Optical Activity as a Consequence of an N–N-Chiral Axis: Resolution of *N*-Benzyl-*N*-(1,2-Dihydro-2-oxo-1-quinolyl)glycine

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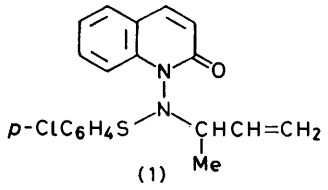
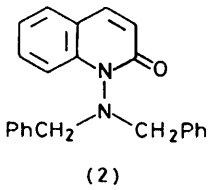
The title compound (6) has been synthesised and the pure, laevorotatory enantiomer separated *via* the quinine salt. Rates of racemisation give a barrier for rotation around the N–N bond of 26 ± 0.5 kcal mol^{-1}.

THE sulphenamide (1) has previously been isolated in two stereoisomeric forms.[1] Examination of a number of analogues of (1) showed that the additional chirality which gave rise to the stereoisomers was the result of restricted rotation around the N–N bond.[2]

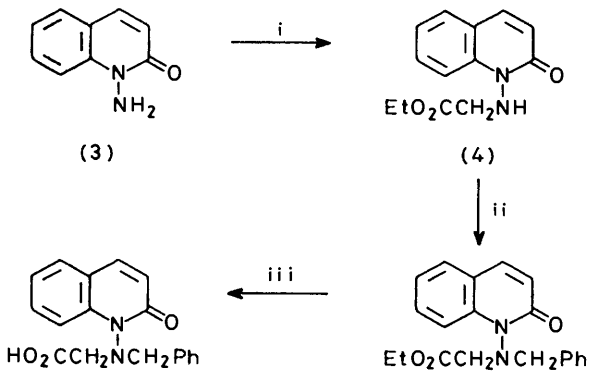


(1)



(2)

This barrier to rotation, it is assumed, is raised as a result of steric interaction between the substituents on the sulphenamide nitrogen (sulphur, α-methylallyl) and the *peri*-H at C-8. The role played by sulphur could, according to this interpretation, be assumed by another alkyl group of analogous steric bulk and, indeed, the n.m.r. spectrum of the dibenzylaminoquinolone (2) shows an AB system for the diastereotopic protons within each benzyl group. No coalescence of this AB system was observed up to 180 °C, in nitrobenzene solution, suggesting that the barrier to N–N bond rotation in this case was >23.5 kcal mol^{-1}.



(3) (4) (5) (6)

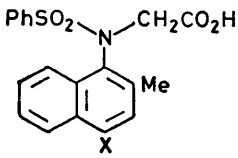
SCHEME *Reagents:* i, $BrCH_2CO_2Et$; ii, $PhCH_2Br$; iii, NaOH–H_2O–EtOH

In this paper we report the synthesis and resolution of *N*-benzyl-*N*-(1,2-dihydro-2-oxo-1-quinolyl)glycine (6), a compound whose chirality is a result of restricted rotation around the N–N bond.[3] The method of synthesis of (6) is outlined in the Scheme.

The nitrogen of the glycine moiety of (4) is particularly unreactive towards alkylation and forcing conditions must be used. Thus benzylation was only successful after heating at 160 °C for 1.5 h. Chirality of the crystalline acid (6) was recognisable in its n.m.r. spectrum from the AB systems observed for the benzyl (δ 4.25) and carboxymethylene (δ 3.97) protons in chlorobenzene solution.

Resolution of (6) was carried out *via* the crystalline salt obtained with quinine. Three crystallisations from ether–ethanol separated one pure, diastereoisomeric salt, as was shown by liberation of the acid (6) and examination of the n.m.r. srectrum of the salt obtained with (*S*)-(−)-1-phenylethylamine. Thus the n.m.r. spectrum of the salt of racemic (6) with (*S*)-(−)-1-phenylethylamine shows two overlapping AB systems for the diastereotopic protons within each benzyl group of the two diastereoisomers, whereas in the material recovered from resolution with quinine, one of these AB systems was completely absent.

The laevorotatory, optically pure acid (6) has $[\alpha]_D^{25}$ −64.8°. The melting point behaviour of the optically pure (6) is of interest; melting occurs at 88—90 °C and then resolidification takes place at >100 °C with remelting at 147—148 °C. Racemisation occurs during this heating and the melting range 147—148 °C corresponds to that of the racemic (6). The rate of this racemisation was followed polarimetrically at two different temperatures (boiling ethanol and boiling methanol) and the resultant Arrhenius plot gave a value for $\Delta G^{\ddagger}$ of 26 ± 0.5 kcal mol^{-1} for the barrier to rotation around the N–N bond.



(7)

It is of interest to compare the optical stability of (6) with that of the chiral aminonaphthalene derivatives (7);[4] thus (5, X = H) has a half-life of 4.6 h, in dimethylformamide at 118 °C ($\Delta G^{\ddagger}$ 30.8 kcal mol^{-1}).

EXPERIMENTAL

For general experimental directions and instrumentation details, see ref. 2.

Ethyl N-(1,2-*Dihydro*-2-*oxo*-1-*quinolyl*)*glycinate* (4).—1-Aminoquinolin-2(1*H*)-one (3) (5.0 g) and ethyl bromoacetate (25 ml) were heated under reflux in a nitrogen atmosphere for 1 h. Excess of bromoacetate was removed by distillation under reduced pressure and dichloromethane (20 ml) was then added. The organic layer was washed with 50% concentrated ammonia solution (2 × 20 ml), and water (10 ml), dried, evaporated, and the residue chromatographed over alumina (230 g) with light petroleum–ethyl acetate (4 : 1). After elution of some of the impurities, ethyl acetate–ethanol (19 : 1) eluted the *ester* (2.5 g, 33%) which formed crystals (from light petroleum–chloroform), m.p. 74—75 °C (Found: C, 63.2; H, 5.8; N, 11.2. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%); δ($CDCl_3$) 8.1—7.1 (m, 4 × ArH + quinoline 4-H), 6.7 (d, *J* 9.5 Hz, quinoline 3-H), 6.1 (t, *J* 6 Hz, exch. D_2O, NH), 4.2 (q, *J* 7 Hz, CH_2Me), 3.8 (d, *J* 6 Hz, $NHCH_2CO$), and 1.2 (t, *J* 7 Hz, Me); $\nu_{max.}$ 3 280m, 1 735s, 1 650s, 1 590s, 1 220s, 1 200s, 1 010m, 830s, and 730s cm^{-1}.

Ethyl N-*Benzyl*-N-(1,2-*dihydro*-2-*oxo*-1-*quinolyl*)*glycinate* (5).—The above ester (4) (1.82 g) was heated with benzyl bromide (10 ml) at 160—170 °C (oil-bath temp.) for 1.5 h with stirring, under nitrogen. The benzyl bromide was removed under reduced pressure and dichloromethane (15 ml) added. The organic layer was washed successively with sodium hydroxide solution (1M, 2 × 10 ml) and water, and then dried. Evaporation gave an oil which was chromatographed over alumina (60 g), with light petroleum–ethyl acetate (4 : 1) as eluant to remove the residual benzyl bromide. Further elution with light petroleum–ethyl acetate (1 : 1) gave the ester (1.03 g, 41%) as an oil, b.p. (Kugelrohr) 195—200 °C/0.15 mmHg; δ($CDCl_3$) 8.40 (d, *J* 9 Hz, quinoline 8-H), 7.65 (d, *J* 9.5 Hz, quinoline 4-H), 7.65—7.10 (m, 8 × ArH), 6.68 (d, *J* 9.5 Hz, quinoline 3-H), 4.57 (AB system, J_{AB} 12.5 Hz, CH_2Ph), 4.25 (s, CH_2CO_2H), 4.05 (q, *J* 7 Hz, CH_2Me), and 1.15 (t, *J* 7 Hz, Me).

N-*Benzyl*-N-(1,2-*dihydro*-2-*oxo*-1-*quinolyl*)*glycine* (6). The above ethyl ester (4) (1.5 g), sodium hydroxide (2M, 11 ml), and ethanol (30 ml) were heated under reflux for 4 h. Ethanol was removed under reduced pressure and the solution extracted with dichloromethane (2 × 10 ml). The aqueous layer was acidified with concentrated hydrochloric acid (3 ml) and extracted with dichloromethane (3 × 15 ml). The dichloromethane extracts were dried and evaporated and the residual foam was crystallised from light petroleum–ethyl acetate to give the crystalline *acid* (980 mg, 71%), m.p. 147–148 °C (Found: C, 69.9; H, 5.3; N, 8.9. $C_{18}H_{16}N_2O_3$ requires C, 70.1; H, 5.2; N, 9.1%); δ($CDCl_3$) 8.9 (br s, CO_2H), 8.2 (d, *J* 8 Hz, quinoline 8-H), 7.8—7.0 (m, 8 × ArH + quinoline 4-H) 6.75 (d, *J* 9.5 Hz, quinoline 3-H), 4.5 (s, CH_2Ph), and 4.25 (s, CH_2CO_2H); in chlorobenzene as solvent, the signal at δ 4.5 appears as an AB system at δ 4.25 (J_{AB} 12.6 Hz) and the signal at δ 4.25 appears at δ 3.97 (J_{AB} 17.4 Hz); $\nu_{max.}$ 2 600m br, 1 720s, 1 650s, 1 580s, 1 280s, 1 260s, 765s, 750s, 740s, and 700s cm^{-1}.

S-(−)-1-*Phenylethylamine Salt of the Racemic Acid* (6).—The acid (6) (400 mg) and (*S*)-(−)-1-phenylethylamine (158 mg) were dissolved in dichloromethane (5 ml), the solution filtered and evaporated, and the residual gum examined by n.m.r. spectroscopy: δ(C_6D_6) 4.60 and 4.65 (2 × AB, J_{AB} 12.5 and 12 Hz, respectively, CH_2Ph), 4.06 and 4.02 (2 × AB, J_{AB} 16.4 and 16.6 Hz, respectively, $CH_2CO_2^-$).

Resolution of the Acid (6).—The acid (6) (460 mg) and dried (−)-quinine (483.5 mg) were dissolved in chloroform (5 ml) and heated under reflux for 5 min. On cooling, the solution was filtered and evaporated, under reduced pressure, to give a foam having $[\alpha]_D^{28}$ −75.6° (*c* 1.37, EtOH). It was dissolved in ethanol (2 ml), ether (15 ml) was added, and the mixture was cooled in ice and scratched to initiate crystallisation. After partial crystallisation had occurred, more ether (5 ml) was added and the solution set aside overnight at −5 °C. The solid which separated (400 mg) had $[\alpha]_D^{27}$ −99.0° (*c* 0.3, EtOH). After a further two crystallisations from ethanol–ether (1 : 12), the resulting quinine salt (233.7 mg, 25%) had m.p. 128—132 °C and $[\alpha]_D^{24}$ −101.3° (*c* 0.3, EtOH). It was dissolved in dichloromethane (5 ml) and the solution washed with dilute sulphuric acid (2M, 3 × 5 ml) and water (5 ml); the organic layer was then dried and evaporated to give the acid (6) (117.7 mg) which was recrystallised from ethyl acetate–light petroleum. After separation of a little racemic material (4.4 mg, m.p. 141—142 °C), the optically pure, laevorotatory acid (6) (100.0 mg, 22%), m.p. 88—90 °C, $[\alpha]_D^{25}$ −64.8° (*c* 1.175, EtOH) was obtained. The n.m.r. spectrum (C_6D_6) of the salt of this acid with (*S*)-(−)-1-phenylethylamine (see above) showed that the AB systems at δ 4.02 and 4.65 were completely absent.

The above mother-liquors, after removal of the quinine salt, were converted into the acid (6) which was shown by examination of its salt with (*S*)-(−)-1-phenylethylamine, to contain a 30% enantiomeric excess of the (+)-acid.

Racemisation of the Acid (6).—A sample of the optically active (+)-acid (400 mg) was dissolved in ethanol and heated under reflux. At measured time intervals, the mixture was concentrated under reduced pressure at room temperature and then made up to 10 ml in a volumetric flask and the optical rotation measured (Table 1). The above procedure was repeated on a fresh sample of acid using boiling methanol (Table 1). The plot of the log terms *vs.* time, gives a straight line, with slope $k_r/2.303$. Rate constants were obtained using a least-squares line-fitting computer programme (Table 2). The activation parameters calculated from these data are E_A = 27 ± 0.5 kcal mol^{-1}, $\Delta H^{\ddagger}$ 26 ± 0.5 kcal mol^{-1}, $\Delta S^{\ddagger}$ 0 ± 1 kcal mol^{-1} K^{-1}, and $\Delta G^{\ddagger}$ 26 ± 0.5 kcal mol^{-1}.*

TABLE 1

T = 65 °C (boiling methanol)

Time (s)	$[\alpha] \times 10^3$	$\log_{10}[\alpha/\alpha_0]$
0	58	0
4 200	44	0.120
9 600	30	0.286
13 200	22	0.421

T = 78 °C (boiling ethanol)

Time (s)	$[\alpha] \times 10^3$	$\log_{10}[\alpha/\alpha_0]$
0	190	0
3 200	61	0.493
4 200	42	0.656
7 200	14	1.136

TABLE 2

T (°C)	k_r (s^{-1})	Half life (min)	Correlation coeff.
65	7.30 ± 0.09 × 10^{-5}	158	0.9985
78	3.62 ± 0.05 × 10^{-4}	32	0.9997

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* 1 cal = 4.184 J.

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