

659. *The Resolution of Secondary and Tertiary Alcohols containing the Pyridyl Group.*

By ALWYN G. DAVIES, J. KENYON, and KUMAR THAKER.

Phenyl-2-pyridylmethanol, phenyl-4-pyridylmethanol, and 1-phenyl-1-2'-pyridylpropanol have been resolved by crystallisation of their salts with (+)-tartaric acid. 1-Phenyl-1-4'-pyridylpropanol and 1-phenyl-1-2'-pyridylethanol did not give crystalline salts with optically active acids, but the latter alcohol was resolved *via* the brucine salt of its hydrogen phthalate.

ALTHOUGH the usual method of resolving alcohols is by recrystallisation of salts of their acid esters with optically active bases, it was decided to take advantage of the basic character of pyridylcarbinols and attempt their resolution by recrystallisation of their salts with optically active acids.

Phenyl-2-pyridylmethanol, prepared by the reduction of phenyl 2-pyridyl ketone with aluminium *isopropoxide*, gave a hydrogen (+)-tartrate which readily crystallised from ethanol. The solid yielded the (–)-alcohol which, after it had been twice recrystallised, was optically pure. The filtrate yielded the (+)-alcohol.

Phenyl-4-pyridylmethanol forms a crystalline hydrogen (+)-tartrate from ethanol. Two recrystallisations of the salt, followed by two crystallisations of the alcohols recovered from the crystals and the mother-liquor respectively, likewise yielded the optically pure (–)- and (+)-alcohol.

By the usual method both these secondary alcohols gave crystalline hydrogen phthalates, but attempts to prepare crystalline alkaloidal salts were unsuccessful. The hydrogen phthalates in 0.3*N*-sodium hydroxide did not disproportionate to the dialkyl phthalates, nor did they react with sodium toluene-*p*-sulphinic acid to form sulphones; instead they were hydrolysed to the alcohols.

The tertiary alcohols 1-phenyl-1-2'-pyridylpropanol, 1-phenyl-1-4'-pyridylpropanol, and 1-phenyl-1-2'-pyridylethanol were prepared by the Grignard reaction from the phenyl pyridyl ketone.

1-Phenyl-1-2'-pyridylpropanol gave a crystalline hydrogen (+)-tartrate from ethanol.

The less soluble fractions yielded the (+)-alcohol which was optically pure after one recrystallisation; the (−)-alcohol was obtained similarly from the more soluble hydrogen tartrate. 1-Phenyl-1-4'-pyridylpropanol, however, did not form a crystalline salt with (+)-tartaric acid, (+)-camphoric acid, or (+)-camphor-10-sulphonic acid and could not be resolved.

Attempts to prepare a crystalline hydrogen (+)-tartrate and (+)-camphorate of 1-phenyl-2'-pyridylethanol were unsuccessful. The hydrogen phthalate of the alcohol, however, yielded a crystalline brucine salt from acetone. After one recrystallisation from ethyl acetate this gave the (−)-hydrogen phthalate which was hydrolysed to the (+)-alcohol. The optically impure (+)-hydrogen phthalate was recovered from the more soluble fraction of the brucine salt.

Like the secondary alcohols and their hydrogen phthalates, 1-phenyl-1-2'-pyridylpropanol, and 1-phenyl-1-2'-pyridylethanol and its hydrogen phthalate show little tendency to undergo unimolecular alkyl-oxygen heterolysis.

EXPERIMENTAL

(±)-*Phenyl-2-pyridylmethanol*.—Phenyl 2-pyridyl ketone (8 g.; m. p. 43–45°; supplied by Messrs. Reilly Tar and Chemical Corporation, New York) was reduced by Tschitschibabin's method¹ with zinc dust in alkaline ethanol to phenyl-2-pyridylmethanol, plates (3.7 g., 47%) (from benzene–light petroleum), m. p. 78° (lit., 78°², 82°¹). A higher yield (73%) of the alcohol, m. p. and mixed m. p. 78°, was obtained when the ketone (40 g.) was reduced with aluminium isopropoxide in boiling propan-2-ol for 2 hr. (Found: C, 77.3; H, 6.2; N, 7.9. Calc. for C₁₂H₁₁ON: C, 77.8; H, 6.0; N, 7.6%).

(+)- and (−)-*Phenyl-2-pyridylmethanol*.—After 2 days at room temperature a solution prepared by dissolving the (±)-alcohol (18.5 g.) and (+)-tartaric acid (15.0 g.) in warm ethanol (50 c.c.) deposited needles of the *hydrogen tartrate* (19.6 g.), m. p. 89–90° (Found, by titration with 0.1N-sodium hydroxide: equiv., 334. C₁₂H₁₁ON, C₄H₆O₆ requires equiv., 335). Recrystallisation of the acid tartrate at this stage did not appreciably increase the rotatory power of the alcohol subsequently liberated.

The less soluble acid tartrate was decomposed with sodium carbonate solution. An ethereal extract yielded the partially active alcohol (9.7 g.), m. p. 73–74°, $[\alpha]_D^{18} -16.5^\circ$ (*l*, 1; *c*, 5.14 in CHCl₃). Recrystallisation from ether–light petroleum (30 c.c.: 20 c.c.) gave large pale yellow plates (6.8 g.), m. p. 73°, $[\alpha]_D^{18} -1.3^\circ$ (*l*, 1; *c*, 4.42 in CHCl₃). From the filtrate the optically pure (−)-alcohol (2.1 g.) was recovered, having m. p. 66°, $[\alpha]_{589}^{18} -67.8^\circ$, $[\alpha]_{589}^{18} -86.2^\circ$, $[\alpha]_{546}^{18} -104.7^\circ$ (*l*, 1; *c*, 4.682 in CHCl₃), $[\alpha]_D^{18} -3^\circ$ (*l*, 1; *c*, 2.713 in EtOH), $[\alpha]_D^{18} -3.2^\circ$ (*l*, 1; *c*, 3.2 in acetone).

The mother-liquor containing the more soluble acid tartrate was concentrated and decomposed with sodium carbonate solution, yielding the alcohol (7.8 g.), m. p. 73–74°, $[\alpha]_D^{18} +17.3^\circ$ (*l*, 1; *c*, 5.44 in CHCl₃). On recrystallisation from ether–light petroleum the almost racemic alcohol separated (5.2 g.), having m. p. 78°, $[\alpha]_D^{18} +1.6^\circ$ (*l*, 1; *c*, 4.55 in CHCl₃). The filtrate yielded the optically pure (+)-alcohol as plates (1.8 g.), m. p. 66°, $[\alpha]_D^{18} +84.8^\circ$ (*l*, 1; *c*, 3.352 in CHCl₃).

(±)-*Phenyl-2-pyridylmethyl Hydrogen Phthalate*.—A mixture of the (±)-alcohol (3.7 g.), phthalic anhydride (2.96 g.), and pyridine (1.6 g.) was heated on a water-bath for 5 hr. Next day the mixture was diluted with iced water. The solid which separated was washed free from pyridine with water, dried (5.8 g.; m. p. 140–145°), and recrystallised from acetone, yielding the *hydrogen phthalate* as plates (3.9 g., 55%), m. p. 145–146° (Found: C, 72.0; H, 4.9; N, 4.5%; equiv., 334. C₂₂H₁₅O₄N requires C, 72.1; H, 4.95; N, 4.2%; equiv., 333). Attempts to prepare a crystalline brucine salt of this acid ester were unsuccessful.

A solution of the hydrogen phthalate (0.5 g.) in 0.3N-sodium hydroxide (10 c.c.) next day had deposited the crystalline alcohol, m. p. and mixed m. p. 78°; no dialkyl phthalate could be isolated.

Solutions of the hydrogen phthalate (0.66 g.) in 0.3N-sodium hydroxide (10 c.c.) and of sodium toluene-*p*-sulphinate (0.43 g.) in water, were mixed. The alcohol gradually separated (m. p. and mixed m. p. 78°). No sulphone was formed.

¹ Tschitschibabin, *Ber.*, 1904, **37**, 1370.

² Ashworth, Daffern, and Hammick, *J.*, 1939, 809.

(±)-*Phenyl-4-pyridylmethanol*.—Phenyl 4-pyridyl ketone (m. p. 71–72°; supplied by Messrs. Reilly Tar and Chemical Corporation, New York) was reduced with zinc dust and alkaline ethanol by Tschitschibabin's method,¹ yielding crude phenyl-4-pyridylmethanol (63%). Two recrystallisations from benzene–light petroleum gave the pure alcohol as light yellow plates (32%), m. p. 120–121° (lit.,¹ m. p. 126°).

A higher yield (70%) of the alcohol, m. p. and mixed m. p. 120–121°, was obtained when the ketone (20 g.) was reduced with aluminium *isopropoxide* in boiling propan-2-ol for 1.5 hr. (Found: C, 77.5; H, 6.2; N, 7.65. Calc. for C₁₂H₁₁ON: C, 77.8; H, 6.0; N, 7.6%).

(+)- and (–)-*Phenyl-4-pyridylmethanol*.—After 2 days at room temperature, a solution prepared by dissolving the (±)-alcohol (18.5 g.) and (+)-tartaric acid (15 g.) in warm ethanol (50 c.c.) deposited the *hydrogen tartrate* (26.1 g.). Two recrystallisations gave the salt (18.4 g.) with m. p. 98–100° (Found: equiv., 334. C₁₂H₁₁ON, C₄H₆O₆ requires equiv., 335).

This least soluble salt was decomposed as described above, yielding the alcohol (9.5 g.), m. p. 123–124°, [α]_D¹⁸ – 8.8° (l, 1; c, 2.44 in CHCl₃). Two recrystallisations from ethanol gave the optically pure (–)-*alcohol*, m. p. 131–132°, [α]_D¹⁸ – 55.5° (l, 1; c, 3.656 in CHCl₃) (Found: C, 78.0; H, 5.97; N, 7.55%).

The first filtrate containing the more soluble hydrogen tartrate yielded the partially active alcohol (2.6 g.), m. p. 123–124°, [α]_D¹⁸ + 11.2°. Two recrystallisations from ethanol gave the (+)-alcohol, m. p. 131–132°, [α]_D¹⁸ + 52.4° (l, 1; c, 2.083 in CHCl₃).

(±)-*Phenyl-4-pyridylmethyl Hydrogen Phthalate*.—By the method described above, the alcohol (1.85 g.) yielded the *hydrogen phthalate* (2.2 g.), m. p. 190–192°, which was insoluble in most of the common organic solvents. It recrystallised from dioxan in plates, m. p. 195° (Found: equiv., 332. C₁₂H₁₅O₄N requires equiv., 334). It did not give a crystalline brucine salt from acetone.

As with the isomeric 2-pyridyl compounds, attempts to prepare the dialkyl phthalate and *p*-tolyl sulphone resulted in the isolation of the alcohol.

(±)-1-*Phenyl-2-2'-pyridylpropanol*.—A solution of phenyl 2-pyridyl ketone (92 g.) in ether was added dropwise to an ethereal solution of ethylmagnesium bromide (from magnesium, 12 g., and ethyl bromide). Next day the mixture was decomposed with ice and ammonium chloride, and the product was recrystallised from ethanol, yielding 1-*phenyl-1-2'-pyridylpropanol* (45 g., 39%) as massive rhombs, m. p. 80–81° (Found: C, 79.0; H, 7.1; N, 6.6. C₁₄H₁₅ON requires C, 78.8; H, 7.1; N, 6.6%). The alcohol gave a *picrate*, m. p. 105–106° (from ethanol) (Found: C, 74.7; H, 4.6; N, 12.2. C₂₀H₁₈O₈N₄ requires C, 74.3; H, 4.1; N, 12.6%).

(±)- and (–)-1-*Phenyl-1-2'-pyridylpropanol*.—After 2 days at room temperature a solution prepared by dissolving the (±)-alcohol (40 g.) and (+)-tartaric acid (28.1 g.) in warm ethanol (100 c.c.) deposited solvated crystals of the *hydrogen tartrate* (33.0 g.), m. p. 114–115° (Found: equiv., 408; after vacuum-desiccation, 362. C₁₄H₁₅ON, C₄H₆O₆, C₂H₅·OH requires equiv., 409. C₁₄H₁₅ON, C₄H₆O₆ requires equiv., 363).

The less soluble hydrogen tartrate (25 g.) was decomposed with aqueous sodium carbonate, liberating the partially active alcohol (14.2 g.), m. p. 71–72°, [α]_D²⁰ + 53.8° (l, 1; c, 3.941 in CHCl₃). This was dissolved in ethanol (100 c.c.) and the solution seeded with the (±)-alcohol. Next day the (±)-alcohol (3.1 g.) had separated; the filtrate yielded the optically pure (+)-alcohol, m. p. 68°, [α]_D²⁰ + 65.9° (l, 1; c, 4.52 in CHCl₃). These data were unchanged when the alcohol was recrystallised from ether–light petroleum.

The mother-liquors of the hydrogen tartrate were concentrated and decomposed, yielding the alcohol (21.8 g.), m. p. 73°, [α]_D²⁰ – 42.6° (l, 1; c, 5.216 in CHCl₃). This was dissolved in ethanol (80 c.c.) and seeded with the (±)-alcohol; next day the (±)-alcohol (7.8 g.) had separated. From the mother-liquor the (–)-*alcohol* was obtained (11.2 g.), m. p. 68°, [α]_D²⁰ – 66.2° (l, 1; c, 4.825 in CHCl₃) (Found: C, 79.0; H, 7.14; N, 6.47%).

Equal amounts (0.1 g.) of the (+)- and (–)-alcohol were dissolved in chloroform. Evaporation of the solvent left the (±)-alcohol, m. p. 78–80°.

The rotatory dispersion of the alcohol in various solvents is tabulated; the results lie on a typical "characteristic diagram" as devised by Armstrong and Walker.³

1-*Phenyl-1-2'-pyridylpropyl Hydrogen Phthalate*.—A mixture of the alcohol (1.065 g.), phthalic anhydride (0.74 g.), and trimethylamine (0.5 g.) was heated on the steam-bath for 6 hr. Next day the *hydrogen phthalate* was isolated in the usual way as crystals, m. p. 98–100° (from ether–light petroleum) (Found: equiv., 360. C₂₀H₂₁O₄N requires equiv., 361).

After 2 days the alcohol was recovered from a solution of the alcohol (0.5 g.) and sodium toluene-*p*-sulphinat in formic acid (12 c.c.).

³ Armstrong and Walker, *Proc. Roy. Soc.*, 1913, A, 88, 388.

Specific rotatory power of 1-phenyl-1-2'-pyridylpropanol (*l*, 1; *t*, 18°).

Solvent	Wavelength (Å)				<i>c</i>
	6563	5893	5463	4861	
Pyridine	+13.1°	+15.1°	+18.7°	—	4.175
Dioxan	-2.6	-3.3	-4.1	-5.2°	5.102
99% EtOH	-6.5	-8.7	-10.4	—	2.20
COMe ₂	-7.5	-10.7	-15.4	—	2.408
MeNO ₂	-17.3	-23.3	-28.9	—	4.511
C ₆ H ₆	-35.6	-45.6	-59.4	-62.4	1.568
CHCl ₃	-52.6	-66.7	-84.6	-122.3	5.167
CS ₂	-56.9	-72.6	-89.1	-101.8	2.29
AcOH	—	-85.3	—	—	2.048
2N-HCl	-83.0	-111.3	-135.5	-176.3	5.115

1-Phenyl-1-4'-pyridylpropanol.—Phenyl 4-pyridyl ketone is only sparingly soluble in ether. When it was added in ethereal suspension to ethereal ethylmagnesium bromide, the tertiary alcohol was obtained in only 12% yield. A better yield was obtained when the reactants were mixed in benzene solution as follows.

Ethyl bromide (27 g.) and magnesium (6 g.) were allowed to react in ether (150 c.c.); the solvent was then distilled off and the Grignard reagent dissolved in dry benzene (50 c.c.) and added dropwise to phenyl 4-pyridyl ketone (35 g.) in benzene (100 c.c.). The mixture was heated under reflux for 2 hr. Next day 1-phenyl-1-4'-pyridylpropanol was isolated in the usual manner and recrystallised from benzene—light petroleum as plates (38 g., 36%), m. p. 153—155° (Found: C, 78.9; H, 7.0; N, 6.6. C₁₄H₁₅ON requires C, 78.8; H, 7.1; N, 6.6%).

(±)-1-Phenyl-1-2'-pyridylethanol.—The reaction between ethylmagnesium iodide (magnesium, 5 g.) and phenyl 2-pyridyl ketone (38.6 g.) gave 1-phenyl-1-2'-pyridylethanol (30 g., 72%), b. p. 118°/0.2 mm., n_D^{20} 1.5812. After 1 month in the refrigerator the alcohol crystallised in large rhombs, m. p. 18—20°. Tilford, Shelton, and van Campen⁴ report b. p. 115—120°/0.1 mm., n_D^{20} 1.5814.

(±)-Phenyl-1-2'-pyridylethyl Hydrogen Phthalate.—A mixture of the alcohol (21.3 g.), phthalic anhydride (14.8 g.), and triethylamine (10.5 g.) was heated on the steam-bath for 12 hr. Next day the mixture was added to sodium carbonate solution, then neutralised (phenolphthalein) with hydrochloric acid. An ethereal extract yielded the hydrogen phthalate (from ether—light petroleum; 17 g., 47%), m. p. 128—129° (decomp.) (Found: equiv., 359. C₂₀H₂₁O₄N requires equiv., 361).

Brucine 1-Phenyl-1-2'-pyridylethyl Phthalate.—A solution of the hydrogen phthalate (42 g.) and brucine (47 g.) in acetone (200 c.c.) deposited the crystalline brucine salt, m. p. 146—150°, during 4 weeks at room temperature. One recrystallisation from ethyl acetate gave the salt (29.8 g.), m. p. 156—158°; the rotatory power of the derived hydrogen phthalate (see below) remained constant on further recrystallisation of this salt.

(+)- and (-)-1-Phenyl-1-2'-pyridylethyl Hydrogen Phthalate.—The least soluble fraction of the brucine salt was triturated with acetone (50 c.c.) and decomposed with 0.5N-sulphuric acid (76 c.c.). The insoluble brucine sulphate was filtered off, and the filtrate extracted with ether (50 c.c.; 2 × 25 c.c.). The dried ethereal extracts yielded the (-)-hydrogen phthalate as plates (11.8 g.), m. p. 136—138° (decomp.), $[\alpha]_D^{20}$ -8.6° (*l*, 1; *c*, 4.25 in CHCl₃).

The filtrate containing the more soluble brucine salt gave the optically impure (+)-hydrogen phthalate, $[\alpha]_D^{20}$ +2.2° (*l*, 1; *c*, 3.55 in CHCl₃).

(+)-1-Phenyl-1-2'-pyridylethanol.—The (-)-hydrogen phthalate (10 g.) was heated with 5N-sodium hydroxide (20 c.c.) on the steam-bath for 30 min. An ethereal extract yielded the (+)-alcohol (3.2 g.), b. p. 128°/0.8 mm., n_D^{20} 1.5813, $[\alpha]_D^{20}$ +38.2° (*l*, 1; *c*, 7.36 in CHCl₃), $[\alpha]_D^{20}$ +72.1° (*l*, 1; *c*, 3.328 in acetic acid), $[\alpha]_D^{20}$ +51.0° (*l*, 1; *c*, 1.47 in CS₂). When seeded at 0° with the (±)-alcohol, it crystallised, and had m. p. 16—18°.

The alcohol did not give a sulphone: nor did its hydrogen phthalate disproportionate.

Thanks are expressed to the Central Research Fund of the University for a Grant.

CHEMISTRY DEPARTMENT, BATTERSEA POLYTECHNIC, LONDON, S.W.11.
WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[Received, May 22nd, 1956.]

⁴ Tilford, Shelton, and van Campen, *J. Amer. Chem. Soc.*, 1948, **70**, 4001.