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# Resolution and Absolute Configuration of 1-Ethyl-2-propynylamine and 1-Propyl-2-propynylamine

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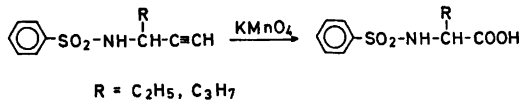
1-Ethyl-2-propynylamine and 1-propyl-2-propynylamine have been resolved and the absolute configurations of the enantiomers have been established by correlation to D-(−)-2-aminobutyric acid and D-(−)-norvaline, respectively.

It has been found in these laboratories that the enantiomers of some *N*-(4-*tert*-amino-1-methyl-2-butynyl)-substituted succinimides and 2-pyrrolidones show strong stereospecificity in blocking the motor effects of the muscarinic agent oxotremorine, *N*-(4-pyrrolidino-2-butynyl)-2-pyrrolidone, and that the pharmacological effect is exerted mainly by the (*R*)-(+)-isomers.[1,2] In continuation of our research in this field we wished to prepare the optical isomers of some analogous compounds substituted by ethyl and propyl groups in the 1-position of the butynyl chain. As starting material for these syntheses we required the enantiomers of 1-ethyl- and 1-propyl-2-propynylamine, and this paper deals with the resolution of these amines and the determination of the configuration of the isomers.

The two acetylenic amines were resolved into their (−)- and (+)-enantiomers using (+)- and (−)-tartaric acid, respectively. The resolution process was followed by measurements of the optical rotation of the benzoyl derivatives, and the optical purities of the enantiomers were determined by NMR spectroscopic analyses of the diastereomeric amides formed by acylation of optically impure amine with (−)-*O*-methylmandelyl chloride.[2,3]

The absolute configurations of the amines were established by oxidation of their benzenesulfonyl derivatives to the corresponding acids.




R = $C_2H_5$, $C_3H_7$

Oxidation of the benzenesulfonyl derivative of (−)-1-ethyl-2-propynylamine (neat) with potassium permanganate afforded dextrorotatory *N*-benzenesulfonyl-α-aminobutyric acid, obviously identical with the benzenesulfonyl derivative of (+)-α-aminobutyric acid, since the benzenesulfonyl derivative prepared from (−)-α-aminobutyric acid was found to be levorotatory. Similarly, the benzenesulfonyl derivative of (+)-1-propyl-2-propynylamine (neat) was transformed to the benzenesulfonyl derivative of (−)-norvaline. Since the dextrorotatory isomers of α-aminobutyric acid and norvaline belong to the L-series (*S*-series),[4,5] the (+)-enantiomers of 1-ethyl-2-propynylamine and 1-propyl-2-propynylamine can be assigned the *R* configuration.

## EXPERIMENTAL

Melting points were determined in a metal block using open capillary tubes and calibrated Anschütz thermometers. Microanalyses were carried out at the Microanalytical Laboratory, Royal Agricultural College, Uppsala. IR spectra were recorded on a Perkin-Elmer 157 G spectrophotometer and $^1H$ NMR spectra on a Perkin-Elmer R 12 B spectrometer. Unless otherwise stated optical rotations were measured in absolute ethanol with a Perkin-Elmer 141 spectropolarimeter.

*Resolution of 1-ethyl-2-propynylamine.* Racemic 1-ethyl-2-propynylamine (10 g, 0.12 mol), prepared as previously described,[6] was added to a hot solution of (+)-tartaric acid (18 g,

0.12 mol) in 800 ml of ethanol-water (10:1). The solution was kept in a refrigerator overnight. The salt obtained (11.7 g, m.p. 181–183 °C) required three recrystallizations from 3 % solutions in ethanol-water (10:1) before constant physical properties of the tartrate, the benzoyl and (−)-*O*-methylmandelyl derivatives were obtained. Yield 7.6 g (54 %) of resolved (+)-hydrogen tartrate, m.p. 186–187 °C, $[\alpha]_D^{22}$ +23.1° (*c* 1.0, $H_2O$). Anal. $C_9H_{15}NO_6$: C, H, N.

The initial filtrate from the above resolution was concentrated *in vacuo* and the residue dissolved in saturated $K_2CO_3$-solution. After extraction of the amine with ether and drying of the extract ($K_2CO_3$), the solution was fractionated through a helix-packed column. The amine fraction [3.8 g, $[\alpha]_D^{22}$ −8.5° (*c* 1.0)] was added to a solution of (−)-tartaric acid in ethanol-water and the salt formed was purified as described above for the enantiomeric salt. The yield, based on recovered amine, of resolved (−)-hydrogen tartrate was 52 %, m.p. 186–187 °C, $[\alpha]_D^{22}$ −23.3° (*c* 1.0, $H_2O$).

*(S)-(−)-1-Ethyl-2-propynylamine.* The resolved (+)-hydrogen tartrate (11.0 g, 0.047 mol) was dissolved in saturated $K_2CO_3$-solution and the pure amine was obtained through the procedure described above, b.p. 104 °C, $n_D^{22}$ 1.442, $[\alpha]_D^{22}$ −20.9° (neat, *d* 0.813), +14.4° (*c* 1.0), yield 2.3 g (58 %), $^1$H NMR ($CDCl_3$, 37 °C): $\delta$ 1.05 (3 H, t, *J* 7.0 Hz, C$H_3$), 1.40–1.92 (4 H, m, N$H_2$, C$H_2$), 2.30 (1 H, d, *J* 2.4 Hz, ≡C*H*), 3.49 (1 H, triplet of doublets, *J* 7.0 and 2.4 Hz, C*H*). *Hydrochloride*: m.p. 198–199 °C (from ethanol-ether), $[\alpha]_D^{22}$ +14.3° (*c* 1.0). Anal. $C_5H_9N$.HCl: C, H, N. *Benzamide*: m.p. 79–80 °C (from ligroin), $[\alpha]_D^{22}$ −48.6° (*c* 0.7). Anal. $C_{12}H_{13}NO$: C, H, N.

*(R)-(+)-1-Ethyl-2-propynylamine* was obtained similarly from the (−)-hydrogen tartrate, b.p. 104 °C, $n_D^{22}$ 1.441, $[\alpha]_D^{22}$ +20.3° (neat, *d* 0.813), −13.3° (*c* 1.2), yield 52 %. *Hydrochloride*: m.p. 199–200 °C, $[\alpha]_D^{22}$ −14.4° (*c* 1.0). *Benzamide*: m.p. 79–80 °C. $[\alpha]_D^{22}$ +49.0° (*c* 1.2).

*N-[(S)-1-Ethyl-2-propynyl]-(R)-O-methylmandelamide.* (*R*)-(−)-*O*-Methylmandelic acid [7] [$[\alpha]_D^{22}$ −148.7° (*c* 0.6)] was converted to its acid chloride with which (*S*)-(−)-1-ethyl-2-propynylamine was acylated according to a method described in the literature,[8] m.p. 66–67 °C (from ligroin), $[\alpha]_D^{22}$ −158.0° (*c* 1.0). $^1$H NMR ($C_6H_6$, 37 °C): $\delta$ 0.88 (3 H, t, *J* 7.0 Hz, C-C$H_3$), 1.36–1.89 (2 H, m, C$H_2$), 1.95 (1 H, d, *J* 2.4 Hz, ≡C*H*), 2.95 (3 H, s, OC$H_3$), 4.52 (1 H, s, ArC*H*), 4.62–5.06 (1 H, m, N-C*H*). Anal. $C_{14}H_{17}NO_2$: C, H, N.

*N-[(R)-1-Ethyl-2-propynyl]-(R)-O-methylmandelamide* was prepared similarly from (*R*)-(+)-1-ethyl-2-propynylamine, m.p. 83–84 °C (from ligroin), $[\alpha]_D^{22}$ −4.8° (*c* 1.0). $^1$H NMR ($C_6H_6$, 37 °C): $\delta$ 0.75 (3 H, t, *J* 7.0 Hz, C-C$H_3$), 1.18–1.73 (2 H, m, C$H_2$), 1.98 (1 H, d, *J* 2.4 Hz, ≡C*H*), 2.94 (3 H, s, OC$H_3$), 4.47 (1 H, s, ArC*H*), 4.65–5.09 (1 H, m, N-C*H*). Anal. $C_{14}H_{17}NO_2$: C, H, N.

*(S)-(−)-N-(1-Ethyl-2-propynyl)benzenesulfonamide.* To a stirred and cooled (0–5 °C) solution of (*S*)-(−)-1-ethyl-2-propynylamine (1.0 g, 0.012 mol) in pyridine (4 ml) was added dropwise benzenesulfonyl chloride (2.3 g, 0.013 mol) dissolved in pyridine (10 ml). The reaction mixture was left overnight at room temperature and the pyridine was evaporated *in vacuo*. Water was then added and the product extracted with ether, the ether layer washed with 5 % HCl and then with water until neutral reaction. After concentration of the dried ethereal solution *in vacuo*, the product crystallized, m.p. 108.5–110 °C (from ethanol-water), $[\alpha]_D^{22}$ −60.9° (*c* 1.0), yield 2.3 g (84 %). Anal. $C_{11}H_{13}NO_2S$: C, H, N, S.

*(S)-(+)-N-Benzenesulfonyl-α-aminobutyric acid. Oxidation of (S)-(−)-N-(1-ethyl-2-propynyl)benzenesulfonamide.* The above sulfonamide (1.8 g, 0.008 mol) was oxidized with $KMnO_4$ as described for the oxidation of the 1-methyl-2-propynyl compound.[2] The product slowly crystallized from the acidified solution, m.p. 138–139 °C (from water), $[\alpha]_D^{22}$ +2.0°, $[\alpha]_{365}^{22}$ +30.2° (*c* 1.0), yield 0.8 g (42 %). Anal. $C_{10}H_{13}NO_4S$: C, H, N, S.

*(R)-(−)-N-Benzenesulfonyl-α-aminobutyric acid. Acylation of* D-*(−)-α-aminobutyric acid.* D-(−)-α-Aminobutyric acid [0.5 g, 0.0048 mol $[\alpha]_D^{22}$ −8.2° (*c* 2.0, $H_2O$), lit.[9] $[\alpha]_D^{20}$ −7.9° (*c* 5.31 %, $H_2O$)], was acylated with benzenesulfonyl chloride according to the method described by Wiley *et al.*[10] to give 0.35 g (30 %) of product, m.p. 137–138 °C (from water), $[\alpha]_D^{22}$ −2.2°, $[\alpha]_{365}^{22}$ −31.0° (*c* 1.1). Anal. $C_{10}H_{13}NO_4S$: C, H, N, S.

*Resolution of 1-propyl-2-propynylamine.* Racemic 1-propyl-2-propynylamine [6] (97 g, 1.0 mol) was added to a hot solution of (+)-tartaric acid (150 g, 1.0 mol) in 600 ml of ethanol-isopropyl alcohol (1:1). The solution was left overnight at room temperature. The salt obtained (105 g, m.p. 120–124 °C) required six recrystallizations from 20 % solutions in ethanol-isopropyl alcohol (1:2) for the separation of the diastereomeric hydrogen tartrates. The resolved (+)-hydrogen tartrate was obtained in 43 % yield (53 g), m.p. 133–134 °C, $[\alpha]_D^{22}$ +25.1° (*c* 1.0, $H_2O$). Anal. $C_{10}H_{17}NO_6$: C, H, N.

The initial filtrate from the above resolution was concentrated *in vacuo*. The residue was dissolved in 5 N NaOH and the solution saturated with solid $K_2CO_3$. After extracting the amine with ether and drying the extract ($K_2CO_3$), the ether was removed through a helix-packed column. The amine was distilled at reduced pressure affording 33 g of product, $[\alpha]_D^{22}$ −8.6° (*c* 1.0), which was converted to the (−)-hydrogen tartrate and purified as described for the enantiomeric salt. The yield, based on recovered amine, of (−)-hydrogen tartrate was 40 % (34 g), m.p. 133–134 °C,

$[\alpha]_D^{22}$ −25.3° (*c* 1.0, $H_2O$). Anal. $C_{10}H_{17}NO_6$: C, H, N.

*(S)-(−)-1-Propyl-2-propynylamine.* Resolved (+)-hydrogen tartrate (30 g, 0.12 mol) was dissolved in saturated $K_2CO_3$ solution and the amine was liberated as described above. Redistillation afforded 10 g (85 %) of the pure amine, b.p. 52–55 °C (40 mmHg), $n_D^{22}$ 1.445, $[\alpha]_D^{22}$ −13.5° (neat, *d* 0.815), +19.2° (*c* 1.7), $^1$H NMR ($CDCl_3$, 37 °C): $\delta$ 0.75–1.1 (3 H, m, $CH_3$), 1.3–1.7 (6 H, m, $NH_2$, $CH_2CH_2$), 2.28 (1 H, d, *J* 2.4 Hz, ≡C*H*), 3.37–3.68 (1 H, m, C*H*). *Hydrochloride:* m.p. 215–216 °C (from ethanol-ether), $[\alpha]_D^{22}$ +19.0° (*c* 1.3). Anal. $C_6H_{11}N.HCl$: C, H, N. *Benzamide*: m.p. 85–86 °C (from ligroin), $[\alpha]_D^{22}$ −42.9° (*c* 1.0). Anal. $C_{13}H_{15}NO$: C, H, N.

*(R)-(+)-1-Propyl-2-propynylamine* was obtained similarly from the (−)-hydrogen tartrate, b.p. 55 °C (48 mmHg), $n_D^{22}$ 1.444, $[\alpha]_D^{22}$ +13.5° (neat, *d* 0.815), −19.9° (*c* 1.0), yield 81 %. *Hydrochloride*: m.p. 215–216 °C, $[\alpha]_D^{22}$ −19.2° (*c* 1.1). *Benzamide*: m.p. 85–86 °C, $[\alpha]_D^{22}$ +41.9° (*c* 1.0).

*N-[(S)-1-Propyl-2-propynyl]-(R)-O-methylmandelamide.* (*S*)-(−)-1-Propyl-2-propynylamine was acylated as described above for the 1-ethyl analogue, m.p. 78–79 °C (from light petroleum), $[\alpha]_D^{22}$ −141.6° (*c* 1.0). $^1$H NMR ($C_6H_6$, 37 °C): $\delta$ 0.60–0.95 (3 H, m, C-$CH_3$), 1.25–1.65 (4 H, m, $CH_2CH_2$), 1.93 (1 H, d, *J* 2.4 Hz, ≡CH), 2.95 (3 H, s, $OCH_3$), 4.53 (1 H, s, ArC*H*), 4.70–5.15 (1 H, m, N-C*H*). Anal. $C_{15}H_{19}NO_2$: C, H, N.

*N-[(R)-1-Propyl-2-propynyl]-(R)-O-methylmandelamide* was prepared similarly from (*R*)-(+)-1-propyl-2-propynylamine, m.p. 78–79 °C (from light petroleum), $[\alpha]_D^{22}$ −13.3° (*c* 1.0). $^1$H NMR ($C_6H_6$, 37 °C): $\delta$ 0.50–0.85 (3 H, m, C-$CH_3$), 1.15–1.55 (4 H, m, $CH_2CH_2$), 2.03 (1 H, d, *J* 2.4 Hz, ≡C*H*), 2.96 (3 H, s, $OCH_3$), 4.50 (1 H, s, ArC*H*), 4.75–5.20 (1 H, m, N-C*H*). Anal. $C_{15}H_{19}NO_2$: C, H, N.

*(R)-(+)-N-(1-Propyl-2-propynyl)benzenesulfonamide* was prepared from (*R*)-(+)-1-propyl-2-propynylamine (2.5 g, 0.026 mol) and benzenesulfonyl chloride (4.2 g, 0.024 mol) in pyridine solution as described above for 1-ethyl-2-propynylamine, m.p. 69–70 °C (from ethanol-water). $[\alpha]_D^{22}$ +47.7° (*c* 1.0), yield 4.1 g (72 %). Anal. $C_{12}H_{15}NO_2S$: C, H, N, S.

*(R)-(−)-N-Benzenesulfonylnorvaline. (A) Acylation of* D-*(−)-norvaline.* D-(−)-Norvaline (0.5 g, 0.0043 mol), $[\alpha]_D^{22}$ −23.8°, $[\alpha]_{365}^{22}$ −95.8° (*c* 1.2, 1 M HCl), lit.[11] $[\alpha]_D^{20}$ −25.1° (*c* 3.0, 20 % HCl), was acylated as described for D-(−)-α-aminobutyric acid, m.p. 139.5–141 °C (from water), $[\alpha]_D^{22}$ −5.7°, $[\alpha]_{365}^{22}$ −39.9° (*c* 0.9), yield 0.46 g (42 %). Anal. $C_{11}H_{15}NO_4S$: C, H, N, S.

*(B) Oxidation of (R)-(+)-N-(1-propyl-2-propynyl)benzenesulfonamide.* (*R*)-(+)-*N*-(1-Propyl-2-propynyl)benzenesulfonamide (2.0 g, 0.008 mol) was oxidized with $KMnO_4$ as previously described for the oxidation of the 1-methyl-2-propynyl compound,[2] m.p. 139–140.5 °C. $[\alpha]_D^{22}$ −5.3, $[\alpha]_{365}^{22}$ −39.0° (*c* 1.1), yield 1.0 g (46 %). Anal. $C_{11}H_{15}NO_4S$: C, H, N, S.

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