth of a number of micro-organisms, and that the activity increased with chain length up to a certain point and then decreased. He suggested that surface active properties might be responsible for the biological activity, and that it would be of interest to determine the activity of amines with branched chains. Fuller also tested a number of amidines, guanidines, and quaternary bases, and found that the decreased basicity of the amines made them relatively more effective against Gram-positive organisms compared with the strongly basic guanidines and quaternary bases, which were relatively stronger against Gram-negative organisms.

The amines prepared by us were selected in order to compare the activities of primary, secondary, and tertiary amines and study the effect of varying the chain length and position of the amino-group in the chain.

Five unbranched primary amines were made, two with a terminal amino-group, one with the amino-group near the end of the chain, and two with the amino-group in the centre of the chain. Unfortunately, attempts to prepare branched-chain primary amines were unsuccessful. Eight aliphatic secondary amines were made, all of which with two exceptions were unbranched. The chain lengths varied from 11 to 20 carbon atoms with the amino-group in the centre of the chain in four instances. In addition, a secondary amine containing a benzyl group was prepared, and five *N*-alkyl*cyclo*hexylamines. Twelve aliphatic tertiary amines with unbranched carbon chains consisting of from 13 to 30 carbon atoms were prepared. A tertiary amine containing a benzyl group was also prepared.

Three methods were used for the preparation of 8-*aminopentadecane*, but both Leuckart's method and reduction of diheptyl ketoxime gave poor yields. The most satisfactory method proved to be reductive amination of diheptyl ketone. Reductive amination was also employed for the preparation of 2-amino-octane and 9-aminoheptadecane. 1-Aminohexadecane was prepared by alkaline hydrolysis of *phthalocetylimide*, and 1-aminoheptadecane was prepared by Jeffrey's modification (*Amer. Chem. J.*, 1899, **22**, 31) of Hofmann's method (*Ber.*, 1882, **15**, 772).

It was our intention to make a series of branched-chain primary amines from dimethyldecylacetaldehyde, prepared by Darzens (*Compt. rend.*, 1932, **195**, 884) by condensation of acetone with ethyl α-chlorolaurate in presence of sodium ethoxide. From ethyl α-bromolaurate, however, none of the expected dimethyldecylacetaldehyde was obtained, but only undecanal, identified as its 2 : 4-dinitrophenylhydrazone. A similar result was obtained when *cyclo*hexanone was used in place of acetone.

Darzens and Levy (*Compt. rend.*, 1933, **196**, 184, 348) showed that α-bromo-acids react with sodium alkoxides to give α-alkoxy-acids and that these on distillation with copper yield aldehydes; they prepared undecanal in this way from α-methoxylauric acid. This is believed to explain the formation of undecanal in the above reaction, the bromine atom, in contrast to the chlorine atom, reacting preferentially with the ethoxy-group instead of with the ketone. Undecanal was reductively condensed with butylamine to give butylundecylamine. Di-*n*-octylamine and di-*n*-nonylamine were prepared by catalytic hydrogenation of the

appropriate nitriles, and the other secondary amines were obtained as by-products in the preparation of the tertiary amines.

With two exceptions, the tertiary amines were prepared by heating an alkyl bromide with ammonia or the appropriate primary amine under pressure, as described by Blicke and Zienty (*J. Amer. Chem. Soc.*, 1939, **61**, 771) and King and Work (*J.*, 1940, 1307; 1942, 401), secondary amines being obtained as by-products. For the preparation of methyldi-*n*-octylamine, this method was found superior to that described for the preparation of diallylamine (*Org. Synth.*, Coll. Vol. I, 195) in which the alkyl bromide is converted into the dialkylcyanamide by treatment with sodium cyanamide, hydrolysed to the dialkylamine with acid, and then alkylated. Methyl-*n*-hexyl-*n*-octylamine and *tri*-n-*nonylamine* were prepared from methyl-*n*-hexylamine and di-*n*-nonylamine respectively by reaction with the appropriate alkyl bromide.

Five alkyl *cyclo*hexylamines were prepared, four being obtained by the action of the corresponding alkyl bromide on *cyclo*hexylamine in presence of pyridine or sodium carbonate, and the fifth by catalytic hydrogenation of a mixture of *cyclo*hexanone and the alkylamine.

Although many of the amines formed crystalline hydrochlorides, some did not, and the long-chain tertiary amines were in general best characterised by means of their oxalates, which had sharp m. p.'s, whilst several of the primary and secondary amines formed beautifully crystalline salts with *m*-nitrobenzenesulphonic acid. So far as we are aware this acid has not previously been used for the characterisation of amines.

The antibacterial activities of the amines were tested against *Streptococcus hæmolyticus* and *Staphylococcus aureus* in a synthetic medium and in glucose broth by a method similar to that used by Fuller (*loc. cit.*). Most of the compounds were also tested against *Escherichia coli* but were relatively ineffective. The dilutions of the most active compounds necessary to inhibit the growth of the other two organisms are recorded in the table. It would appear from these and other results not reported in detail that the antibacterial activity of the aliphatic amines increases to a maximum with substances containing about 17—20 carbon atoms and then decreases. There was very little difference in the activities of secondary and tertiary amines containing the same number of carbon atoms. An insufficient number of compounds was available, however, to judge the effect of chain branching. Several of the compounds were inhibitory towards *Mycobacterium tuberculosis*; the results with this organism will be described elsewhere. Unfortunately, the most potent compounds *in vitro* had no effect *in vivo*, and it was shown that the amines on injection disappeared rapidly from the blood stream.

In view of recent attempts to correlate the biological and the physical properties of chemically related substances, it was considered of interest to compare the dissociation constants of certain of these amines with their antibacterial activities.

The dissociation constants of some simple aliphatic amines have been measured by Bredig (*Z. physikal. Chem.*, 1894, **13**, 297), using a conductivity procedure, and by Hall and Sprinkle (*J. Amer. Chem. Soc.*, 1932, **54**, 3469), using an electrometric titration method. We used the latter, which was more convenient and gave sufficiently accurate results for our purpose. Three series of amines were investigated: (*a*) dialkylamines containing between 4 and 18 carbon atoms; (*b*) trialkylamines containing between 6 and 27 carbon atoms; and (*c*) dioctylamine and alkyldioctylamines containing between 17 and 24 carbon atoms. The results are recorded in the tables together with the antibacterial activities. There would appear to be little or no correlation between dissociation constants and antibacterial activities in this particular series of compounds. All the amines tested proved to be relatively strong bases, whereas no marked antibacterial activity appeared until the number of carbon atoms exceeded 12.

Experimental.

Preparation of Amines.—*8-Aminopentadecane.* A mixture of diheptyl ketone (38 g.), ammonium carbonate (36 g.), and 85% formic acid (37 g.) was heated at 185—190° for 4 hours, and the reaction mixture poured into water. The resulting oil was extracted with ether and distilled, the fraction, b. p. 220—230°/15 mm., being collected; yield 16 g. This was redistilled, giving *formamidopentadecane* (Found: C, 75·1; H, 12·7; N, 5·2. $C_{16}H_{33}ON$ requires C, 75·3; H, 13·0; N, 5·5%). Hydrolysis of this compound was sluggish but was eventually accomplished by heating with anhydrous hydrogen chloride at 150°. The resulting oil formed a m-*nitrobenzenesulphonate*, fine needles, m. p. 150°, from benzene (Found: C, 59·1; H, 8·9; N, 6·4; S, 7·1. $C_{21}H_{38}N_2O_5S$ requires C, 58·6; H, 8·9; N, 6·5; S, 7·4%). 8-Aminopentadecane was also prepared in 5% yield by the reduction of diheptyl ketoxime (Kipping, *J.*, 1893, **63**, 454) with sodium and alcohol, according to the method of Thoms and Mannich (*Ber.*, 1903, **36**, 2554), but a much better method was reductive amination of diheptyl ketone. A mixture of the ketone (40 g.), ammonia (*d*, 0·880, 40 ml.), and ethyl alcohol (400 ml.) was hydrogenated at 72 atm. and 150° in presence of Raney nickel (5 g.). After the catalyst had been filtered off, the filtrate was acidified, filtered, and the filtrate made alkaline and extracted with ether. The oil remaining after removal of the ether was distilled, the 8-aminopentadecane distilling at 157°/12 mm.; yield 30·5 g. (56%).

9-Aminoheptadecane was prepared by reductive amination of dioctyl ketone (15 g.; prepared from the lead salt of pelargonic acid) in presence of Raney nickel as described for the preparation of 8-aminopentadecane. The catalyst was filtered off, and alcohol removed from the filtrate by distillation. *m*-Nitrobenzenesulphonic acid was added to the solution, and the precipitated *9-aminoheptadecane m-nitrobenzenesulphonate* was recrystallised from light petroleum (b. p. 60—80°), forming a micro-crystalline powder, m. p. 142—143° (12 g.) (Found: C, 60·4; H, 9·1; N, 5·7; S, 6·9. $C_{23}H_{42}O_5N_2S$ requires C, 60·3; H, 9·2; N, 6·1; S, 7·0%).

2-Amino-octane was prepared as described above by reductive amination of methyl *n*-hexyl ketone (64 g.). The amine was extracted with ether and distilled, the fraction, b. p. 164—166°, being collected (lit., b. p. 164°); yield 41 g.

1-*Aminohexadecane.* Cetyl iodide (28 g.) and potassium phthalimide (14·4 g.) were heated together for 4 hours, cooled, digested with water, and then extracted with ether. The extract was washed with sodium hydroxide solution and water, and the ether removed. On boiling the residue with alcohol, *phthalocetylimide* crystallised out; this was recrystallised from ethyl alcohol, m. p. 73—74° (25 g., 84%) (Found: C, 77·6; H, 10·3; N, 4·6. $C_{24}H_{37}O_2N$ requires C, 77·6; H, 10·0; N, 3·8%). The compound was resistant both to acid hydrolysis and to the hydrazine method of Ing and Manske (*J.*, 1926, 2348). On heating 10 g. with a mixture of 40% sodium hydroxide solution (100 ml.) and ethyl alcohol (120 ml.), however, 1-aminohexadecane was obtained (4·5 g.). This formed a hydrochloride, m. p. 140—145°, and a picrate, m. p. 75—78°.

1-*Aminoheptadecane.* Stearamide (28·7 g.), prepared from stearic acid *via* the acid chloride, was dissolved in methyl alcohol (250 ml.), and a solution of sodium (4·6 g.) in methyl alcohol (143 ml.) added to the warm solution, followed by bromine (16 g.) drop by drop with shaking. After addition of all the bromine, the mixture was warmed on the steam-bath for 10 mins. and allowed to stand. The mixture of unchanged stearamide and *N*-*n*-heptadecyl-*N'*-stearylurea was filtered off, and the filtrate diluted with water. The precipitated stearylurethane, recrystallised from ethyl alcohol, had m. p. 70—75°. A solution of the crude urethane (5 g.) in 10% aqueous alcoholic sodium hydroxide was heated under reflux for 16 hours, and the reaction mixture extracted with ether. The oil left after removal of the ether solidified, m. p. *ca.* 40°, and was converted into 1-aminoheptadecane hydrochloride, m. p. 162—164° (lit., 158°), by dissolving the base in ether and passing in dry hydrogen chloride (Found: N, 5·0; Cl, 12·0. Calc. for $C_{17}H_{38}NCl$: N, 4·8; Cl, 12·2%). The *acetyl* compound had m. p. 62° (Found: N, 5·0. $C_{19}H_{39}ON$ requires N, 4·7%). The recovered *N*-*n*-heptadecyl-*N'*-stearylurea was freed from stearamide by extraction with methanol, and the crude urea, m. p. 104—105°, fused with potassium hydroxide, as described by Hofmann (*loc. cit.*). A further crop of 1-aminoheptadecane was thereby obtained.

2-*Octylamino-octane.* A mixture of 2-amino-octane (41 g.), octyl bromide (62 g.), ethyl alcohol (250 ml.), and sodium carbonate (10 g.) was heated in an autoclave at 160° for 9 hours. The reaction mixture was acidified, the alcohol distilled off, and water added to the residue. The mixture was then made alkaline, extracted with ether, and the oil remaining after removal of the ether distilled. The 2-octylamino-octane distilled at 165°/14 mm. It formed a *hydrochloride* as a microcrystalline powder, m. p. 151—152° from acetone (Found: N, 5·1; Cl, 12·4. $C_{16}H_{36}NCl$ requires N, 5·0; Cl, 12·8%), and a *m-nitrobenzenesulphonate* as iridescent prisms, m. p. 75—76° from light petroleum (Found: C, 59·0; H, 8·8; N, 6·6; S, 7·7. $C_{22}H_{40}N_2O_5S$ requires C, 59·5; H, 9·0; N, 6·3; S, 7·2%).

Hexadecylethylamine was prepared from ethylamine hydrochloride (24 g.), sodium hydroxide, and cetyl iodide (55 g.) by the method used for 2-octylamino-octane. It had b. p. 210°/15 mm. and formed a *hydrochloride*, m. p. 206—207° (from ethyl alcohol) (Found: C, 70·9; H, 12·8; N, 4·5; Cl, 11·0. $C_{18}H_{40}NCl$ requires C, 70·7; H, 13·1; N, 4·6; Cl, 11·6%).

Butylundecylamine. An attempt to prepare αα-dimethyldecylacetaldehyde by Darzens's method (*loc. cit.*) was unsuccessful. A solution of ethyl α-bromolaurate (154 g.; prepared by bromination of lauryl chloride, followed by esterification) in dry acetone (30 g.) and dry ether (150 ml.) was cooled to − 10°, sodium ethoxide (made by dissolving 12·5 g. of sodium in dry ethyl alcohol and evaporation to dryness) added, and the mixture left with occasional shaking for 24 hours; sodium bromide separated out. Dilute acetic acid was then added, and the solution extracted with ether. The residue left after removal of the ether was distilled, the fraction, b. p. 165—170°/5 mm., being collected (71 g.). The redistilled aldehyde gave a 2 : 4-dinitrophenylhydrazone, m. p. 102°, which was shown by analysis to be *undecanal 2 : 4-dinitrophenylhydrazone* (Found: C, 57·8; H, 7·4; N, 16·0. $C_{17}H_{26}O_4N_4$ requires C, 58·3; H, 7·4; N, 16·0%). A mixture of undecanal and *n*-butylamine was hydrogenated in presence of Raney nickel as described for 2-octylamino-octane, giving butylundecylamine, characterised as its *m-nitrobenzenesulphonate*, m. p. 92—94° (Found: C, 58·2; H, 8·8; N, 6·6. $C_{21}H_{38}N_2O_5S$ requires C, 58·6; H, 8·8; N, 6·5%). Undecanal was also obtained when ethyl α-bromolaurate was treated with *cyclo*hexanone and sodium ethoxide.

Di-*n*-hexylamine, b. p. 125—130°/16 mm., was obtained as a by-product from the preparation of tri-*n*-hexylamine (*q.v.*). It yielded a *m-nitrobenzenesulphonate*, m. p. 119—120° (Found: C, 55·8; H, 8·3; N, 7·1; S, 8·2. $C_{18}H_{32}O_5N_2S$ requires C, 55·7; H, 8·25; N, 7·2; S, 8·25%).

Di-*n*-octylamine was prepared by hydrogenating a solution of octoic nitrile (40 g.) in ethyl alcohol (300 ml.) at 75 atm. and 80° in presence of Raney nickel (3 g.). The oil remaining after removal of the alcohol was distilled, di-*n*-octylamine distilling at 178°/15 mm. (yield 16 g., 45%), together with *n*-octylamine. Di-*n*-octylamine was also obtained as a by-product in the preparation of tri-*n*-octylamine. It formed a hydrochloride, m. p. 238°, and a *m-nitrobenzenesulphonate*, m. p. 115—116° (Found: C, 60·3; H, 9·3; N, 6·1. $C_{22}H_{40}N_2O_5S$ requires C, 59·5; H, 9·6; N, 6·3%).

Di-*n*-nonylamine was similarly prepared by hydrogenation of a solution of nonoic nitrile (44 g.) in alcohol (270 ml.) at 78 atm. and 65° in presence of Raney nickel (cf. Mailhe, *Bull. Soc. chim.*, 1918, **23**, 235). After removal of the alcohol, the residue was distilled, di-*n*-nonylamine boiling at 188°/12 mm. (23 g., 66%) (Found: C, 80·0; H, 14·3; N, 5·1. Calc. for $C_{18}H_{39}N$: C, 80·3; H, 14·5; N, 5·2%). In moist air it solidified to a *monohydrate*, which melted at 42°, passed through a mesomorphic smectic phase, and gave a clear stable liquid phase at 52° (Found: C, 75·8; H, 14·1; N, 5·0. $C_{18}H_{39}N,H_2O$ requires C, 75·3; H, 14·3; N, 4·9%). Mailhe (*loc. cit.*) gives m. p. 29°. It formed a *m-nitrobenzene-*

sulphonate which crystallised in waxy platelets, m. p. 107—108°, from light petroleum (Found : C, 61·3; H, 9·3; N, 5·6; S, 7·2. $C_{24}H_{44}N_2O_5S$ requires C, 61·0; H, 9·3; N, 5·9; S, 6·8%), and a hydrochloride, m. p. 230—232°, from *cyclo*hexane–dioxan. Di-*n*-nonylamine (13 g.) was also prepared by refluxing *n*-nonylamine (30 g.) with Raney nickel (3 g.) for 3 hours.

Di-*n*-decylamine was prepared by heating decyl bromide with ammonia (*d*, 0·880) in an autoclave. The appropriate fraction solidified on standing, m. p. 44—49° (lit., 47·5°). It formed a *hydrochloride*, m. p. 208—210°, from acetone (Found : C, 72·9; H, 12·7; N, 4·3; Cl, 9·3. $C_{20}H_{44}NCl$ requires C, 72·0; H, 13·2; N, 4·2; Cl, 10·7%).

*iso*Amyl-*n*-hexylamine was obtained as the main product in the preparation of *iso*amyldi-*n*-hexylamine (*q.v.*). It had b. p. 100—105°/22 mm. and formed a hydrobromide, m. p. 247—250°, and an *oxalate*, m. p. 219—220° (Found : C, 59·2; H, 9·9; N, 4·9. $C_{13}H_{27}O_4N$ requires C, 59·8; H, 10·3; N, 5·4%).

Benyl-*n*-hexylamine was obtained as a by-product in the preparation of benzyldi-*n*-hexylamine (*q.v.*). It had b. p. 128—130°/12 mm. and formed a *hydrobromide*, m. p. 217—218° from benzene (Found : C, 57·2; H, 8·0; N, 4·8; Br, 29·4. $C_{13}H_{22}NBr$ requires C, 57·3; H, 8·1; N, 5·1; Br, 29·4%).

Methyl-di-*n*-hexylamine was prepared from *n*-hexyl bromide and methylamine by the method of Blicke and Zienty (*loc. cit.*). It had b. p. 121—122°/19 mm. and formed a hydrochloride, m. p. 144—145° (Found : N, 5·6. Calc. for $C_{13}H_{30}NCl$: N, 5·9%). *iso*Amyldi-*n*-hexylamine was prepared in a similar manner from *n*-hexyl bromide (85 g.) and *iso*amylamine (20 g.). The product was distilled, the fraction, b. p. 100—105°/22 mm. (16 g.), yielding *iso*amyl-*n*-hexylamine (*q.v.*), and the fraction, b. p. 140—145° 22 mm. (3 g.), *iso*amyldi-*n*-hexylamine. This gave an *oxalate*, m. p. 128—130° (Found : C, 65·6; H, 10·9; N, 4·2. $C_{19}H_{39}O_4N$ requires C, 66·1; H, 11·3; N, 4·1%). Tri-*n*-hexylamine was prepared in a similar manner from *n*-hexyl bromide (100 g.) and alcoholic ammonia. The product was distilled, the fraction, b. p. 125—130°/16 mm. (10 g.), yielding di-*n*-hexylamine (*q.v.*), and the fraction, b. p. 165—170°/16 mm. (15 g.), yielding tri-*n*-hexylamine. The latter gave an *oxalate*, m. p. 120° (from water) (Found : C, 66·8; H, 11·4; N, 4·0. $C_{20}H_{41}O_4N$ requires C, 66·8; H, 11·4; N, 3·9%). It also formed an oily hydrochloride and a crystalline *m*-nitrobenzenesulphonate, m. p. 107—108°.

Benzyldi-*n*-hexylamine was prepared from benzylamine (20 g.) and hexyl bromide (62 g.) by the method of King and Work (*J.*, 1940, 1307). The product was distilled, the fraction, b. p. 128—130°/12 mm. (17 g.), yielding benzyl-*n*-hexylamine (*q.v.*), and the fraction, b. p. 185—195°/30 mm. (15 g.), yielding benzyldi-*n*-hexylamine. The latter formed a micro-crystalline *oxalate*, m. p. 95° (from benzene) (Found : C, 68·3; H, 9·2; N, 3·5. $C_{21}H_{35}O_4N$ requires C, 69·0; H, 9·6; N, 3·8%).

Methyl-*n*-hexyl-*n*-octylamine was prepared by heating methyl-*n*-octylamine (17 g.; obtained as a by-product in the preparation of methyldi-*n*-octylamine) with *n*-hexyl bromide (25 g.) in benzene (150 ml.) at 160° for 7 hours. The benzene was distilled off, and the residue made alkaline and extracted with light petroleum. The tertiary amine distilled at 140—145°/22 mm. It formed a microcrystalline *oxalate*, m. p. 227—228° (decomp.), when crystallised from aqueous alcohol (Found : C, 64·3; H, 10·8; N, 4·7. $C_{17}H_{35}O_4N$ requires C, 64·3; H, 11·0; N, 4·4%).

Methyldi-*n*-octylamine was best prepared by the method of Blicke and Zienty (*loc. cit.*) from *n*-octyl bromide (250 g.; 2 mols.) and 30% methylamine solution (200 ml.; 3 mols.) by heating for 10 hours at 165°. The mixture was made alkaline and extracted with light petroleum. The oil remaining after removal of the ether was distilled, the fraction, b. p. 140—160°/15 mm. (5 g.), consisting of methyl-*n*-octylamine, and that of b. p. 162—165°/15 mm. or 158°/10 mm. (6·8 g.; 42%) of methyldi-*n*-octylamine, and that boiling above this range largely of tri-*n*-octylamine. Methyldi-*n*-octylamine is stated by Blicke and Zienty (*loc. cit.*) to boil at 136—138°/5 mm., and by Westphal and Jerchel (*Ber.*, 1940, **73**, 1002) at 143—145°/3 mm. Methyldi-*n*-octylamine hydrochloride, m. p. 149—150° (lit. 149—150°), was prepared by passing dry hydrogen chloride into a solution of the amine in light petroleum.

Ethyldi-n-*octylamine*, prepared by a similar method from *n*-octyl bromide and ethylamine, had b. p. 166—167°/10 mm. (Found : C, 80·1; H, 14·4; N, 4·7. $C_{18}H_{39}N$ requires C, 80·3; H, 14·5; N, 5·2%). n-*Propyldi*-n-*octylamine* was similarly prepared from *n*-octyl bromide and *n*-propylamine; it had b. p. 174°/10 mm. (Found : C, 80·7; H, 13·7; N, 5·1. $C_{19}H_{41}N$ requires C, 80·6; H, 14·5; N, 5·0%). Tri-*n*-octylamine was similarly prepared from *n*-octyl bromide (130 g.) and ammonia (*d*, 0·880; 150 ml.). On distillation of the product, the fraction of b. p. 190—195°/16 mm. yielded di-*n*-octylamine (10 g.) (*q.v.*), and that of b. p. 225—230°/16 mm. tri-*n*-octylamine (30 g.). The latter, purified by redistillation, had b. p. 212—218°/12 mm. or 164—168°/0·7 mm. (Found : C, 82·3; H, 13·7; N, 4·3. Calc. for $C_{24}H_{51}N$: C, 81·6; H, 14·4; N, 4·0%).

Methyldi-*n*-nonylamine was prepared by a similar method to that used by King and Work (*J.*, 1942, 401) from *n*-nonyl bromide and methylamine. It had b. p. 204°/25 mm. and formed a micro-crystalline *hydrochloride*, m. p. 149—150°, from benzene (Found : C, 71·6; H, 13·0; N, 4·6; Cl, 11·2. $C_{19}H_{42}NCl$ requires C, 71·3; H, 13·1; N, 4·4; Cl, 11·1%). *Ethyldi*-n-*nonylamine* was similarly prepared from *n*-nonyl bromide and ethylamine. It had b. p. 208°/20 mm. and formed a micro-crystalline *hydrochloride*, m. p. 78—79°, from light petroleum (Found : C, 71·9; H, 12·8; N, 4·6; Cl, 10·1. $C_{20}H_{44}NCl$ requires C, 72·0; H, 13·2; N, 4·2; Cl, 10·61%).

Tri-n-*nonylamine* was prepared by heating di-*n*-nonylamine (7 g.), *n*-nonyl bromide (20 g.), anhydrous sodium carbonate (10 g.), and ethyl alcohol (200 ml.) at 160° for 9 hours with stirring. The reaction mixture was filtered, the filtrate acidified to Congo-red with dry hydrogen chloride, and again filtered, and the solvent removed. The residue was made alkaline with sodium hydroxide and extracted with ether. The extract was evaporated and the residue distilled in a vacuum, tri-*n*-nonylamine distilling at 178—180°/0·01 mm.; yield 5 g. (49%) (Found : C, 81·8; H, 14·6; N, 3·53. $C_{27}H_{57}N$ requires C, 82·0; H, 14·5; N, 3·54%). It formed a microcrystalline *oxalate*, m. p. 107—108°, from dioxan (Found : C, 71·8; H, 11·8; N, 3·35. $C_{29}H_{59}O_4N$ requires C, 71·7; H, 12·2; N, 2·9%).

Tri-*n*-dodecylamine was prepared from *n*-dodecyl iodide (82 g.) and ammonia (*d* 0·880; 300 ml.) by the method described above. The product was distilled in a vacuum, the fraction, b. p. 290—310°/15 mm., (13 g.) consisting mainly of di-*n*-dodecylamine. The residue (25 g.), which would not distil at 15 mm. pressure, was converted into the hydrochloride by passing dry hydrogen chloride into a light

petroleum solution; this had m. p. 78—79° (lit. 78—79°) (Found: C, 77·5; H, 13·4; N, 2·6; Cl, 6·1. Calc. for $C_{36}H_{76}NCl$: C, 77·5; H, 13·6; N, 2·5; Cl, 6·3%).

cyclo*Hexyl*-n-*hexylamine*. *cyclo*Hexylamine (22 g.), *n*-hexyl bromide (73·5 g.), sodium carbonate (10 g.), and alcohol (250 ml.) were heated together at 160° for 6 hours and worked up as previously described. The product was distilled in a vacuum, the fraction of b. p. 125—135°/15 mm. (16 g.) being collected. By passing dry hydrogen chloride into a light petroleum solution of the amine, this was converted into cyclo*hexyl*-n-*hexylamine hydrochloride*, m. p. 240°, after recrystallisation from water (Found: C, 65·1; H, 11·8; N, 6·9; Cl, 16·1. $C_{12}H_{26}NCl$ requires C, 65·6; H, 11·8; N, 6·4; Cl, 16·2%).

*cyclo*Hexyl-*n*-octylamine was prepared by heating a mixture of *cyclo*hexylamine (38 g.) and *n*-octyl bromide (74 g.) with pyridine (80 ml.) under reflux for 4½ hours. The reaction mixture was poured into water, made alkaline with sodium hydroxide, and extracted with light petroleum. The residue remaining after removal of the petroleum was distilled, the secondary amine distilling at 145—150°/13 mm. (38 g.). It gave a *hydrochloride*, m. p. 212°, which formed a micro-crystalline powder from acetonitrile (Found: C, 68·0; H, 12·1; N, 5·6; Cl, 14·2. $C_{14}H_{30}NCl$ requires C, 67·9; H, 12·1; N, 5·7; Cl, 14·3%) and platelets from dioxan (Found: C, 67·9; H, 11·9; N, 5·5%).

*cyclo*Hexyl-*n*-nonylamine was prepared by hydrogenating a solution of *cyclo*hexanone (14·3 g.) and *n*-nonylamine (21 g.) in alcohol (175 ml.) at 100 atm. and 140° in presence of Raney nickel (5 g.). The compound was isolated in the usual way, b. p. 160°/12 mm.; yield 17 g. It formed a *hydrochloride*, m. p. 216°, which crystallised from acetone–light petroleum as a flocculent powder (Found: C, 68·8; H, 12·5; N, 5·5; Cl, 13·9. $C_{15}H_{32}NCl$ requires C, 68·8; H, 12·2; N, 5·4; Cl, 13·6%).

*cyclo*Hexyl-*n*-decylamine was prepared from *cyclo*hexylamine (26 g.), *n*-decyl bromide (50 g.), and pyridine (50 ml.) as described for the octyl compound. It had b. p. 155—160°/16 mm. and formed a *hydrobromide*, m. p. 228—230°, which crystallised from acetone in fine needles (Found: C, 60·6; H, 10·2; N, 4·4; Br, 25·0. $C_{16}H_{34}NBr$ requires C, 60·0; H, 10·6; N, 4·4; Br, 25·0%). *cyclo*Hexyl-*n*-dodecylamine was prepared in a similar manner from *cyclo*hexylamine (32 g.), *n*-dodecyl iodide (96 g.), and pyridine (80 g.). It had b. p. 200—205°/15 mm.; yield 24 g. (28%). It formed a hydrochloride, m. p. 202°, which crystallised from acetone (lit., 204—205°) (Found: C, 71·1; H, 12·3; N, 4·8; Cl, 11·3. Calc. for $C_{18}H_{38}NCl$: C, 71·2; H, 12·5; N, 4·6; Cl, 11·7%).

Dissociation Constants.—A standard sealed glass–saturated calomel electrode system was used, in conjunction with a Cambridge bench pH meter, for most of the electrometric titrations. For pH measurements of strongly alkaline solutions, however, the standard sealed glass electrode was replaced by a special "Alki" electrode, which permits accurate measurements in the pH range 9·0—14·0. All measurements were performed in a water thermostat at 25°. During the titrations, the solution was agitated by passing through it nitrogen which had previously been bubbled through a flask containing 70% aqueous alcohol at 25°.

Dissociation Constants and Bacteriostatic Activities.

Amine.	B. p.	pK_a in 70% alcohol.	Bacteriostatic activity × 10^{-3}. Synthetic medium. Staph. aureus No. 663.	Synthetic medium. Strep. No. 618.	Glucose broth. Staph. aureus No. 663.	Glucose broth. Strep. No. 618.
(1) *Secondary amines.*						
*Diethylamine	55—56°	9·78	50	5	5	5
*Dipropylamine	110	9·47	5	5	5	5
*Dibutylamine	159—160	9·57	1	5	1	1
*Diamylamine	202—204	9·53	5	1	1	1
Dihexylamine	112—114/12 mm.	9·33	5	10	1	5
Dioctylamine	164/12 mm.	9·20	50	100	100	100
Dinonylamine	188/12 mm.	9·29	50	100	100	500
(2) *Tertiary amines.*						
*Triethylamine	89—90	9·25	5	5	1	5
*Tripropylamine	156	9·0	5	1	1	1
*Tributylamine	209—214	8·92	5	5	1	1
*Triamylamine	127/11 mm.	8·79	5	5	5	5
Trihexylamine	150—159/12 mm.	8·53	5	10	5	5
Trioctylamine	164—168/0·7 mm.	8·35	50	50	10	10
Trinonylamine	178—180/0·01 mm.	8·21	50	50	10	10
(3) *Dioctyl- and alkyldioctyl-amines.*						
Dioctylamine	164/12 mm.	9·20	50	100	100	100
Methyldioctylamine	158/10 mm.	8·56	500	500	100	500
Ethyldioctylamine	166—167/10 mm.	8·70	100	100	100	100
Propyldioctylamine	174/10 mm.	8·51	100	100	10	50
Trioctylamine	164—168/0·7 mm.	8·35	50	50	10	10

* Prepared from commercial specimens.

All the amines were examined in 70% aqueous alcoholic solution. This was the minimum concentration of alcohol at which a 0·002M-solution of the least soluble amine (*i.e.*, trinonylamine) could be prepared. The alcohol used for preparing the solutions was freshly distilled. Conductivity water (supplied by Mr. James, of Battersea Polytechnic) was used for some of the experiments; this did

not offer any advantages over freshly redistilled water, which was therefore used in the other experiments. Blank titrations were performed on each sample of alcohol and redistilled water to ensure that they were suitable. All the amines were freshly purified by redistillation.

It is well known that alcohol depresses the dissociation constants of acids (cf. Hall and Sprinkle, *loc. cit.*), and in order to compare our results with previously published data, we measured some of the simpler amines in aqueous solution. These results were in good agreement with published data.

Each of the dissociation constants recorded in the tables is the mean of six determinations.

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