123. *The Preparation, Resolution, and Optical Properties of* 2-*Amino*-n-*octane.*

By Frederick G. Mann and J. W. Geoffrey Porter.

The preparation and optical resolution of 2-amino-*n*-octane have been critically examined. Apart from the original purpose of this examination, the amine is of interest for two reasons: (*a*) its ready resolution provides an optically active amine of great value as a stereochemical reagent, (*b*) its optical properties present some striking features. The hydrochloride of the amine is freely soluble in a variety of solvents, both ionising and non-ionising; in the latter type of solvent it is apparently uniformly associated. These properties are connected with the "acid-effect" which the amine shows. For instance, the hydrochloride of the *l*-amine is dextrorotatory in ionising solvents, its rotation being little influenced by the concentration; it is also dextrorotatory in non-ionising solvents at moderately high concentrations, but such solutions on dilution become first optically neutral and then lævorotatory. The implication of these results is briefly discussed, but the available data are at present insufficient for their full interpretation.

It is known that the stereoisomeric forms of many drugs differ in the intensity of their physiological activity, this difference being shown most markedly by certain optical enantiomorphs, *e.g.*, *d*- and *l*-adrenaline, *d*- and *l*-hyoscyamine. Cushny ("Biological Relations of Optically Isomeric Substances," Baltimore, 1926) has suggested that a clear differentiation in this action of enantiomorphs indicates combination of each with an optically active tissue constituent, the compounds so formed possessing different physicochemical properties and hence different physiological activities. This view has, however, been criticised recently by Ing (*Trans. Faraday Soc.*, 1943, **39**, 372) in the light of the "receptor" theory of drug action.

Monolayer measurements upon suitable optical enantiomorphs should provide a comparatively simple method of testing the validity of Cushny's suggestion. This technique can detect molecular associations of a very labile nature under conditions which approximate to those occurring in biological systems, and mixed monolayers of optically inactive, long-chain, aliphatic acids and similar amines have already been studied in detail by Schulman and his co-workers (cf. *Ann. Reports*, 1939, **36**, 94). We have therefore critically investigated the preparation and optical resolution of two compounds, 1-bromopalmitic acid and 2-amino-*n*-octane, suitable for this purpose; the mixed monolayer properties of the optical enantiomorphs thus obtained are being studied in the Department of Colloid Science, Cambridge University, and the results will be published elsewhere. Meanwhile, we now describe the preparation and resolution of 2-amino-*n*-octane, because its ready isolation makes it a valuable resolving agent in stereochemical work, and because it possesses optical properties of considerable interest.

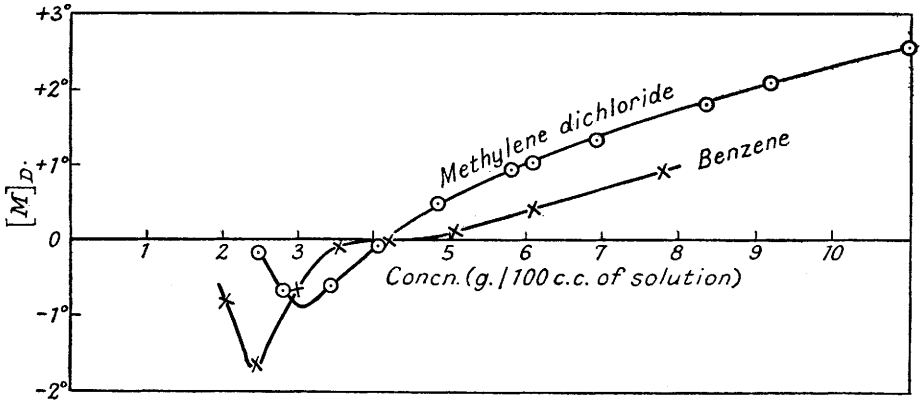
Methyl *n*-hexyl ketone was obtained in *ca.* 95% yield by chromic acid oxidation of 2-hydroxy-*n*-octane (Verhulst and Glorieux, *Bull. Soc. chim. Belg.*, 1932, **41**, 501). The ketone readily furnished the corresponding oxime and *phenylhydrazone*. Reduction of the oxime with sodium and alcohol gave pure 2-amino-*n*-octane in 70% yield and is the best preparative method we have found. Reduction of the phenylhydrazone with sodium amalgam in ethyl alcohol–acetic acid also readily furnished the amine, but even after repeated fractional distillation the amino-octane still contained traces of aniline. The amine is almost insoluble in water, but soluble in most organic solvents.

2-Amino-*n*-octane has been obtained optically active by Levene and Rothen (*J. Biol. Chem.*, 1936, **115**,

415) by the reactions: *d*-2-hydroxy-*n*-octane ⟶ *l*-2-iodo-octane ⟶ *d*-2-azido-octane ⟶ *d*-2-amino-octane. Their amine had $[M]_D^{25°}$ +5·41°, but our results show that it was probably optically impure.*

2-Amino-octane d-*camphorsulphonate* and d-*bromocamphorsulphonate* underwent no resolution during fractional recrystallisation. The *amine* d-*hydrogen tartrate*, when recrystallised from methyl or ethyl alcohol, however, readily furnished the *l*-amine *d*-hydrogen tartrate, which in turn gave the optically pure l-2-*amino*-n-*octane*, $[M]_D^{17°}$ −8·53°. Recrystallisation of the *d*-hydrogen tartrate from water gave the d-*amine* d-*hydrogen tartrate*; although after 25 such recrystallisations no further change in rotation of the tartrate could be observed, the regenerated amine had only $[M]_D$ +5·5°, and the optically pure *d*-amine cannot apparently be obtained in this way. The racemic amine was therefore converted into the *l*-hydrogen tartrate, which, recrystallised from methyl alcohol, furnished the *d*-amine *l*-hydrogen tartrate, and the latter then readily gave the optically pure *d*-2-amino-octane, $[M]_D^{17°}$ +8·62°.

The activity of this amine is almost unaffected in benzene solution, but is markedly changed in ethyl-alcoholic solution; *e.g.*, the *d*-amine in 5·95% benzene solution has $[M]_D$ +8·50°, but in 8·06% ethyl-alcoholic solution has $[M]_D$ +0·88°, this value being unaffected by the concentration of the solution (p. 460). This marked change in the optical properties of the amine in alcoholic solution probably indicates a fundamental chemical change (due to association with the solvent) and is discussed later. The change in rotation would probably be shown in other hydroxylic solvents also, and it is particularly unfortunate that the rotation of an aqueous solution cannot be measured owing to the minute solubility of the amine in water.



The molecular rotation ($[M]_D$) *of solutions of the hydrochloride of* l-2-*amino*-n-*octane in methylene dichloride and in benzene.*

The hydrochlorides of the *d*- and the *l*-amine are of particular interest. Not only are they freely soluble in water, and in methyl and ethyl alcohol, but they are also freely soluble in cold methylene dichloride, chloroform, carbon tetrachloride, ethylene dichloride, benzene, toluene, *p*-xylene, and other similar solvents. The solubility in the first group of liquids is, of course, typical of a normal ionised salt, but that in the second group is characteristic of a true covalent compound, and the difference provides a strong indication that the nature of the solvent may profoundly affect the constitution of the hydrochloride.

Furthermore, the hydrochlorides of the active amines show a very pronounced " acid-effect " (cf. Lowry and Baldwin, *Proc. Roy. Soc.*, 1937, *A*, **162**, 204; Baldwin, *ibid.*, pp. 215, 228; 1938, *A*, **167**, 539), *i.e.*, the hydrochloride of the *l*-amine is strongly dextrorotatory when dissolved in water, methyl or ethyl alcohol, acetone, formamide, and other solvents. The rotation in ethyl alcohol is almost independent of the concentration of the solution, in marked distinction to that in other solvents discussed below. Baldwin (*loc. cit.*) has shown that most alkyl- and arylalkyl-amines reveal this " acid-effect " on salt formation. It is due to the fact that such free amines have two active absorption bands, one usually at 2400—2000 A., and the second at 1800—1500 A. (cf. Mulliken, *J. Chem. Physics*, 1935, **3**, 507). The former band owes its existence to the unbound electrons of the nitrogen atom, and the rotatory power of the free amine is due almost entirely to this band alone. On neutralisation of the amine, this band ceases to be circularly dichroic and thus disappears, together (usually) with most of the rotatory power; the rotation of the salt is thus due entirely to the second band, which in many amines may have a rotation of opposite sign to that of the first band. Neutralisation of the amine may therefore cause either a marked decrease in the rotation, or may switch it completely over to the reverse rotation. The *hydrochloride* of our *l*-amine has, *e.g.*, $[M]_D$ +6·61° in 7·77% aqueous solution, $[M]_D$ +7·73° in 6·32% methyl-alcoholic solution, $[M]_D$ +13·9° in 4·310% ethyl-alcoholic solution, and $[M]_D$ +8·65° in 5·02% acetone solution; in all these and many other solvents the " acid-effect " has caused a reversal of sign of rotation, and in ethyl alcohol the *dextro*-molecular rotation has considerably exceeded the *lævo*-molecular rotation of the original undissolved amine.

* In spite of the low rotation of Levene and Rothen's free *d*-amine, the hydrochloride of their amine, in 9·00% aqueous solution, had $[M]_D$ −6·44°, whereas the hydrochloride of our *l*-amine, in 7·77% aqueous solution, had $[M]_D$ +6·61° (p. 460). It is possible, therefore, that Levene and Rothen's products were optically pure, and that their value for the free amine has been incorrectly determined

The above " acid-effect " can be regarded as a normal property of most aliphatic amines, but the hydrochlorides of our active amines show one strikingly abnormal property. The hydrochloride of *l*-2-amino-octane is dextrorotatory at moderately high concentration in methylene dichloride, ethylene dichloride, chloroform, and benzene, but progressive dilution in each case leads first to optical inactivity and then to a lævorotation, which increases to a limit as dilution proceeds and then necessarily decreases again as the concentration of the salt becomes negligible. The detailed optical data are listed on p. 461, but the curves given illustrate clearly this change of rotation with concentration in benzene and in methylene dichloride solution. This phenomenon must be shown in many other solvents, but the range of solubility is often too small to allow the complete reversal of sign of rotation to be manifest. For instance, solutions in toluene and dioxan that were almost saturated at room temperature were optically inactive, but dilution produced a lævorotation: there is little doubt that had higher temperatures been employed with these solvents to obtain more concentrated solutions, they would have shown a dextrorotation. It is the unusually high solubility of the salt in methylene dichloride and in benzene that allowed the wide range of concentration–rotation measurements (p. 461) to be made. It must be emphasised that there is no question of even slight racemisation affecting the above results: the free amine can be distilled, and its hydrochloride boiled in aqueous solution for 6 hours, without change of activity. Moreover, the hydrochloride used in the above organic solvents was always recovered and its optical purity checked.

These remarkable optical properties of 2-amino-octane and its salts warrant detailed investigation, but until full ultra-violet rotatory dipersion and absorption-spectra measurements can be carried out on the base and its salts in many solvents and at various concentrations, we postpone a full discussion of the results.

It is noteworthy, however, that the hydrochlorides of both the racemic and the *l*-amine are greatly associated in all solvents except those which exert a simple ionising action. This is shown in the following table, where *c* represents the concentration of the solution as g. of solute per 100 g. of solution, and " Eb." and " Cr." represent ebullioscopic and cryoscopic methods of molecular-weight determination; ε is the dielectric constant, and μ the dipole moment of the solvent. The " normal " molecular weight of the hydrochloride is 165·5.

				Hydrochloride of racemic amine.		Hydrochloride of *l*-amine.	
Solvent.	ε.	$\mu \times 10^{18}$.	Method.	*c.*	*M.*	*c.*	*M.*
Water	81·5	1·85	Cr.	2·29	86·9	1·46	87·2
Ethyl alcohol *	25·8	1·70	Eb.	2·40	136	3·312	144
Formamide	—	3·22	Cr.	2·03	81·9	1·83	85·0
Acetonitrile	37·5	3·51	Eb.	3·00	320	2·456	364
Methylene dichloride	9·14	1·55	Eb.	0·539	452	0·646	620
				0·785	511	1·139	628
Chloroform	4·64	1·18	Eb.	0·7079	604	0·6466	606
				1·217	543	0·9745	541
Carbon tetrachloride	2·22	0	Eb.	0·899	559	0·6626	667
				1·318	633	1·716	761
Ethylene dichloride	10·13	1·38	Eb.	1·821	1100	1·550	1820
Ethylene dibromide	4·73	1·12	Cr.	(*a*)	—	0·93	342
Dioxan	2·23	0·45	Eb.	2·325	286	1·936	395
Benzene	2·30	0	Cr.	2·94	808	2·33	792
Toluene	2·38	0·4	Eb.	1·89	680	1·75	709
				2·82	757	3·20	709
p-Xylene	2·27	0	Cr.	1·216	1160	0·835	[2600] (*b*)
				2·128	1180		

* The ethyl alcohol used contained 0·9% of water.
(*a*) The low solubility in freezing ethylene dibromide made measurement impossible.
(*b*) The low solubility in freezing *p*-xylene caused this value to be only approximate.

Whatever the exact interpretation of molecular weights determined by cryoscopic and ebullioscopic methods, there is no doubt about the association of these hydrochlorides in the non-ionising solvents, for our results were obtained with carefully purified solvents, and the molecular depression and elevation constants were based on determinations made with pure solutes (naphthalene, acenaphthene, and diphenyl) at approximately the same molecular concentrations as those used for the amine hydrochlorides in the same apparatus.

The association of many amine salts in various solvents has been critically examined by Turner *et al.* (J., 1911, **99**, 880; 1912, **101**, 1923; 1914, **105**, 1751, 1786; *J. Amer. Chem. Soc.*, 1915, **37**, 2063), who found that, in general, high association occurred in solvents of low dielectic constants, and *vice versa*: our results for the above two hydrochlorides do not, however, follow this rule, and their association must be partly or wholly determined by other factors.

Furthermore, Rule and his co-workers (J., 1931, 674, 2652; 1932, 1400, 1409, 2332; 1933, 376, 1217) have shown that the rotation of a compound in a series of solvents depends largely on the dipole moment of the solvents, since the polar properties of the latter will largely determine the degree of association between the solute and the solvent. It is difficult to detect any similar relationship in our results, where the rotation is so often determined far more by the concentration of the solution than by the polarity of the solvent.

In explanation of our results, we tentatively suggest that the free amine, represented by $R{\cdot}NH_2$, may combine in alcoholic solution with the solvent by hydrogen-bond formation, giving an unstable product

$RH_2N \cdots H{-}OEt$. This would account for the abnormal rotations of alcoholic solutions of the amine, whilst benzene solutions, in which such combination is impossible, show normal rotations. (On the other hand, an addition product of the above structure might be expected to show the " acid-effect," which alcoholic solutions of the amine do not show over the limited range of our measurements : in this respect, however, these solutions may correspond optically to very dilute solutions of the hydrochloride in methylene dichloride, etc.) The amine hydrochloride in aqueous and alcoholic solution undoubtedly has the normal salt structure $[\overset{+}{R}NH_3]\overset{-}{Cl}$. It is possible, however, that in non-ionising solvents such as methylene dichloride and benzene, this salt changes to a similar hydrogen-bond product, $RH_2N \cdots H{-}Cl$, and that it is the resonance between the two hydrogen valencies that makes the compound virtually covalent and hence soluble in such solvents. If this is true, then it is this hydrogen-bond product which associates so readily and must be the essential unit in the molecular aggregates, which may consist of hydrochloride molecules alone, or of the latter associated in addition with solvent molecules.

When a change in concentration of an optically active substance in solution causes a progressive change in the sign of rotation, the substance almost invariably is undergoing some chemical change (*e.g.*, tautomerisation, isomerisation, or combination with the solvent), the degree of change being determined by the concentration. It is highly probable, therefore, that the associated aggregates of the amine hydrochloride in the non-ionising solvents undergo some fundamental change as their solutions are diluted. Since, however, we are ignorant of both the composition and the structure of these micelles, it is useless to attempt to interpret the nature of this change.

Experimental.

All rotations were measured at 17° ± 1°. Those on the free amine (without a solvent) were measured in a 4-cm. tube; all other rotations (*i.e.*, those on all solutions) were measured in a 4-dm. tube.

Methyl n-*Hexyl Ketone*.—Commercial *sec.*-octyl alcohol (120 g., 147 c.c.) was added dropwise during 1·5 hours to a vigorously stirred solution of sodium dichromate dihydrate (90 g.) and concentrated sulphuric acid (120 g., 66 c.c.) in water (600 c.c.). The mixture was then heated under reflux on a boiling water-bath for 2 hours, and the ketone finally isolated by steam distillation : b. p. 172—173°; 110—115 g. (92—96%) (cf. Verhulst and Glorieux, *loc. cit.*).

Methyl n-*Hexyl Ketoxime*.—This was prepared in 90—95% yield and had b. p. 106—108°/12 mm.; Moureu and Delange (*Compt. rend.*, 1903, **136**, 754) give b. p. 116·5°/15 mm.

Reduction. A solution of the oxime (50 g.) in alcohol (200 c.c.) was refluxed on a boiling water-bath during the gradual addition of sodium (75 g., 6 atoms), more alcohol (*ca.* 300 c.c.) being added in small quantities to maintain vigorous reaction. When all the sodium had dissolved, the solution was cooled, diluted with water (250 c.c.), and then gently distilled until the b. p. reached 96°; more water (200 c.c.) was added, and the distillation repeated to ensure complete removal of alcohol, leaving the amine floating on the strongly caustic aqueous solution. (A small quantity of amine was recovered from the distillates and added to this alkaline liquid.) The amine was now extracted from the solution with ether, the solvent removed from the dried extract (sodium hydroxide), and the 2-amino-octane distilled under reduced pressure; b. p. 58—59°/13 mm., 163—164°/760 mm. (Found : C, 74·0; H, 14·6; N, 11·2. Calc. for $C_8H_{19}N$: C, 74·4; H, 14·7; N, 10·9%); 30—32 g. (62—69%).

Reduction of the oxime with sodium amalgam in cold acetic acid, or with aluminium amalgam in warm alcoholic solution (cf. Mann and Pope, *Proc. Roy. Soc.*, 1925, *A*, **107**, 86) gave unsatisfactory results.

The *dl*-amine was characterised by its *benzoyl* derivative, m. p. 73—74° (Found : C, 77·4; H, 10·0; N, 6·0. $C_{15}H_{33}ON$ requires C, 77·4; H, 9·9; N, 6·0%), from aqueous alcohol. Its *hydrochloride*, recrystallised from petrol (b. p. 60—80°), had m. p. 91—92° (Found : Cl, 21·4. $C_8H_{19}N$,HCl requires Cl, 21·4%).

Methyl n-*Hexyl Ketone Phenylhydrazone*.—Prepared by normal methods, this *phenylhydrazone* was obtained in 65—70% yield as a pale yellow liquid (Found : N, 13·0. $C_{14}H_{22}N_2$ requires N, 12·8%); b. p. 119—120°/0·05 mm. When the crude product was distilled at 12 mm., the hydrazone had b. p. 179—181°, but was impure (Found : N, 11·7%).

Reduction. Best results were obtained by small alternate additions of 2·5% sodium amalgam (600 g.) and glacial acetic acid (100 c.c.) to a solution of the hydrazone (30 g.) in alcohol (300 c.c.) kept below 20°. The product was poured into excess of dilute hydrochloric acid, and alcohol removed by steam-distillation. The residue was basified (sodium hydroxide) and again steam-distilled to isolate the amine, but after the usual procedure, distillation afforded two fractions : (*a*) b. p. 55—64°/13 mm., which after two further fractional distillations afforded 10 g. (60%) of 2-amino-octane, b. p. 58—60°/13 mm., analytically pure (Found : C, 74·0; H, 14·3; N, 11·1%) but still containing a trace of aniline; (*b*) b. p. 65—72°/13 mm., mainly aniline.

dl-2-*Amino*-n-*octane* d-*camphorsulphonate* was obtained by mixing equimolecular quantities of the amine and the acid in alcoholic solution and then evaporating the solvent in a vacuum desiccator, the residual syrupy sulphonate ultimately crystallising. The salt was readily soluble in cold water, methyl and ethyl alcohols, moderately soluble in cold ethyl acetate, but almost insoluble in benzene, toluene, and *cyclo*hexane. After four recrystallisations from ethyl acetate–*cyclo*hexane, the sulphonate was obtained as soapy crystals, m. p. 162—165°, unchanged by further crystallisation (Found : N, 3·9. $C_8H_{19}N,C_{10}H_{16}O_4S$ requires N, 3·9%). A 2·817% aqueous solution had α_D +1·54°, $[M]_D^{19°}$ +49·5°; since a 2% solution of the camphorsulphonate ion has $[M]_D$ +50·0° (Graham, J., 1912, **101**, 746), no resolution was occurring.

The d-α-*bromocamphorsulphonate*, similarly prepared and recrystallised, had m. p. 180—185° (Found : N, 2·9. $C_8H_{19}N,C_{10}H_{15}O_4BrS$ requires N, 3·2%). The amine, liberated from this salt by sodium hydroxide, was optically inactive.

Resolution of the dl-*Amine*.—Full optical data are collected on p. 460. In the following description, only sufficient data are cited to show the course of the resolution.

(A) *Using methyl alcohol*. The *dl*-amine (150 g.) and *d*-tartaric acid (174 g., 1 mol.) were dissolved together in hot methyl alcohol (750 c.c.), and the crystals which separated on cooling were then recrystallised eight times more from methyl alcohol (using 400, 300, 250, 200, 150, 120, 120, 120 c.c. of solvent). The d-*hydrogen tartrate* thus obtained separated as the *hemi-methyl alcoholate* (Found : C, 50·6; H, 9·3; N, 4·85; CH_4O, 5·1. $C_8H_{19}N,C_4H_6O_6,\frac{1}{2}CH_4O$ requires C, 50·8; H, 9·15; N, 4·75; CH_4O, 5·4%); confinement in a vacuum readily gave the solvent-free *salt*, m. p. 75—83° (Found : C, 51·3; H, 8·7; N, 4·85. $C_8H_{19}N,C_4H_6O_6$ requires C, 51·6; H, 9·0; N, 5·0%). A portion of this salt was decomposed with 10% aqueous sodium hydroxide, the liberated amine extracted with ether, and the extract dried over powdered sodium hydroxide. Fractional distillation of the filtered extract, protected from carbon dioxide, in an all-

glass lubricant-free apparatus gave the amine, b. p. 76°/30 mm.; the distillate was finally dried over sodium and then had α_D −2·00°, α_{4358} −3·92°; $[M]_D$ −8·36°, $[M]_{4358}$ −16·4°. This amine was reconverted into the *d*-hydrogen tartrate, added to the main bulk of the salt, and the whole recrystallised again (120 c.c.). A portion now furnished the free amine, α_D −2·04°, α_{4358} −4·02°, $[M]_D$ −8·53°, $[M]_{4358}$ −16·8°. This procedure was repeated, the salt now being recrystallised twice more (100, 100 c.c.); the *d*-hydrogen tartrate had m. p. 75—84° and gave the pure l-*amine*, α_D −2·04°, α_{4358} −4·02°

		Wave length (A.) of light.								
		Li, 6708.	Li, 6104.	Na, 5893.	Hg, 5780.	Hg, 5461.	Hg, 4358.	k (calc.).	λ_0^2 (calc.).	λ_0, A.
d-*Amine.*										
(*a*) Without solvent	*a*, obs.	+1·57°	+1·92°	+2·06°	+2·16°	+2·44°	+4·05°	—	—	—
	[*M*]	6·56	8·03	8·62	9·03	10·2	16·9	—	—	—
	a, calc.	1·57	1·92	2·07	2·16	2·44	4·03	0·6694	0·0238	1540
	a, obs.—*a*, calc.	0·00	0·00	−0·01	0·00	0·00	+0·02	—	—	—
(*b*) In 5·953% benzene solution	*a*, obs.	+1·18	+1·47	+1·57	+1·65	+1·84	+3·03	—	—	—
	[*M*]	6·34	7·96	8·50	8·99	9·97	16·4	—	—	—
	a, calc.	1·22	1·47	1·58	1·64	1·84	2·91	0·5441	0·00324	1800
	a, obs.—*a*, calc.	−0·04	0·00	−0·01	+0·01	0·00	+0·12	—	—	—
(*c*) In 2·77% ethyl alcohol solution	*a*, obs.	*	*	+0·08	+0·09	+0·11	—	—	—	—
	[*M*]	—	—	0·9	1·0	1·3	—	—	—	—
In 8·06% ethyl alcohol solution	*a*, obs.	*	*	+0·22	+0·24	+0·32	†	—	—	—
	[*M*]	—	—	0·88	0·96	1·34	—	—	—	—
l-*Amine.*										
(*a*) Without solvent	*a*, obs.	−1·56	−1·91	−2·04	−2·15	−2·43	−4·02	—	—	—
	[*M*]	6·52	7·98	8·53	8·99	10·2	16·8	—	—	—
	a, calc.	1·56	1·91	2·06	2·15	2·43	4·03	0·660	0·0262	1620
	a, calc.—*a*, obs.	0·00	0·00	−0·02	0·00	0·00	−0·01	—	—	—
Hydrochloride of d-*amine in* EtOH.										
(i) In 3·08% solution	*a*, obs.	*	*	−1·00	*	−1·10	*	—	—	—
	[*M*]	—	—	13·4	—	14·8	—	—	—	—
(ii) In 4·29% solution	*a*, obs.	*	*	−1·44	−1·51	−1·74	−3·13	—	—	—
	[*M*]	—	—	13·8	14·5	16·7	30·0	—	—	—
(iii) In 4·58% solution	*a*, obs.	*	*	−1·55	*	−1·84	*	—	—	—
	[*M*]	—	—	14·0	—	16·7	—	—	—	—
(iv) In 6·88% solution	*a*, obs.	*	*	−2·33	*	2·79	*	—	—	—
	[*M*]	—	—	14·0	—	16·8	—	—	—	—
(v) In 10·31% solution	*a*, obs.	−2·63	−3·28	−3·60	−3·75	−4·26	−7·35	—	—	—
	[*M*]	10·6	13·2	14·5	15·0	17·1	29·5	—	—	—
	a, calc.	2·64	3·28	3·56	3·72	4·27	7·55	1·058	0·0500	2240
	a, obs.—*a*, calc.	−0·01	0·00	+0·04	+0·03	−0·01	−0·20	—	—	—
(vi) In 15·47% solution	*a*, obs.	*	*	−5·6	*	−6·9	*	—	—	—
	[*M*]	—	—	14·9	—	18·5	—	—	—	—
Hydrochloride of l-*amine.*										
(*a*) In 7·77% aqueous solution	*a*, obs.	+0·96	+1·14	+1·24	+1·30	+1·45	+2·42	—	—	—
	[*M*]	5·11	6·08	6·61	6·94	7·74	12·9	—	—	—
	a, calc.	0·93	1·14	1·23	1·31	1·45	2·42	0·3943	0·0266	1630
	a, obs.—*a*, calc.	+0·03	0·00	+0·01	−0·01	0·00	0·00	—	—	—
(*b*) In 6·32% methyl alcohol solution	*a*, obs.	+0·88	+1·09	+1·18	+1·24	+1·42	+2·54	—	—	—
	[*M*]	5·76	7·14	7·73	8·12	9·30	16·6	—	—	—
	a, calc.	0·88	1·09	1·18	1·24	1·42	2·58	0·3445	0·0564	2370
	a, obs.—*a*, calc.	0·00	0·00	0·00	0·00	0·00	−0·04	—	—	—
(*c*) In 4·310% ethyl alcohol solution	*a*, obs.	+1·08	+1·34	+1·45	+1·51	+1·75	+3·12	—	—	—
	[*M*]	10·4	12·9	13·9	14·5	16·8	29·9	—	—	—
	a, calc.	1·08	1·34	1·45	1·52	1·75	3·16	0·4249	0·0554	2350
	a, obs.—*a*, calc.	0·00	0·00	0·00	−0·01	0·00	−0·04	—	—	—
(*d*) In 5·02% acetone solution	*a*, obs.	+0·79	+0·97	+1·05	+1·10	+1·27	+2·29	—	—	—
	[*M*]	6·51	8·00	8·65	9·06	10·5	18·9	—	—	—
	a, calc.	0·78	0·97	1·05	1·10	1·27	2·31	0·3050	0·0580	2410
	a, obs.—*a*, calc.	+0·01	0·00	0·00	0·00	0·00	−0·02	—	—	—
(*e*) In 5·37% formamide solution	*a*, obs.	+0·40	+0·50	+0·53	+0·56	+0·65	+1·07	—	—	—
	[*M*]	3·09	3·96	4·09	4·32	5·01	8·26	—	—	—
	a, calc.	0·40	0·50	0·54	0·57	0·65	1·09	0·1577	0·0572	2390
	a, obs.—*a*, calc.	0·00	0·00	−0·01	−0·01	0·00	−0·02	—	—	—
(*f*) In 3·180% acetonitrile solution	*a*, obs.	*	*	+0·69	+0·73	+0·81	+1·43	—	—	—
	[*M*]	—	—	8·95	9·48	10·5	18·6	—	—	—
(*g*) In 2·31% carbon tetrachloride solution	*a*, obs.	*	*	+0·55	*	*	*	—	—	—
	[*M*]	—	—	9·85	—	—	—	—	—	—
In 4·17% carbon tetrachloride solution	*a*, obs.	*	*	+1·17	+1·24	+1·44	+2·44	—	—	—
	[*M*]	—	—	11·6	12·3	14·3	24·2	—	—	—
(*h*) In 2·16% chloroform solution	*a*, obs.	*	*	−0·08	*	*	*	—	—	—
	[*M*]	—	—	1·5	—	—	—	—	—	—
In 4·45% chloroform solution	*a*, obs.	*	*	+0·09	+0·10	+0·13	+0·22	—	—	—
	[*M*]	—	—	0·8	0·94	1·2	2·05	—	—	—

* Not measured. † Not observable.

(Found: N, 10·6%). The resolution had thus been complete after the tenth recrystallisation. The tartrate in the mother-liquors of the last two recrystallisations was therefore recovered, added to the final fraction, and the pure *l*-amine liberated; 12·5 g. It is noteworthy that the m. p. of the tartrate is not markedly affected by the optical purity of the salt and so gives no reliable indication of the course of the resolution.

The mother-liquors from the first four above recrystallisations were evaporated, and the amine liberated from the residue had α_D +0·52°. This was converted into the *l*-hydrogen tartrate, and the latter recrystallised seven times from methyl alcohol. The product, treated as before, furnished the optically pure *d*-amine, b. p. 70°/25 mm., α_D +2·06°, α_{4358} +4·05°; $[M]_D$ +8·62°, $[M]_{4358}$ +16·9°; 6·0 g. Further recrystallisation of the tartrate did not change the rotation of the liberated amine.

(B) *Using ethyl alcohol.* When the *d*-hydrogen tartrate of the *dl*-amine was prepared as above, but in ethyl alcohol, the *l*-amine *d*-hydrogen tartrate was again the less soluble; 13 or 14 recrystallisations (depending on the volume of solvent used) were, however, now required to complete the resolution and to furnish the optically pure *l*-amine. The use of methyl alcohol is therefore preferable.

(C) *Using water.* Earlier work showed that recrystallisation of the *d*-hydrogen tartrate of the *dl*-amine from water furnished the less soluble d-*amine* d-*hydrogen tartrate*. This resolution was therefore investigated in detail, as it appeared a valuable alternative to the use of the costly *l*-tartaric acid. The *dl*-amine (463 g.) and *d*-tartaric acid (549 g., 1 mol.) were dissolved together in boiling water, and the crop of hydrogen tartrate which separated was recrystallised thrice more from water; m. p. 78—82° (Found: C, 51·2; H, 8·8; N, 5·0%). The amine, liberated from a portion of this salt, had α_D +0·08°. The salt was then repeatedly recrystallised from water. Test samples showed a steadily increasing rotation of the liberated amine until the salt had been recrystallised 23 times; the liberated amine now had b. p. 55—56°/12 mm., α_D +1·32°, $[M]_D$ +5·5°. Further recrystallisations of the salt did not sensibly affect the rotation of the liberated amine, and this method of resolution was therefore abandoned.

The *hydrochloride* of the *l*-amine was prepared by neutralising the amine with dilute hydrochloric acid and evaporating the solution in a vacuum at room temperature; the residual solid, recrystallised from petrol (b. p. 60—80°), had m. p. 90—91° (Found: Cl, 21·6. $C_8H_{19}N,HCl$ requires Cl, 21·4%). The hydrochloride of the *d*-amine, similarly prepared, also had m. p. 90—91°.

The *benzoyl* derivative of the *l*-amine recrystallised from *cyclo*hexane as colourless needles, m. p. 101—102° with slight preliminary softening (Found: N, 6·1. $C_{15}H_{23}ON$ requires N, 6·0%). It is appreciably less soluble in *cyclo*hexane than the racemic compound.

In the optical rotation data given below, the rotation constant (k) and the dispersion constant (λ_0) have been calculated throughout on the simple dispersion equation $\alpha = k/(\lambda^2 - \lambda_0^2)$. It must be emphasised, however, that our measurements of the rotatory dispersion, being limited to six wave-lengths in the visible spectrum, provide too narrow a basis for accurate calculation of the dispersion constants, and the values recorded are necessarily only approximate. For this reason, the dispersion constants have not been calculated when less than the full six readings were made.

In the following solvents, the concentration (c, g. of solute/100 c.c. of solution) of the hydrochloride of the *l*-amine has been varied, but the rotations have been measured solely for the Na_D light. Rotations measured at very great dilution, or at concentrations near the change of sign, were necessarily very small, and high accuracy cannot be claimed for these readings; they indicate clearly, however, the nature of the change of rotation. Great care was necessary to ensure that the solutions were anhydrous.

Methylene dichloride.

c	2·44	2·80	3·36	4·04	4·85	5·82	6·11	6·98	8·38	9·17	11·0
α, obs.	−0·01°	−0·05°	−0·05°	−0·01°	+0·06°	+0·13°	+0·15°	+0·21°	+0·35°	+0·46°	+0·66°
$[M]$	−0·2	−0·7	−0·6	−0·1	+0·5	+0·92	+1·0	+1·24	+1·73	+2·1	+2·5

Benzene.

c	2·04	2·45	2·94	3·53	4·24	5·09	6·11	7·73
α, obs.	−0·04°	−0·10°	−0·05°	−0·01°	0°	+0·01°	+0·06°	+0·17°
$[M]$	−0·8	−1·7	−0·7	−0·1	0	+0·1	+0·4	+0·91

	Ethylene dichloride.			*Toluene.*		*Dioxan.*		*Ethylene dibromide.*
c	2·23	3·35	5·03	2·28	3·20	2·02	2·66	2·75
α, obs.	−0·02°	+0·08°	+0·30°	−0·08°	0°	−0·05°	0°	0°
$[M]$	−0·4	+1	+2·5	−1·5	0	−1	0	0

Optical Stability.—A 5·31% aqueous solution of this hydrochloride, having α, obs. +0·65°, $[M]$ +5·1°, was refluxed for 6 hours; the solution when cold, still had α, obs. +0·65°, $[M]$ +5·1°.

Benzoyl derivative of l-amine.	λ, A.	6708.	6104.	5893.	5780.	5461.	4358.	k (calc.).	λ_0^2 (calc.).	λ_0, A.
In 1·950% ethyl alcohol solution	α, obs.	−1·62°	−1·92°	−2·08°	−2·17°	−2·46°	−4·20°	—	—	—
	$[M]$	48·4	57·3	62·1	64·8	73·5	125	—	—	—
	α, calc.	1·56	1·92	2·08	2·16	2·46	4·17	0·6501	0·0339	1840
	α, obs.−α, calc.	−0·06	0·00	0·00	+0·01	0·00	+0·03	—	—	—

We gratefully acknowledge much helpful discussion with Dr. C. B. Allsopp, and a grant from the Department of Scientific and Industrial Research (J. W. G. P.).

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 26th*, 1944.]