11. Wideqvist, S. *Acta Chem. Scand.* 3 (1949) 303.
12. Akin, R. B., Stamatoff, G. S. and Bogert, M. T. *J. Am. Chem. Soc.* 59 (1937) 1268.
13. Bell, V. L. and Cromwell, N. H. *J. Org. Chem.* 23 (1958) 789.

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Resolution and Absolute Configuration of 2-Hydroxylamino-1-phenylpropane (*N*-Hydroxyamphetamine)

BJÖRN LINDEKE, ELISABET ANDERSON and ULLA PAULSEN

Department of Organic Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, Box 574, S-751 23 Uppsala, Sweden

In recent years it has been well established that *N*-hydroxyphenylalkylamines are formed during the metabolism of several phenylalkylamines.¹⁻⁴ These aliphatic hydroxylamines are unstable compounds which further metabolize or undergo chemical conversion to various compounds.

During investigations of the chemical and biological properties of *N*-hydroxyphenylalkylamines access to the optical isomers of 2-hydroxylamino-1-phenylpropane (*N*-hydroxyamphetamine, *1*) became desirable. Thus by using optically active substrates information could be gained as to the stereochemical properties of the nitroso compounds formed during autoxidation of *1*.⁵ Furthermore pure enantiomers of *1* were needed to assess the influence of its chirality on the enzymatic binding during metabolism.⁶

N-Hydroxyamphetamine was resolved into its (+)- and (-)-enantiomers using (+)- and (-)-tartaric acid, respectively. Five recrystallizations from 5 % solutions in ethanol were required to produce salts with constant physical properties. The absolute configuration of (+)-*1* was established by reduction to (*S*)-amphetamine with LiAlH₄. Consequently (+)-*1* can be assigned the (*S*)-configuration.

A synthetic route leading to optical isomers of *1* was recently reported.⁷ Optically pure amphetamine was converted into the benzylimine, oxidation of which with *m*-chloroperoxybenzoic acid, gave the 3-phenyloxaziridine. Subsequent acidic hydrolysis yielded *1*. Although no optical rotations were presented,

dextrorotatory amine was claimed to yield dextrorotatory *N*-hydroxylamine. Our results confirm this statement. As *1* easily forms crystalline tartrates resolution is a convenient alternative to the production of the optical antipodes. Racemic *1* can be prepared in reasonable good yield (35 %) by partial reduction of 1-phenyl-2-nitropropene-(1),⁸ or in excellent yield (80 %) by a modification⁹ of the method of Borch *et al.*¹⁰ utilizing 1-phenyl-2-propanone oxime and cyanoborohydride.

Experimental. Melting points were determined in an electrically heated metal block using open capillary tubes and calibrated Anschütz thermometers. Optical rotations were measured with a Perkin-Elmer 141 spectropolarimeter.

2-Hydroxylamino-1-phenylpropane was prepared in up to 35 % yield by LiAlH₄ reduction of 1-phenyl-2-nitropropene(1).⁸ The phenyl-nitropropene used as the starting material was from seizures and was kindly supplied by the National Laboratory of Forensic Science. The compound contained some impurities and was recrystallized from ethanol (96 %) prior to use.

Resolution of 2-hydroxylamino-1-phenylpropane(1). Racemic *1* (8.0 g, 0.05 mol) was added to a hot solution of (+)-tartaric acid (7.9 g, 0.05 mol) in 300 ml of ethanol (abs.). The solution was kept at room temperature overnight. The salt obtained (11.4 g, m.p. 152–154 °C) required five recrystallizations from 5 % solutions in ethanol (96 %) before it exhibited constant physical properties. Yield 3.5 g (44 %) of resolved (+)-hydrogen tartrate m.p. 163–164 °C, $[\alpha]_D^{25} + 21.3^\circ$ (c 1.0, H₂O).

Refrigeration of the initial filtrate yielded 2.0 g of pure (-)-*1*-(+)-tartrate, m.p. 143–145 °C, $[\alpha]_D^{25} + 6.3^\circ$ (c 1.0, H₂O).

The combined filtrates from the above resolution were concentrated *in vacuo* and the residue was dissolved in saturated NaHCO₃-solution (25 ml). Extraction with CHCl₃ (2 × 25 ml), subsequent drying (Na₂SO₄) and evaporation of the solvent yielded 4.1 g of recovered hydroxylamine. This was added to a hot solution of (-)-tartaric acid (4.4 g, 0.027 mol) in ethanol (96 %). Two recrystallizations from the latter solvent gave 1.3 g of resolved (-)-hydrogen tartrate with constant physical properties, m.p. 164–165 °C, $[\alpha]_D^{25} - 21.4^\circ$ (c 1.0, H₂O).

The total yield of salts containing resolved (-)-*1* was 3.3 g (41 %).

(*S*)- and (*R*)-2-Hydroxylamino-1-phenylpropane. The hydroxylamines were obtained from the resolved (+)- and (-)-hydrogen tartrates by dissolution in saturated NaHCO₃-solutions and extraction with chloroform as described above. (*S*)-2-Hydroxylamino-1-phenylpropane, m.p. 79–80 °C (from light petroleum), $[\alpha]_D^{25} + 1.9^\circ$ (c 1.0, EtOH) + 21.2° (c 1.0, CH₂Cl₂). (*R*)-2-Hydroxylamino-1-phenylpropane obtained from (+)-tartrate m.p. 79–80 °C $[\alpha]_D^{25} - 20.6^\circ$ (c 1.0, CH₂Cl₂), obtained from (-)-tartrate m.p. 79–80 °C, $[\alpha]_D^{25} - 1.9^\circ$ (c

1.0, EtOH) -20.4° (c 1.0, CH_2Cl_2).

Determination of the absolute configuration of 2-hydroxylamino-1-phenylpropane (1). An ethereal solution (25 ml) of (+)-1 (200 mg, 1.3 mmol) was added dropwise to a well stirred slurry of LiAlH_4 (326 mg, 8.6 mmol) in dry ether (40 ml). The mixture was refluxed for 2 h. After cooling the LiAl -complex was decomposed by cautious addition of H_2O (0.3 ml), 15 % NaOH (0.3 ml) and finally H_2O (0.9 ml). The resulting suspension was refluxed for 30 min, then filtered and the precipitate washed with ether. The combined filtrate and washings were dried (K_2CO_3) and the solvent evaporated *in vacuo*, affording 142 mg of the crude base. The base was converted to the sulfate by addition of an equivalent amount of ethereal H_2SO_4 to a cold ethereal solution of the base. Two recrystallizations from diluted ethanol yielded 50 mg of pure amphetamine sulfate, m.p. $318-320^\circ\text{C}$ decomp. $[\alpha]_{\text{D}}^{25} +22.2^\circ$ (c 1.0, H_2O), (Lit.¹¹ (*S*)-1-phenyl-2-aminopropane sulfate m.p. $>300^\circ\text{C}$ decomp. $[\alpha]_{\text{D}}^{25} +22.1^\circ$ (c 2.0, H_2O)).

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1. Gorrod, J. W. *Chem.-Biol. Interact.* **7** (1973) 289.
2. Lindeke, B., Cho, A. K., Thomas, T. L. and Michelson, L. *Acta Pharm. Suec.* **10** (1973) 493.
3. Beckett, A. H. and Bélanger, P. M. *J. Pharm. Pharmacol.* **26** (1974) 205.
4. Caldwell, J., Köster, U., Smith, R. L. and Williams, R. T. *Biochem. Pharmacol.* **24** (1975) 2225.
5. Lindeke, B., Anderson, E., Lundkvist, G., Jonsson, U. and Eriksson, S. O. *Acta Pharm. Suec.* **12** (1975) 183.
6. Jonsson, J. and Lindeke, B. *Ibid.* **13** (1976). *In press.*
7. Beckett, A. H., Haya, K., Jones, G. R. and Morgan, P. H. *Tetrahedron* **31** (1975) 1531.
8. Gilsdorf, R. T. and Nord, F. F. *J. Am. Chem. Soc.* **74** (1952) 1837.
9. Wright, J., Cho, A. K. and Gal, J. *Xenobiotica*. Submitted.
10. Borch, R. F., Bernstein, M. D. and Durst, H. D. *J. Am. Chem. Soc.* **93** (1971) 2897.
11. Felder, E., Pitré, D. and Bovie, S. *Helv. Chim. Acta* **52** (1969) 329.

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Substituent Effects on ^{13}C Chemical Shifts of Benzoyl Stabilised Phosphonium Ylides

PAUL FRØYEN^a and DAVID G. MORRIS^b

^a Department of Chemistry, University of Oslo, Blindern, Oslo 3, Norway and ^b Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, Scotland.

Recent studies of ^{13}C chemical shifts, *inter alia*, of phosphorus ylides have indicated that the ylide carbon is best described as sp^2 hybridised and carries a significant negative charge.^{1,2} Additionally, the existence of $d_\pi-p_\pi$ bonding between phosphorus and the ylide carbon has been recognised, although the extent of this bonding is thought to be moderate;¹ for calculated values of a non-stabilised ylide see Ref. 3. As a result of these studies and in extension of our own studies on ^{13}C chemical shifts in arsenic ylides,⁴ we have investigated the ylide, C(7), and carbonyl carbon, C(8), chemical shift variation as a function of substituent, X, in a series of phosphonium ylides containing an *m*-substituted benzoyl group 1–8. The relevant ^{13}C chemical shifts are given in Table 1.

The present results confirm¹ that the ylide carbon C(7) in stabilised phosphonium ylides absorbs at rather high field; the C(7) shifts correlate with the linear free energy parameter σ_m (from Ref. 5) in the sense that electron-withdrawing substituents cause deshielding. The carbonyl carbons, C(8), are however

Table 1. ^{13}C chemical shifts of exocyclic carbons in metasubstituted acetophenones and phosphorus ylides. ^{13}C chemical shifts (ppm) determined on solutions (0.2 M) in CDCl_3 with internal TMS as standard are accurate to 0.05 ppm. σ_m from Ref. 5.

	Ylide C(7) ^a	C(8) ^b	Substituent	Acetophenone C(7)	C(8)	σ_m
1	50.54	184.80	H	26.52	198.00	0.0
2	50.47	185.12	Me	26.54	198.13	-0.7
3	50.79	184.45	OMe	26.63	197.74	0.12
4	51.31	182.95	F	26.59	196.56	0.34
5	51.36	182.79	Cl	26.58	196.60	0.37
6	51.33	182.90	Br	26.55	196.51	0.39
7	52.01	181.91	CN	26.64	196.06	0.68
8	52.33	181.47	NO_2	26.71	195.75	0.71

^a $^1\text{J}_{\text{P-C}(7)}$ 111.4–112.4 Hz. ^b $^1\text{J}_{\text{P-C}(8)}$ = 3.4–3.8 Hz.