90. *Experiments relating to the Resolution of Tertiary Alcohols: the Resolution and Deamination of α-Naphthylphenyl-*p*-tolylmethylamine, and the Curtius, Hofmann, and Schmidt Reactions with 2-Methyl-2-phenylhexanoic Acid.**

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α-Naphthylphenyl-*p*-tolylmethylamine has been resolved *via* the (+)- and (−)-camphorsulphonates. The (+)-amine hydrochloride with sodium nitrite yielded (±)-α-naphthylphenyl-*p*-tolylcarbinol. (±)-2-Methyl-2-phenylhexanoic acid * (I) gave, *via* the chloride and azide, (±)-2-amino-2-phenylhexane (II); the (+)-acid gave the (−)-amine. The amide of (I) with sodium hypochlorite gave (II) in low yield. Sodium azide in sulphuric acid–chloroform decomposed (I), yielding aniline (55%); the mechanism of this reaction is discussed. The preparation of some ω-alkylacetophenones is described.

NUMEROUS secondary alcohols have been resolved through the alkaloidal salts of their hydrogen phthalates (or succinates), but the many similar attempts with tertiary alcohols have failed, with the exception of *iso*butylethylmethylcarbinol (Doering and Zeiss, *J. Amer. Chem. Soc.*, 1948, **70**, 3966; 1950, **72**, 147). It was considered desirable to ascertain if amines of the type $CRR'R''\cdot NH_2$, where R, R′, R″ are alkyl or aryl groups, could be obtained in optically active forms. No report of the resolution of such an amine or of its preparation by the degradation of an optically active acid $CRR'R''\cdot CO_2H$ has been found, although the following optically active amines have been prepared by the Hofmann reaction with amides the α-carbon atoms of which are tertiary and form part of an alicyclic ring: (+)-aminodihydrocampholytic acid (Noyes and Phillips, *Amer. Chem. J.*, 1900, **24**, 290), (+)-fenchelylamine hydrochloride (Wallach, *Annalen*, 1909, **369**, 81), (+)-aminolauronic acid (Weir, *J.*, 1911, **99**, 1270), (−)-amino*iso*dihydrocampholytic acid (Noyes and Nickell, *J. Amer. Chem. Soc.*, 1914, **36**, 118). Amines of similar type which were presumably optically active but for which no rotation data are given have been prepared as follows: camphelylamine, by the Hofmann reaction with the corresponding amide (Errera, *Gazzetta*, 1892, **22** (i), 205); and, by the Schmidt reaction with the corresponding acid, camphelylamine, fenchelylamine, dimethylcamphelylamine (von Braun, *Annalen*, 1931, **490**, 125; von Braun and Kurtz, *Ber.*, 1934, **67**, 225).

α-Naphthylphenyl-*p*-tolylmethylamine, prepared by the action of ammonia on the corresponding methyl chloride, has now been resolved by fractional crystallisation of the (+)- and the (−)-camphorsulphonate, the enantiomeric amines having $[\alpha]_{5893}^{17} \pm 1{\cdot}3^\circ$ in carbon disulphide. Reaction of the (+)-amine hydrochloride (optical purity, 51%) with sodium nitrite gave optically inactive α-naphthylphenyl-*p*-tolylcarbinol. It is inferred that the intermediate

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* Geneva numbering, $CO_2H = 1$.

carbonium cation is of sufficiently long life to yield equal amounts of (+)- and (−)-carbinol by reaction with a hydroxyl ion or water and that shielding by the released nitrogen molecule is here unimportant.

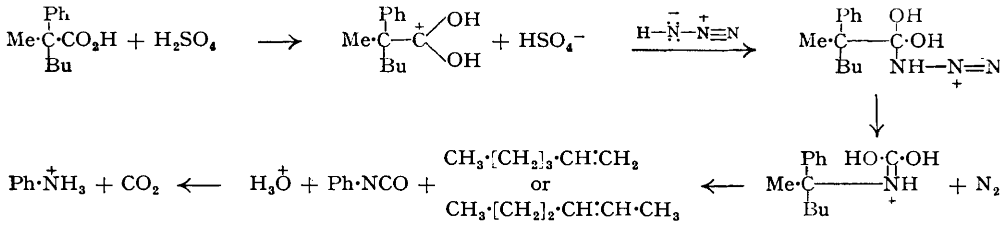
$$\mathrm{R{\cdot}NH_2,HCl + NaNO_2 \longrightarrow NaCl + H_2O + R{\cdot}N_2^+ + OH^-}$$
$$\mathrm{R{\cdot}N_2^+ \longrightarrow R^+ + N_2;\ R^+ + OH^-\ (or\ H_2O) \longrightarrow ROH(+H^+)}$$

Since Hofmann, Curtius, and Schmidt reactions with (+)-α-phenylpropionic acid gave (−)-1-phenylethylamine with a high degree of retention of asymmetry and of configuration (Arcus and Kenyon, *J.*, 1939, 916; Kenyon and Young, *J.*, 1941, 263; Campbell and Kenyon, *J.*, 1946, 25) it was decided to carry out these reactions with optically active 2-methyl-2-phenylhexanoic acid * (I). The chloride of the (±)-acid with sodium azide in aqueous acetone and in toluene gave (±)-2-amino-2-phenylhexane (II) in 27 and 25% yield respectively. Repetition of the reaction in aqueous acetone with the chloride of the (+)-acid (optical purity, 29%) gave (II) having α^{16}_{5893} −0·66° (homogeneous; *l.*, 0·5) which yielded a benzoyl derivative having $[\alpha]^{18}_{5893}$ +3·5° (in benzene).

From the reaction of the (±)-amide of (I) with sodium hypochlorite, the (±)-amine (II) was isolated as the benzoyl derivative in 10% yield; the reaction was not repeated with optically active material.

$\mathrm{CH_3{\cdot}[CH_2]_3{\cdot}CPhMe{\cdot}CO_2H}$ (I.) $\mathrm{CH_3{\cdot}[CH_2]_3{\cdot}CPhMe{\cdot}NH_2}$ (II.)

Aniline (55% yield) was the sole basic product isolated from the reaction of the (±)-acid (I) with sodium azide in chloroform–sulphuric acid. Addition of bromine to the neutral products of reaction, and distillation, yielded a fraction the boiling point and bromine content of which indicated it to be dibromohexane(s). The most probable course of reaction appears to be the following:



It is intended to investigate in greater detail the mechanism of this reaction; it may be noted that (*a*) 1-methyl-1-phenyl-*n*-amyl *iso*cyanate is not abnormally unstable in the absence of sulphuric acid, because the Curtius reaction yielded the expected amine (II); (*b*) the Schmidt reaction with triethylacetic acid gave a mixture of lower amines, lower ketones, and triethylacetamide (Schuerch and Huntress, *J. Amer. Chem. Soc.*, 1949, **71**, 2238); (*c*) in contrast to the disintegration occurring with these two acids, trimethylacetic acid, 1-methyl*cyclo*hexanecarboxylic acid (Schuerch and Huntress, *ibid.*, p. 2233), the terpene acids investigated by von Braun (*loc. cit.*), and podocarpic acid (Briggs, De Ath, and Ellis, *J.*, 1942, 62) yield as the principal product of the Schmidt reaction the expected amine having the amino-group attached to a tertiary carbon atom.

The preparation of (±)-α-benzylpropiophenone, (±)-2-benzyl-2-methylhexanoylbenzene * and (±)-2-ethyl-2-methylhexanoylbenzene is described.

EXPERIMENTAL.

*α-Naphthylphenyl-*p*-tolylmethylamine.*—α-Naphthylphenyl-*p*-tolylcarbinol and its chloride were prepared by a modification of the method of Schlenk and Meyer (*Ber.*, 1919, **52**, 17), who record m. p. 109—110° and 142—144° for the carbinol and chloride respectively.

To a solution of α-naphthylmagnesium bromide, prepared from α-bromonaphthalene (45·5 g.) and magnesium (5·4 g.), in ether (135 ml.), heated under reflux, was added gradually, with stirring, a solution of phenyl *p*-tolyl ketone (43·5 g.) in ether (200 ml.). After 4 hours the mixture was cooled and decomposed with ice–ammonium chloride, yielding (±)-α-naphthylphenyl-*p*-tolylcarbinol, m. p. 109°. This material was dissolved in ether and a current of hydrogen chloride passed in for several hours. A little acetyl chloride was added to remove the water formed during the reaction. The solvent was distilled and the residue on crystallisation from light petroleum (b. p. 40—60°) yielded α-naphthylphenyl-*p*-tolylmethyl chloride, m. p. 142° (25 g., 33% yield from the ketone).

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* Geneva numbering, $\mathrm{CO_2H} = 1$.

Dry ammonia was passed through a solution of the chloride (25 g.) in benzene (550 ml.), until no more ammonium chloride separated. After filtration, and evaporation of the solvent, addition of light petroleum (b. p. 40—60°) to the residue gave a light brown powder, which on recrystallisation from alcohol gave (±)-*α-naphthylphenyl-*p*-tolylmethylamine*, small white needles, m. p. 127—128° (Found : C, 89·1; H, 6·5; N, 4·2. $C_{24}H_{21}N$ requires C, 89·1; H, 6·6; N, 4·3%).

Resolution. To a solution of (±)-α-naphthylphenyl-*p*-tolylmethylamine (21·0 g.) in alcohol (300 ml.) was gradually added a solution of (+)-camphorsulphonic acid (15·1 g.) in water (80 ml.); a salt (15·8 g.) gradually separated. Four recrystallisations from aqueous alcohol yielded a camphorsulphonate (8·2 g.), the amine from which had attained a constant rotation. This salt (4 g.) was agitated with 0·1N-sodium carbonate (300 ml.) and ether. The ethereal layer was repeatedly washed with aqueous sodium carbonate, then dried ($CaSO_4$), and the solvent evaporated. The residue was recrystallised from alcohol and gave α-naphthylphenyl-*p*-tolylmethylamine (2·2 g.), m. p. 128°, $[\alpha]^{17}_{5893}$ −1·3° (*c*, 3·7 in carbon disulphide). A similar resolution with (−)-camphorsulphonic acid yielded α-naphthylphenyl-*p*-tolylmethylamine having $[\alpha]^{17}_{5893}$ +1·3° (*c*, 4·7 in carbon disulphide).

On passing dry hydrogen chloride through a solution of (±)-α-naphthylphenyl-*p*-tolylmethylamine in dry ether, the hydrochloride separated as a white precipitate, m. p. 150—155° (decomp.). The amine was recovered nearly quantitatively on treating the hydrochloride with aqueous sodium carbonate. A specimen of the amine having $[\alpha]^{17}_{5893}$ +1·0° (*c*, 5·5 in carbon disulphide) yielded a hydrochloride having $[\alpha]^{17}_{5893}$ +1·5° (*c*, 6·7 in water), +1·3° (*c*, 6·1 in 0·1N-hydrochloric acid).

Deamination. To a solution of (±)-α-naphthylphenyl-*p*-tolylmethylamine hydrochloride (4·2 g.) in water (75 ml.) was added a solution of sodium nitrite (2·4 g.) in water (25 ml.). A white crystalline mass separated; water (50 ml.) was added and the whole boiled. Benzene was then added and the mixture stirred with heating under reflux for 24 hours. The benzene layer was washed repeatedly with 3N-hydrochloric acid and with warm water, dried ($CaSO_4$), and treated with charcoal and with alumina. After removal of the benzene under reduced pressure, the residue (2·9 g.) was allowed to crystallise slowly from ligroin, (±)-α-naphthylphenyl-*p*-tolylcarbinol (1·2 g., 31%), m. p. 109° alone or mixed with authentic material, being obtained (Found : C, 88·3; H, 6·2. Calc. for $C_{24}H_{20}O$: C, 88·7; H, 6·4%). Repetition with α-naphthylphenyl-*p*-tolylmethylamine hydrochloride having $[\alpha]_{5893}$ +1·0° (in water) gave optically inactive carbinol.

Curtius, Hofmann, and Schmidt Reactions with 2-*Methyl*-2-*phenylhexanoic Acid*.—To a solution of α-phenylpropionitrile (79 g.; b. p. 114°/16 mm.; prepared according to Campbell and Kenyon, *loc. cit.*) and *n*-butyl bromide (85 g.) in dry benzene (100 ml.) was added a suspension of sodamide (24·5 g.) in benzene. After an initial brisk reaction the whole was heated, with stirring, on a steam-bath for several hours. Water was then added and the benzene layer repeatedly washed with water and dried ($CaSO_4$). After distillation of the benzene, the residue was distilled and gave 1-*methyl*-1-*phenylamyl cyanide*, b. p. 147°/16 mm. (80 g., 71%) (Found : C, 83·2; H, 9·2; N, 7·6. $C_{13}H_{17}N$ requires C, 83·3; H, 9·2; N, 7·5%).

The nitrile (17 g.) was heated under reflux for 10 days in a solution of potassium hydroxide (16 g.) in alcohol (90 ml.) and water (25 ml.). The alcohol was then distilled off, water added, and the whole acidified and extracted with benzene. Evaporation of the benzene extract yielded a mixture of the acid, the amide, and some unchanged nitrile. Fractionation of the mixture gave the acid still containing some amide. This material was dissolved in excess of alkali and repeatedly extracted with chloroform; acidification of the alkaline solution gave 2-methyl-2-phenylhexanoic acid, b. p. 173°/16 mm. (Found : (equiv., 208·0. Calc. for $C_{12}H_{17}\cdot CO_2H$: equiv., 206·3).

Resolution of the acid was carried out according to Conant and Carlson (*J. Amer. Chem. Soc.*, 1932, **54**, 4055), by recrystallising the quinine salt from aqueous alcohol until the acid obtained on decomposing a portion of the salt had attained a constant rotation. The fully-active acid had the rotatory powers recorded in the table.

Solvent.	*c*.	Temp.	λ :	4358	4678	4800	5086	5461	5893	6438
						2-*Methyl*-2-*phenylhexanoic acid.*				
None	—	15°	α (*l*, 0·5) :						+8·65°	
Et_2O	6·41	15°	[α] :	+23·3°	+19·4°	+19·3°	+16·4°	+13·8°	+11·6°	+9·4°
CS_2	1·00	17°	[α] :					+26·0°	+21·4°	
						2-*Amino*-2-*phenylhexane.*				
None	—	16°	α (*l*, 0·5) :	−1·70°	−1·32°	−1·25°	−1·03°	−0·83°	−0·66°	−0·56°
Et_2O	1·00	17°	[α] :					−1·3°	−1·2°	
CS_2	1·00	17°	[α] :						−2·3°	
0·5N-HCl	1·00	16°	[α] :						+0·3°	

2-Methyl-2-phenylhexanoyl chloride (11·1 g.), b. p. 123°/18 mm. (Found : equiv., 114. Calc. for $C_{12}H_{17}\cdot COCl$: equiv., 112·3), was prepared by the action of thionyl chloride (50 ml.) on the acid (11·5 g.). To an ice-cooled solution of the acid chloride (15·4 g.) in acetone (150 ml.) was added, with stirring, a solution of sodium azide (5 g.) in water (20 ml.). After ½ hour sufficient water was added to give a homogeneous solution and stirring was continued for 1 hour. Water (200 ml.) was added and the oil which separated was extracted with ether and dried ($CaSO_4$); after filtration, toluene was added, the ether distilled off, and the remaining solution refluxed for several hours. Concentrated hydrochloric acid (150 ml.) was added and the whole heated with stirring on a steam-bath for 6 hours. After extraction with benzene, the aqueous layer was evaporated to small volume, and excess of sodium hydroxide solution was added. An oil separated which was extracted with ether; evaporation of the latter and distillation of the residue yielded 2-amino-2-phenylhexane (2·7 g.), b. p. 127°/18 mm., which by Schotten–Baumann benzoylation gave *2-benzamido-2-phenylhexane* (3·4 g.) which separated from benzene–ligroin in small silky needles, m. p. 146—147° (Found : C, 80·9; H, 8·5; N, 4·9. $C_{19}H_{23}ON$ requires C, 81·0; H, 8·2; N, 4·9%). Evaporation of the toluene layer (above) and addition of ether gave a material which separated from benzene–light petroleum (b. p. 40—60°) as small crystals (0·6 g.) of *2-amino-2-phenylhexane hydrochloride*, m. p. 144—147°, soluble in water (Found : Cl, 16·5. $C_{12}H_{20}NCl$ requires Cl, 16·1%). It yielded a benzoyl derivative having m. p. 146—147° alone or mixed with the above benzoyl derivative. By this procedure 2-methyl-2-phenylhexanoic acid (9·7 g.) having $[\alpha]^{18}_{5893}$ +6·3° (*c*, 1·00 in carbon disulphide) gave (—)-2-amino-2-phenylhexane (1·6 g.) having the rotatory powers recorded in the table, which yielded a benzoyl derivative having $[\alpha]^{18}_{5893}$ +3·5° (*c*, 1·00 in benzene).

To a solution of 2-methyl-2-phenylhexanoyl chloride (8·8 g.) in dry toluene (40 ml.) was added sodium azide which had been activated with hydrazine hydrate according to Nelles (*Ber.*, 1932, **65**, 1345). The mixture was heated under reflux with stirring for 8 hours, cooled, and filtered, the solvent removed by distillation, and the residue heated for several hours on the steam-bath with concentrated hydrochloric acid. The aqueous layer was made alkaline with sodium hydroxide solution and extracted with ether; after drying ($CaSO_4$) and removal of the ether, the residue gave on distillation 2-amino-2-phenylhexane, b. p. 127°/18 mm., which was converted into the benzoyl derivative (1·7 g.), m. p. 146—147°.

2-Methyl-2-phenylhexanoyl chloride (12 g.) was gradually added to aqueous ammonia (200 ml.; *d* 0·88), and the whole evaporated on a steam-bath. The oil so obtained was extracted with benzene and dried (NaOH), the solvent removed, and the *2-methyl-2-phenylhexanoamide* distilled; it had b. p. 187°/15 mm. (Found : C, 75·6; H, 8·8; N, 6·5. $C_{13}H_{19}ON$ requires C, 76·0; H, 9·3; N, 6·8%). The amide (2·0 g.) was shaken with sodium hypochlorite solution (60 ml.; prepared from 2·2 g. of chlorine and 6 g. of sodium hydroxide) at 40° until it dissolved. The solution was then heated to 80°; a yellow oil separated which was extracted with benzene, concentrated hydrochloric acid was added to the extract, the benzene was evaporated, and the residue heated for several hours. After extraction with ether, the aqueous solution was evaporated to small volume; Schotten–Baumann benzoylation then gave 2-benzamido-2-phenylhexane, m. p. 146—147° (0·3 g.).

To a solution of 2-methyl-2-phenylhexanoic acid (5·5 g.) in chloroform (45 ml.) was added concentrated sulphuric acid (13 ml.); sodium azide (2·1 g.) was added, with vigorous stirring, at such a rate that the temperature was kept at 40—45°. Stirring was continued for 1 hour with heating on the steam-bath, and the reaction mixture poured into water. The aqueous layer was repeatedly extracted with small quantities of chloroform and then made alkaline with aqueous sodium hydroxide. An oil was liberated which was extracted with benzene, the extract dried (K_2CO_3), and the benzene distilled off. The residue on distillation yielded aniline (1·2 g.), b. p. 80°/18 mm. (Found : C, 77·4; H, 7·7; N, 14·7. Calc. for C_6H_7N : C, 77·4; H, 7·5; N, 15·1%), identified by conversion into toluene-*p*-sulphonanilide, m. p. 103°, and acetanilide, m. p. 113°.

The chloroform extract was subjected to alkaline extraction [whereby unchanged acid (0·6 g.) was recovered] and dried (K_2CO_3), and bromine added gradually until a brown colour just persisted. The chloroform solution was washed with aqueous sodium thiosulphate and the solvent evaporated off; the residue on distillation gave dibromohexane, b. p. 95°/15 mm. (Found : Br, 64·3. Calc. for $C_6H_{12}Br_2$: Br, 65·4%). Repetitions of the Schmidt reaction with the reactants in the same proportions at temperatures between 37° and 54° gave aniline in similar yields.

To a solution of propiophenone (170 g.) in dry benzene (650 ml.) was slowly added a suspension of sodamide (51 g.) in benzene; the whole was heated under reflux with stirring for several hours until no further ammonia was evolved. Benzyl chloride (160 g.) was then added with continued stirring and heating. Water was added to the cooled reaction mixture, the benzene layer washed with water and dried (Na_2SO_4), and the solvent evaporated off. The residue on distillation yielded (±)-*α-benzylpropiophenone* (159 g.), b. p. 181°/10 mm. (Found : C, 85·7; H, 7·4. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%).

Reaction, under similar conditions, of (±)-α-benzylpropiophenone (155 g.) with sodamide (27 g.) and *n*-butyl bromide (95 g.) gave (±)-*2-benzyl-2-methylhexanoylbenzene* (58 g.), b. p. 192—196°/13 mm. (Found : C, 85·2; H, 8·1. $C_{20}H_{24}O$ requires C, 85·6; H, 8·6%).

Under similar conditions propiophenone (53 g.) in benzene (650 ml.), sodamide (53 g.), and *n*-butyl bromide (186 g.) in benzene (100 ml.) yielded (±)-2-methylhexanoylbenzene (148 g.), b. p. 123°/23 mm. This material (148 g.) in benzene (650 ml.) was treated similarly with sodamide (38 g.) and ethyl iodide (122 g.), the latter being run beneath the surface of the reaction mixture; there was obtained (±)-*2-ethyl-2-methylhexanoylbenzene* (100 g.), b. p. 140°/13 mm. (Found : C, 82·2; H, 10·0. $C_{15}H_{22}O$ requires C, 82·5; H, 10·2%).

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