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Synthesis of Ipratropium Bromide-Related Compounds

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Synthesis of Ipratropium Bromide–Related Compounds

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Abstract: Synthesis of ipratropium bromide metabolites is described.

Keywords: ipratropium bromide, related compound, synthesis, HPLC

Ipratropium bromide, (endo, syn)-(±)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo [3.2.1] octane bromide **10**, belongs to the group of tropane alkaloids. It is in fact a diastereomer of the N-isopropyl quaternary salt of atropine 8S-ipratropium bromide **18**. As depicted in Fig. 1, the isopropyl group in ipratropium bromide **10** is axial, whereas in 8S-ipratropium bromide **18**, it is in the equatorial position. Both compounds are active anticholerinergic agents, though the former displays stronger activity and fewer clinical side effects.[1,2]

Synthesis of ipratropium bromide has been described by Banholzer et al.[3–5] (Fig. 2). Accordingly, Robinson condensation of succindialdehyde **1**, isopropylamine **2**, and acetonedicarboxylic acid **3** provides *N*-isopropylnortropinone **4**, which is then catalytically hydrogenated to produce *N*-isopropylnortropine **5**. Transesterification with ethyl α-formylphenylacetate **7** followed by sodium borohydride reduction yields *N*-isopropylnoratropine **9**. Finally, the product is N-alkylated with methylbromide to give ipratropium bromide **10**.

The in vivo metabolism of ipratropium bromide generates different products[6–9] (Fig. 3). Also, the preparation of ipratropium bromide is accompanied by the formation of several by-products. Synthesis of these by-products and metabolites are important to trace the generated impurities

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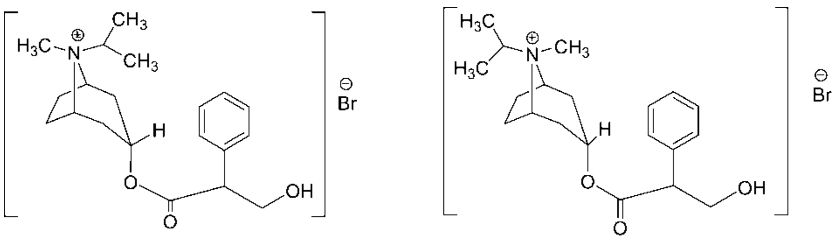

10 18

Figure 1. Isomers of methyl isopropyl derivatives of atropine.

in the final product, as, well as to study the pharmacokinetic and stability of ipratropium bromide **10**.

A number of procedures have been reported for this purpose. Herein, we introduce an alternative route to some of these impurities and metabolites: N-isopropylnoratropine **9**, apo-ipratropium bromide **15**, N-isopropylnortropine methylbromide **17**, and 3-(2-phenyl-acryloyloxy)-8-isopropyl-8-methyl-8-azoniabicyclo [3.2.1] octane bromide **16**. The quantification and the purity of these compounds are evaluated by high-performance liquid chromatography (HPLC).

There are numerous articles in the literature concerning the synthesis of atropine from tropine and tropic acid.[10,11] We found that the one depicted in Fig. 4 provides the most reliable route to the synthesis of N-isopropylnoratropine **9**. A modification of the procedure of Fodor et al. was used.[11] Thus, tropic acid 11 was first protected by reaction with acetyl chloride. The product was then converted by treatment with thionyl chloride to the corresponding acid chloride 12. Condensation by heating with N-isopropylnoratropine 5 followed by hydrolysis provided N-isopropylnoratropine 9 in 30% overall yield (Fig. 4). The required N-isopropylnortropine 5 was prepared by the route presented in Fig. 2.

The synthesis of apo-ipratropium bromide **15** is depicted in Fig. 5. The dehydratation of atropine **13** on treatment with sulfuric acid provided apoatropine **14**, which was then N-alkylated by isopropyl bromide[13] (Fig. 5).

The N-alkylation of apoatropine **14** proceeds diastereoselectively.[14] As determined by a rule discovered by Fodor,[10] the substituent introduced last at the nitrogen preferably becomes situated over the pyrrollidine ring. Thus the apo-ipratropium bromide **15** and 3-(2-phenyl-acryloyloxy)-8-isopropyl-8-methyl-8-azoniabicyclo [3.2.1] octane bromide **16** were obtained as a 1:9 diastereoisomeric endo/exo mixture. Their stereochemistry was confirmed by ^{1}H NMR, ^{13}C NMR, and correlation spectroscopy (COSY) spectroscopy.

The last compound of interest in this study was N-isopropylnortropine methylbromide **17**. This compound was obtained via the reaction of methyl bromide with N-isopropylnortropine **5** (Fig. 6). NMR and MS spectroscopy confirmed the expected structure.

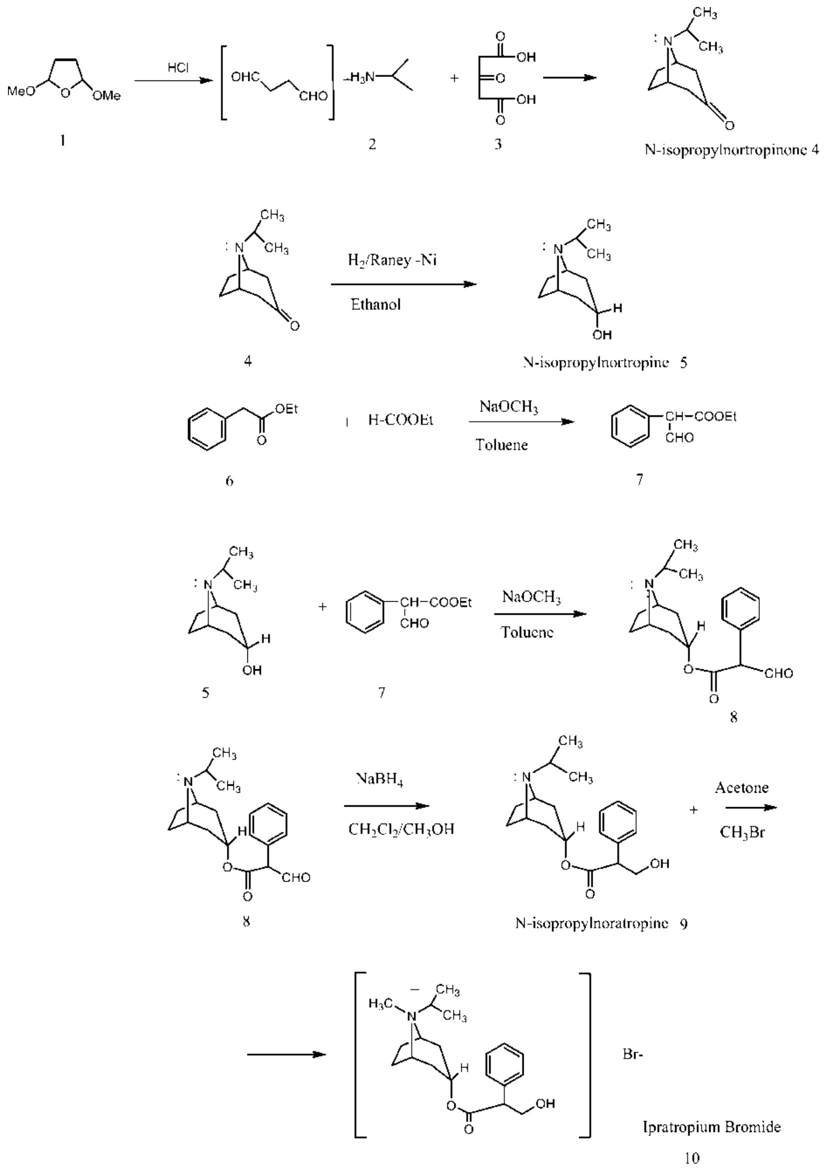

Figure 2. Synthesis of ipratropium bromide.

EXPERIMENTAL

NMR spectra were recorded on a 400-MHz Bruker instrument. Mass spectra were performed on a Micromass Autospec-TOF spectrometer. The microanalysis was performed on an EA 1108 CHNS model analyzer.

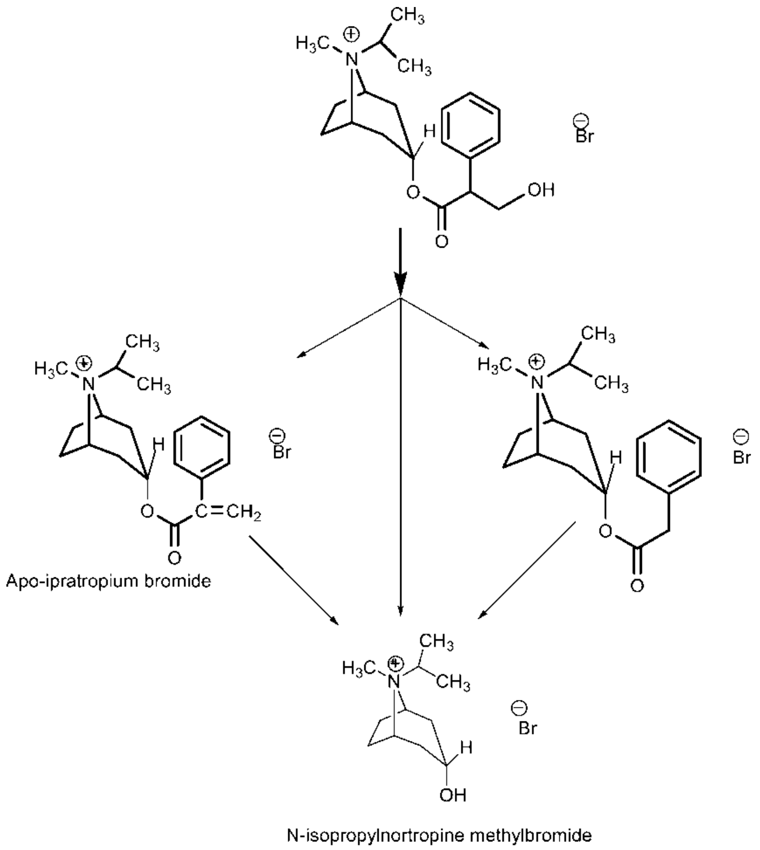

Figure 3. In-vivo metabolism of ipratropium bromide.

High-Performance Liquid Chromatography

Liquid chromatography was performed using a HPLC system composed of an Agilent model G1311A pump equipped with a ternary gradient controller and a Agilent model G1315A diode array detector, wavelength 210 nm. The computer is equipped with Agilent LC3D Chemstation for Analytical program, Revision A:09.03.

Apoatropine

A 250 mm × 4.0 mm, 5-μm Lichrosphere 60 RP-Select column was used for the determination of apoatropine. A mobile phase consisting of a water solution (0.1% H_3PO_4) and acetonitrile was delivered at a rate of 1 mL/min, holding the composition at 65:35 for 10 min.

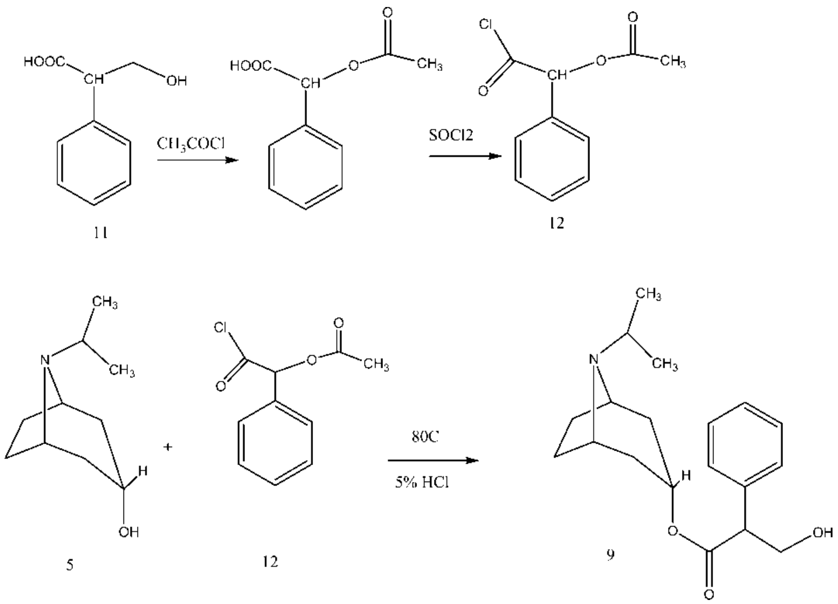

Figure 4. Synthesis of the N-isopropylnoratropine.

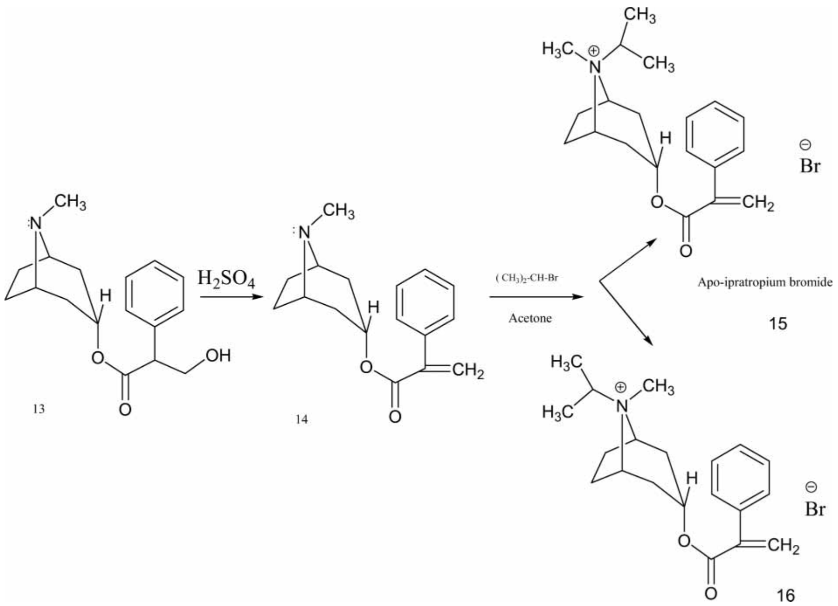

Figure 5. Synthesis of apo-ipratropium bromide and its diastereoisomer.

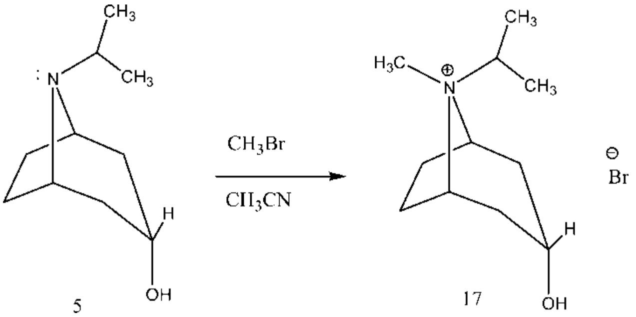

Figure 6. Synthesis of the N-isopropylnortropine.

Others

A 250 mm × 4.0 mm, 5-μm Lichrosphere 60 RP-Select column was used for determination of degradation products. A mobile phase A consisting of a buffer solution (50 mM of tetramethylamonium hydroxide, pH 3.0) and acetonitrile was delivered at a rate of 1.5 mL/min, holding the composition at 92:8 for 40 min, then as a linear gradient to 50:50 in 10 min. A post time of 10 min is added.

N-Isopropylnoratropine 9

A mixture of acetyltropyl chloride (4.33 g, 16.9 mmol)[12] and N-isopropylnortropine **5** (2.69 g, 16 mmol) was heated at 85°C for 4 h. The mixture was cooled and dissolved in chloroform (75 mL). The chloroform solution was poured into an aqueous solution of 5% hydrochloric acid (250 mL). The two-phase mixture was stirred vigorously for 18 h. The aqueous phase was extracted with 2 × 50 mL of chloroform, and the chloroform extracts were discarded. The aqueous phase was adjusted to pH 10 with a saturated sodium carbonate solution and extracted with 3 × 50 mL of chloroform. The combined chloroform extracts were washed with water, followed by a saturated sodium chloride solution, and dried with sodium sulfate. Removal of solvent under reduced pressure left a colored liquid (2.52 g, 50% crude yield). Crystallization from acetone gave 0.89 g of a white solid. The yield evaluated by HPLC is 34%, and the purity is 99.9%. H^1 NMR (400 MHz, CD_3OD) δ: 7.3 (m, 5H); 5.0 (t, 1H); 4.15 (t, 1 H); 3.76 (m, 2H); 3.3 (1H); 2.74 (m, N-CH); 2.19–1.4 (m, 8H); 1.08 (d, $J = 16.6$). MS m/z (M+) 318. $C_{19}H_{27}NO_3$ calc. C, 71.89%; H, 8.57%; N, 4.41%; found C, 71.82%; H, 8.53%; N, 4.39%.

Apoatropine 14

Atropine (1.00 g, 3.45 mmol) was dissolved in conc. H_2SO_4 (2.00 g, 14.4 mmol), and the mixture was allowed to stand for 2 h at room temperature. Finely cracked ice (5.00 g) was added carefully in small portions to this solution under cooling. After regeneration with 10% KOH solution, apoatropine was extracted with ether (50 mL) three times. The ether layers were washed with sat. NaCl solution and dried with Na_2SO_4. Evaporation of the solvent gave a colorless oil, which crystallized on standing, mp 60°C. The yield evaluated by HPLC is 86% and the purity is 94%. H^1 NMR (400 MHz, $CDCl_3$) δ: 7.39–7.26 (m, 5H); 6.35 (s, 1H); 5.87 (s, 1H); 5.14 (t, 1H); 3.08 (s, 2H); 2.27 (d, 3H); 2.18–1.73 (m, 8H). Ms m/z (M+) 272.2. $C_{17}H_{21}NO_2$ calc. C, 75.25%; H, 7.80%; N, 5.16%; found C, 75.19%; H, 7.67%; N, 5.15%.

Apo-ipratropium Bromide 15

To the solution of apoatropine (0.7 g, 2.58 mmol) in acetonitrile (10 mL), isopropylbromide (0.97 mL, 0.01 M) was added under stirring. The resulting mixture was heated under reflux for 5 days. After cooling, white precipitates were collected on a filter. Recrystallization from chloroform gave a white solid. The yield evaluated by HPLC is 6.4%, and the purity is 98%. H^1 NMR (400 MHz, $CDCl_3$) δ: 7.33 (s, 5H Ar); 6.38 (s, 1H); 5.91 (s, 1H); 5.27 (s, 1H); 4.1 (m, 2H); 3.68 (m, 1H); 2.85 (s, 3H); 2.75–1.99 (m, 8H); 1.4 (d, 6H, $J = 5.9$). MS m/z (M+) 314 (100%). $C_{20}H_{28}BrNO_2$ calc. C, 60.91%; H, 7.16%; N, 3.55%; Br, 20.26%; found C, 59.72%; H, 6.94%; N, 3.22%.

3-(2-Phenyl-acryloyloxy)-8-isopropyl-8-methyl-8-azoniabicyclo [3.2.1] octane bromide 16

This stereoisomer of apoipratropium bromide **15** was obtained in the same reaction (Fig. 5). The yield evaluated by HPLC is 58%, and the purity is 99.2%. H^1 NMR (400 MHz, $CDCl_3$) δ: 7.33 (s, 5H Ar); 6.38 (s, 1H); 5.83 (s, 1H); 5.26 (m, 1H); 4.1 (m, 2H); 3.68 (m, 1H); 3.0 (s, 3H); 2.75–1.99 (m, 8H); 1.4 (d, 6H, $J = 5.9$). MS m/z (M+) 314 (100%). $C_{20}H_{28}BrNO_2$ calc. C, 60.91%; H, 7.16%; N, 3.55%; Br, 20.26%; found C, 60.79%; H, 7.09%; N, 3.41%.

N-Isopropylnortropine-methylbromide 17

To a solution of N-isopropylnortropine **5** (1.00 g, 6 mmol) in acetonitrile, a solution of 2 N methylbromide (11.8 mL, 23.6 mmol) in ether was added. This mixture was stirred for 5 days. The reaction was monitored by TLC (butanol–H_2O–AcOH 4:3:1). Removal of solvent under reduced pressure resulted in a crude solid. Recrystallization from methanol left 1.45 g of a white solid. The yield is 93%, and the purity is 98.6%. H^1 NMR (400 MHz,

CD_3OD) δ: 4.04 (q, 2H); 3.9 (m, 2H); 2.83 (s, 3H); 2.57–2.47 (m, 4H); 2.31–2.28 (m, 4H); 1.88 (d, $J = 16.4$ Hz, 2H); 1.32 (dd, $J = 6.4$ Hz; 6H). C^{13} NMR (400 MHz, CD_3OD) δ: 68.1 (C_1/C_5); 60.96 (C_3); 57.03 (C_{isopr}); 40.5 (C_{CH3}); 35.3 (C_2/C_4); 26.4 (C_6/C_7); 17.0 ($C_{CH3\text{-}isopr}$); MS m/z (M+)184.1 (100%). $C_{11}H_{22}BrNO_2$ calc. C, 50.01%; H, 8.39%; N, 5.3%; Br, 30.24%; found C, 49.69%; H, 8.03%; N, 4.94%.

REFERENCES

1. Bauer, R.; Kuhn, F.; Stockhaus, K.; Wiek, H. *Drug. Res.* **1976**, *26*, 974–980.
2. Bauer, R.; Banholzer, R.; Greiben, C.; Middelton, D. A.; Sarafana, L.; Schulz, W.; Wahl, D. *Pharmacological and Biochemical Property of Drug Substances*; Washington, DC, 1979; Vol. 2, pp. 489–515.
3. Deckes, W. Postgraduate Medical Journal **1975**, *51* (suppl. 7), 76–81.
4. Zeile, K.; Schulz, W.; Banholzer, R.; Wick, H. *US Pat.* **1970**, 3,505,337.
5. Schulz, W.; Banholzer, R.; Pook, K. Arzneimittel-Forschung **1976**, *26* (5a), 960–974.
6. Foerster, H. J.; Kramer, I.; Pook, K. H.; Wahl, D. Arzneimittel-Forschung **1976**, *26* (5A), 992–1005.
7. Adlung, J.; Hoehle, K. D.; Zeren, S.; Wahl, D. Arzneimittel-Forschung **1976**, *26* (5A), 1005–1010.
8. Ohnuma, N.; Kiyoki, M.; Kubo, J.; Niki, T.; Hashimoto, Y. Iyakuhin Kenkyu **1978**, *9* (2), 382–392.
9. Simms, P.; Towne, R.; Gross, C.; Miller, R. J. *Pharmac. and Biomed. Analysis* **1998**, *17* (4–5), 841–849.
10. Fodor, G.; Chastian, R.; Frenel, D.; Coopes, M.; Manava, N.; Gooden, E. J. *Am. chem. Soc.* **1971**, *27* (1), 403–413.
11. Fung, V. A.; DeGraw, I. *Synthesis* **1976**, 311–312.
12. Tommy, R.; Riegel, R. J. *Org. Chem.* **1952**, *17*, 1492.
13. Takeuchi, Y.; Koga, K.; Takayuki, S.; Yamada, S. *Chem. Pharm. Bull.* **1971**, *19* (12), 2603–2608.
14. (a) Pook, K.; Schulz, W.; Banholezer, R. *Liebigs Ann. Chem.* **1975**, 1499–1512; (b) Nador, K.; Scheiber, P.; Karpati, E.; Grober, K. Arzneimittel-Forschung/Drug. Res **1987**, *37(II)* (12), 1324–1327.