Some Optically Active \(N\)-(4-\textit{tert}-Amino-1-methyl-2-butynyl)-substituted Succinimides and 2-Pyrrolidones and their Absolute Configurations*

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The enantiomers of \(N\)-(1-methyl-4-pyrrolidino-2-butynyl)-2-pyrrolidone, \(N\)-(1-methyl-4-pyrrolidino-2-butynyl)succinimide and \(N\)-(1-methyl-4-perhydroazepino-2-butynyl)succinimide have been prepared from the enantiomers of 1-methyl-2-propynylamine in order to study their stereoselectivity as oxotremorine antagonists. The absolute configurations of the optically active compounds have been established in two independent ways by correlation to \((S)\)-1-methylpropylamine and to \((R)\)-alanine.

Previous work in our laboratories has shown that a number of \(N\)-(tert- aminoalkynyl)-substituted succinimides and 2-pyrrolidones are rather potent in blocking the motor effects of the muscarinic agent oxotremorine, \(N\)-(4-pyrrolidino-2-butynyl)-2-pyrrolidone.\(^1\)\(^2\)

Common to the most active compounds is the intermediate chain connecting the two nitrogens in the molecule. As this chain contains an asymmetrically substituted carbon atom, we decided to prepare the enantiomers of compounds \(\text{I} - \text{III}\) in order to study their stereoselectivity as oxotremorine antagonists.

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\begin{align*}
\text{I} & : X = \text{CH}_3, \quad n = 4 \\
\text{II} & : X = \text{C}=\text{O}, \quad n = 4 \\
\text{III} & : X = \text{C}=\text{O}, \quad n = 6
\end{align*}
\]

The enantiomers of \(\text{I} - \text{III}\) were synthesized from the optically active forms of 1-methyl-2-propynylamine. This amine has been resolved and its \((-)\)-enantiomer prepared in pure form by Marszak-Fleury.\(^3\) We resolved the amine into its \((+)\) and \((-)\)-enantiomers using \((+)\) and \((-)\)-tartaric acid, respectively. The resolution process was followed by measurements of the optical rotation of the benzoyl derivatives. The optical purity was determined by NMR spectroscopic analysis of the diastereomeric amides formed when optically impure amine is acylated with \((-)\)-O-methylmandely chloride.\(^4\)\(^5\) The anisochronous signals from the \(\text{C}\)-methyl (\(\delta\) 1.48 and 1.39) and \(\text{O}\)-methyl groups (\(\delta\) 3.36 and 3.39) were especially suitable for this purpose.

The enantiomers of 1-methyl-2-propynylamine were acylated with 4-chlorobutyryl chloride or succinim anhydride and the amides formed were cyclized to \(N\)-(1-methyl-2-propynyl)-2-pyrrolidone and \(N\)-(1-methyl-2-propynyl)succinimide, respectively, from which compounds the enantiomers of \(\text{I} - \text{III}\) were prepared through the Mannich reaction as described for the racemates.\(^5\)\(^6\) The sign of rotation was unchanged through the reaction sequences.

When the six optically active compounds were tested in mice for antagonism towards tremor induced by oxotremorine, and for mydriatic activity, and on isolated guinea-pig ileum preparations for antagonistic activity towards acetylcholine, it was found that the
(+)-isomers were considerably more active than their enantiomers. In several tests the (+)-isomers were about twice as active as their corresponding racemates, whereas the (−)-isomers were practically inactive. As the three (+)-enantiomers were all prepared from (+)-1-methyl-2-propynylamine we found it of great interest to establish its absolute configuration. This was carried out in two independent ways. Upon catalytic hydrogenation, the benzoyl derivatives of (−)-1-methyl-2-propynylamine afforded the benzoyl derivative of (S)-(−)-1-methylpropylamine, the absolute configuration of which has been established by the Ingold school and by Kjaer and Hansen. A correlation was also made with (R)-alanine (D-alanine). Oxidation of the benzenesulfonyl derivative of (+)-1-methyl-2-propynylamine with potassium permanganate afforded the benzenesulfonyl derivative of D-(−)-alanine. Thus, (+)-1-methyl-2-propynylamine as well as the (+)-enantiomers of compounds I–III can be assigned the R configuration.

EXPERIMENTAL

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

Resolution of 1-methyl-2-propynylamine. Racemic 1-methyl-2-propynylamine (79 g, 1.1 mol) was added in small portions to a solution of (−)-tartaric acid (171 g, 1.1 mol) in water (170 ml) and the solution was left for a few days at room temperature. The salt formed (89 g) was recrystallized from a concentrated aqueous solution containing about 60% of salt. After each recrystallization, amine was liberated from a small sample of the salt and converted to the benzoyl and (−)-O-methylmandelate derivatives. After four recrystallizations constant physical properties of the salt and the derivatives were obtained. Yield 10.9 g of the resolved (−)-tartrate, m.p. 151.5–154°C, [α]D25 +24.4° (c 1.1, H2O). (Found: C 41.8; H 6.0; N 6.0. Calc. for C9H11NO4·H2O: C 42.1; H 6.2; N 6.1.)

The combined mother liquors from the above solution were saturated with K2CO3 and the amine was extracted with ether. The ether solution was dried and fractionated through a helix-packed column. The amine fraction was added to an aqueous solution of (−)-tartaric acid and the salt formed was purified as described above for the enantiomeric salt. The product had m.p. 153.5–155°C, [α]D25 −24.1° (c 1.3, H2O). (Found: C 42.1; H 6.0; N 6.2. Calc. for C9H11NO4·H2O: C 42.1; H 6.2; N 6.1.)

(R)-(−)-1-Methyl-2-propynylamine. The resolved (+)-tartrate (8.0 g, 0.04 mol) was dissolved in a small amount of water; the solution was saturated with K2CO3 and extracted with ether. After drying, the ether solution was fractionated through a helix-packed column. The amine fraction was distilled, affording the pure amine (1.3 g, 47%), b.p. 82–84°C, [α]D25 +53.2° (neat, d 0.8175). (S)-(−)-1-Methyl-2-propynylamine was obtained similarly in 51% yield from the (−)-tartrate, b.p. 82–84°C, [α]D25 −52.7° (neat, d 0.8175). Marszak-Fleury reports [α]D25 −52.2° (neat, d 0.822).

(R)-(−)-N-(1-Methyl-2-propynyl)benzamide. Benzylation of the amine liberated from the resolved (−)-tartrate under customary Schotten-Baumann conditions afforded the benzamide, m.p. 90–91°C (from ligroin), [α]D25 +45.3° (c 1.1). NMR (CDCl3): δ 1.49 (3 H, d, J = 7.02 Hz, CH3), 2.28 (1 H, d, J = 2.36 Hz, ≡CH), 5.02 (1 H, m, CHCH3), 6.70–7.20 (1 H, m, NH), 7.20–7.95 (5 H, m, ArH). (Found: C 76.2; H 6.4; N 8.2. Calc. for C11H11NO3: C 76.3; H 6.4; N 8.1.)

(S)-(−)-N-(1-Methyl-2-propynyl)benzamide was prepared similarly, m.p. 90–91°C, [α]D25 −45.8° (c 0.7). (Found: C 76.0; H 6.1; N 8.3. Calc. for C11H11NO3: C 76.3; H 6.4; N 8.1.)

N-(R)-(−)-1-Methyl-2-propynyl)-(R)-(−)-O-methylmandelamide. O-Methylmandelic acid was resolved via the (−)-ephedrine salt to give (R)-(−)-O-methylmandelic acid, [α]D25 −148.7° (c 0.6). This acid was converted to the acid chloride and (R)-(−)-1-methyl-2-propynylamine was acylated according to a method described in the literature. The amide was obtained in 40% yield, m.p. 104–105°C (from ligroin), [α]D25 −9.6° (c 0.8). NMR (CDCl3): δ 1.39 (3 H, d, J = 7.0 Hz, CH2CH3), 2.29 (1 H, d, J = 2.4 Hz, ≡CH), 3.39 (3 H, s, OCH3), 4.60 (1 H, s, CH2CH3), 4.50–5.10 (1 H, m, CHCH3), 6.70–7.20 (1 H, m, NH), 7.38 (5 H, s, ArH). (Found: C 71.5; H 6.8; N 6.7. Calc. for C17H17NO4: C 71.9; H 7.0; N 6.5.)

N-(S)-(−)-1-Methyl-2-propynyl)-(R)-(−)-O-methylmandelamide was prepared as described above for the diastereomeric compound from (S)-(−)-1-methyl-2-propynylamine and (R)-(−)-O-methylmandelic acid, m.p. 87–88°C (from ligroin), [α]D25 −186.5° (c 0.6). NMR (CDCl3): δ 1.48 (3 H, d, J = 7.0 Hz CH2CH3), 2.28 (1 H, d, J = 2.4 Hz, ≡CH), 3.36 (3 H, s, OCH3), 4.60 (1 H, s, CH2CH3), 4.50–5.10 (1 H, m, CHCH3), 6.70–7.20 (1 H, m, NH), 7.38 (5 H, s, ArH). (Found: C 71.9; H 6.9; N 6.6. Calc.

for C₆H₅NO₂: C 71.9; H 7.0; N 6.5).

Hydrogenation of (S)-(+)-(1-methyl-2-propynyl) benzamide. (S)-(+)-(1-methyl-2-propynyl)benzamide (0.6 g), [α]D +45.1° (c 0.8), was dissolved in ethanol (25 ml) and hydrogenated at room temperature over-night under a hydrogen pressure of 3 atm using Pt – C as catalyst. The catalyst was filtered off and the solvent removed. The residue was recrystallized first from ligroin and then from ethanol-water affording crystals (0.35 g, 57 %) of (S)-(+)-(1-methylpropyl)benzamide, m.p. 95 - 96 °C, [α]D +32.9° (c 1.0). The highest values reported for this compound are m.p. 97 °C, [α]D +34.9° (c 1).

(R)-(+)-(1-Methyl-2-propynyl)benzenesulfonamide. Resolved (+)-bitartrate of 1-methyl-2-propynylamine (6.9 g, 0.031 mol) was dissolved in water (10 ml). The benzoyl derivative of the amine liberated from this salt had [α]D +42.6° (c 1). After addition of 2 M NaOH (25 ml), benzenesulfonyl chloride (5.8 g, 0.032 mol) was added dropwise with vigorous shaking and occasional cooling with tap-water. The mixture was then shaken for 3 h and acidified with 1 M HCl. The product separated as an oil which rapidly solidified. It was filtered off, washed with water and recrystallized 3 times from 60 % EtOH. Yield 5.3 g (82 %), m.p. 99 - 100 °C, [α]D +76.1° (c 1). (Found: C 57.5; H 5.5; N 6.5; S 15.3. Calc. for C₃H₄NO₃S: C 57.4; H 5.3; N 6.7; S 15.3.).

(R)-(+)-(1-Benzylsulfonfyl)alanine. A. Acylation of D-(+)-(1-d-alanine. D-(+)-(1-Alanine (2.7 g, 0.03 mol), [α]D +14.6° (c 5, 1 M HCl) was acetylated with benzenesulfonyl chloride according to a method described by Wiley, Smith and Johansen to give 3.4 g (50 %) of product, m.p. 126 - 127 °C. (from benzene-ethyl acetate), [α]D +9.9° (c 1). [α]D +30.0° (c 0.4, Na salt in H₂O), [α]D +36.1° (c 0.4, Na salt in H₂O). Gibson and Levin who prepared this compound by resolution of the racemate, report m.p. 126 - 127 °C, [α]D +33.4° (c 0.4, Na salt in H₂O).

B. Oxidation of (R)-(+)-(1-Methyl-2-propynyl)benzenesulfonamide. A saturated (~6 %) solution of KMnO₄ in water was added dropwise to a stirred suspension of the above sulfonamide (3.14 g, 0.015 mol), [α]D +76.1° (c 1), in water (50 ml) at 0 - 5 °C. When no more KMnO₄ was consumed, the reaction mixture was filtered. The filtrate was washed twice with ether and acidified. Sodium pyrosulfite was added to remove excess permanganate and the clear solution was evaporated to dryness under reduced pressure. From the residue, the product was extracted with boiling ethanol. Evaporation of the solvent yielded (R)-(+)-(1-Benzylsulfonfyl)alanine, which after three recrystallizations from benzene-ethyl acetate afforded crystals (1.9 g, 55 %) of m.p. 126 - 127 °C, [α]D +9.0° (c 1), [α]D +28.6° (c 0.4, Na salt in H₂O), [α]D +35.0° (c 0.4, Na salt in H₂O). The product was in every respect (mixed m.p., IR, NMR) identical with that obtained by method A.

(R)-(+)-(1-Methyl-2-propynyl)4-chlorobutryramide. (R)-(+)-(1-Methyl-2-propynylamine was acylated with 4-chlorobutyryl chloride as previously described for the racemic amine, m.p. 75 - 76 °C (from cyclohexanone), [α]D +88.2° (c 0.8); yield 61 %. (Found: C 55.0; H 6.9; N 8.1; Cl 20.4. Calc. for C₆H₅NOCl: C 55.3; H 7.0; N 8.1; Cl 20.4). (S)-(+)-(1-Methyl-2-propynyl)4-chlorobutryramide was prepared similarly, m.p. 75 - 76 °C, [α]D -91.7° (c 0.9); yield 61 %.

(R)-(+)-(1-Methyl-2-propynyl)-2-pyrrolidone. Ring closure of the (R)-(+)-(1-Methyl-2-propynyl)-4-chlorobutryramide prepared above with sodium ethoxide in ethanol afforded the title compound, b.p. 65 - 67 °C (0.4 mmHg), nD +1.4683; yield 55 %. The oily product gradually crystallized, m.p. 36 - 38 °C (from petroleum ether), [α]D +111.2° (c 1.2). (Found: C 69.9; H 8.0; N 10.0. Calc. for C₆H₁₁NO: C 70.0; H 8.1; N 10.2.).

(S)-(+)-(1-Methyl-2-propynyl)-2-pyrrolidone was prepared similarly, b.p. 75 °C (0.6 mmHg), nD +1.4883; yield 73 %. M.p. 37 - 39 °C, [α]D -112.4° (c 0.9). (S)-(+)-(1-Methyl-4-pyrrolidino-2-butyramidine [(R)-(+)-(1-Methyl-4-pyrrolidino-2-butyramidine [(R)-(+)-(1)] was prepared by the Mannich reaction from (R)-(+)-(1-[(N-1,methyl-2-propynyl)-2-pyrrolidone, formaldehyde and pyrrolidine in dioxan in the presence of small amounts of CuCl as described for the racemate, b.p. 120 - 125 °C (0.2 mmHg), nD +1.5085, [α]D +112.3° (c 1.1); yield 68 %.

Oxalate, m.p. 125 - 125.5 °C (from ethanol), [α]D +88.2° (c 0.6). (Found: C 57.9; H 7.0; N 9.2. Calc. for C₆H₁₂NO₄CO₂H: C 58.0; H 7.2; N 9.0). (S)-(+)-(1-[(N-1-Methyl-4-pyrrolidino-2-butyramidine)] was prepared similarly, b.p. 140 - 142 °C (0.4 mmHg), nD +1.5100, [α]D -113.5° (c 1.0); yield 63 %.

Oxalate, m.p. 125 - 125.5 °C, [α]D -88.5° (c 1.0).

(R)-(+)-(1-Methyl-2-propynyl) succinamic acid. (R)-(+)-(1-Methyl-2-propynylamine was acylated with succinic anhydride in acetone as previously described for the racemic amine, m.p. 120.5 - 121.5 °C (from acetone-light petroleum), [α]D +93.9° (c 0.9); yield 74 %.

(S)-(+)-(1-Methyl-2-propynyl) succinamic acid was prepared similarly, m.p. 120 - 121°C, [α]D +96.2° (c 0.7); yield 80 %. (Found: C 56.5; H 6.4; N 8.4. Calc. for C₆H₁₃NO₂C: 56.8; H 6.6; N 8.3). (R)-(+)-(1-Methyl-2-propynyl) succinimide. (R)-(+)-(1-Methyl-2-propynyl) succinamic acid was cyclized with the aid of AcO and anhydrous NaOH, b.p. 90 - 93 °C (0.6

* In a preliminary note on this work the salt has erroneously been reported to be a sesquioxide like the racemate. 
mmHg), \( n^\text{D}_{25} \) 1.5039, [\( \lambda \)]_{D}^{25} + 31.6° (c 0.3); yield 90 %.

(S)-(-)-N-(1-Methyl-2-propynyl)succinimide was prepared similarly, b.p. 75 °C (0.3 mmHg), \( n^\text{D}_{20} \) 1.5020, [\( \lambda \)]_{D}^{25} - 34.3° (c 1.0); yield 92 %. (Found: C 63.7; H 6.2; N 9.3. Calc. for \( \text{C}_7\text{H}_6\text{NO}_2 \): C 63.6; H 6.0; N 9.3.)

(R)-(+)-N-(1-Methyl-4-pyrrolidino-2-butylnyl)succinimide [(R)-(+)-II] was prepared by the Mannich reaction from (R)-(+)-N-(1-methyl-2-propynyl)succinimide, formaldehyde and pyrrolidine as described for the racemate, m.p. 75 - 75.5 °C (from ligroin), [\( \lambda \)]_{D}^{25} + 53.1° (c 0.9); yield 75 %. (Found: C 66.9; H 7.8; N 11.8. Calc. for \( \text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2 \): C 66.6; H 7.7; N 12.0.)

(S)-(-)-N-(1-Methyl-4-pyrrolidino-2-butylnyl)succinimide [(S)-(-)-II] was prepared similarly, m.p. 75 - 75.5 °C, [\( \lambda \)]_{D}^{25} - 54.0° (c 0.7); yield 55 %.

(R)-(+)-N-(1-Methyl-4-perhydroazepino-2-butylnyl)succinimide perchlorate [(R)-(+)-III] was prepared similarly by the Mannich reaction using perhydroazepine as the cyclic secondary amine, m.p. 192 - 193 °C (from ethanol), [\( \lambda \)]_{D}^{25} + 49.7° (c 0.3); yield 58 %.

(S)-(-)-N-(1-Methyl-4-perhydroazepino-2-butylnyl)succinimide perchlorate [(S)-(-)-III] was prepared similarly, m.p. 193 - 194 °C, [\( \lambda \)]_{D}^{25} - 51.1° (c 0.4); yield 65 %. (Found: C 49.5; H 6.3; N 7.8; Cl 9.8. Calc. for \( \text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_2\cdot\text{HClO}_4 \): C 49.7; H 6.4; N 7.8; Cl 9.8.)

Acknowledgement. A grant from the Swedish Medical Research Council (Project B74-03X-533-10B) is gratefully acknowledged.

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Received October 28, 1975.