Tetrahedron Vol. 43, No. 6, pp. 1177 to 1182, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

INTERMEDIATES IN THE EPIMERIZATION OF RITODRINE BY ACID

A. D. SILL, C. L. HOUSMYER*, AND K. GIBBONEY

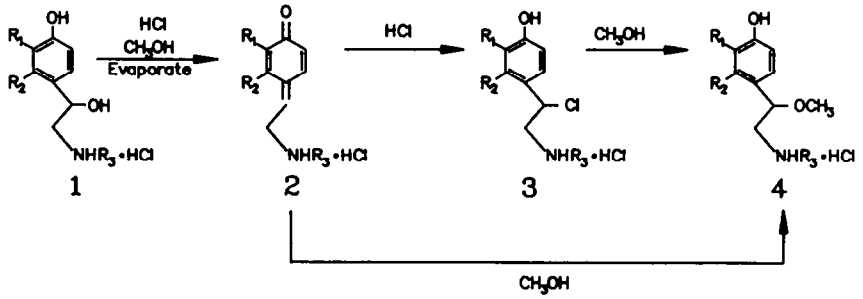
Merrell Dow Research Institute
Cincinnati, Ohio 45215

(*Received in USA* 11 *February* 1987)

Abstract--In contrast to the racemization reported for *l*-epinephrine in aqueous HCl, (R*,S*)-4-hydroxy-α-[1-[[2-(4-hydroxyphenyl) ethyl]amino]ethyl] benzenemethanol hydrochloride, known as ritodrine hydrochloride, is converted to the corresponding threo enantiomers by evaporating an aqueous acidic solution of the material to dryness and dissolving the residue in aqueous acid or base. Two unstable intermediates are characterized as 1) the product resulting from halogen displacement of the alcohol group and 2) a trans-substituted spiro piperidine derivative. The latter intermediate stereospecifically converts to the threo enantiomers in aqueous acid with retention of configuration. The threo enantiomers produce the same two intermediates. Reaction of either intermediate with methanol yields the corresponding methoxy derivative.

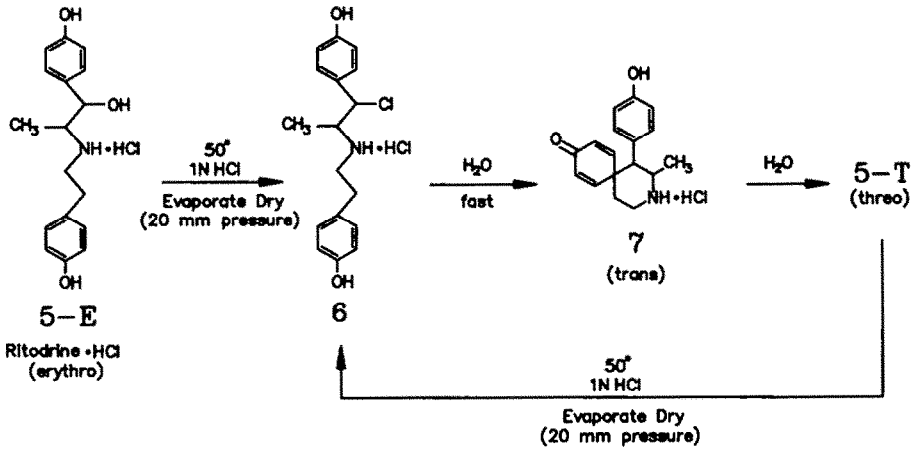
INTRODUCTION

Venter and Greef [1] reported that *l*-epinephrine (1, R_1=OH, R_2=H, R_3=CH_3) and other related compounds undergo the following reaction in MeOH/HCl:



They found that the p-hydroxy group was critical for the reaction because only starting material was recovered from compounds containing OMe or H in that position. In aqueous acid, the analogous reaction leads to the racemization of *l*-epinephrine as reported by Schroeter and Higuchi. [2] It was, therefore, surprising to find that the related compound, ritodrine (5-E, the erythro enantiomers), isomerizes in high yield to the threo enantiomers (5-T) on evaporating an aqueous HCl or HBr solution and redissolving in aqueous acid.

Two intermediates are formed in the process as shown below:



Intermediate 6 is rapidly converted to 7 on treatment with water. Intermediate 7 is more stable in water and 0.1M acetic or boric acid, but is rapidly converted to 5-T in the presence of stronger acid or base.

RESULTS AND DISCUSSION

Compound 7 was initially observed by HPLC analyses of solutions prepared from evaporate residues of ritodrine in 1M HCl. Typically, these solutions showed up to 75% loss of ritodrine that was accompanied by nearly stoichiometric production of 7. Intermediate 7, in turn, was converted to 5-T while the residual ritodrine content remained constant. The pseudo first order conversion kinetics show a direct dependency on acidity (k_{obs}: 0.01M HCl = 0.0022 min^{-1}, 0.1M HCl = 0.0227 min^{-1}, 1M HCl ca 0.3 min^{-1}). The conversion is also base-catalyzed as evidenced by a similar rate in 0.1M Na_2CO_3 as in 0.1M HCl.

Compound 6 was observed by proton NMR of deuteroacetone solutions of the evaporate residue. The spectrum showed essentially equal amounts of the erythro and threo forms, indicating that racemization occurs upon the conversion of 5-E to 6. Upon evaporation of the deutereoacetone and reconstitution in D_2O, the spectrum indicated exclusively 7. Thus, racemic 6 is converted to the single diastereomer 7 (trans) in neutral aqueous media.

This diastereomer, 7, is converted stereospecifically to 5-T, that is without formation of 5-E. This is indicated by the presence of a constant amount of 5-E during the conversion, under conditions where 5-E is stable. The exclusive conversion to 5-T is not the result of relative thermodynamic stability as indicated by the equilibration ratio of 38/62 [5-E/5-T] obtained on refluxing 5-E in 0.1M H_2SO_4. The conversion of 7 to 5-T is observed to occur with retention of configuration which requires the formation of another intermediate. The aziridine derivative is a possiblity, but no supportive data are available.

An attempt was made to epimerize 5-T by the usual process in 1M HCl. However, the same two intermediates formed and yielded 5-T in aqueous acid. A mixture of 16/84 [5-E/5-T], prepared in the usual manner, was evaporated under vacuum at 50°C in 1M HCl. In a single experiment, HPLC analysis of the residue dissolved in water indicated 18/35/47 [5-E/7/5-T]. After 20 minutes in aqueous acid, the mixture contained 18/82 [5-E/5-T].

The overall reactions have not produced 5-T quantitatively from 5-E. Small amounts of uncharacterized by- products appear, and residual 5-E is always present, probably due to incomplete conversion to 6 and to hydrolysis of 6 under acidic conditions.

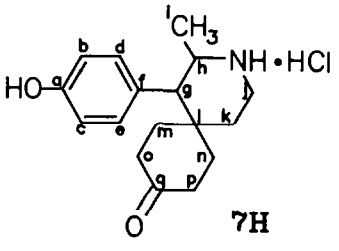
Intermediate 7

A sample of 7 was isolated by HPLC. Its NMR spectrum was significant in that the doublet for the benzylic CHO proton of ritodrine .HCl had disappeared and 3 new doublets of doublets were seen at 7.83, 6.13 and 5.85. These are attributed to 3 of the 4 dienone protons of 7; the fourth is presumably under the aromatics. This pattern is characteristic of the dienone system, e.g., that of triamcinolone. [3] The mass spectrum (EI) of 7 gave a molecular ion at m/z 269 (i.e., for loss of H_2O from ritodrine) with a small peak at m/z 311 which is attributed to an acetyl derivative of 7 (acetate was used in the fractionation step).

The UV spectrum is qualitatively similar to that of ritodrine .HCl except for a shoulder near 240 nm. The shoulder is consistent with the dienone chromophore as in triamcinolone, λ_{max}^{EtOH} 239 nm, ε=15,900. [3] In contrast, quinonemethides give λmax~290 nm, ε>10,000. [4] The ^{13}C-NMR spectrum of an unfractionated sample of 7 (52% pure by HPLC) gives a signal at 189.1 ppm consistent with that for a dienone carbonyl. The sample is polarographically reducible at a mercury electrode (E_p at -0.75V vs SCE in 0.1N HCl, 100 mV sec^{-1} scan rate) and the disappearance rate coincides with the kinetics of 5-T formation found by HPLC.

Hydrogenation of Intermediate 7

Confirmation of the presence of the spiro (quaternary) carbon in 7 was approached by first forming a stabilized form of this intermediate. Hydrogenation of 7 gave the following product:



7H

The presence of the spiro carbon was confirmed by ^{13}C-NMR using an attached proton test pulse sequence with a delay of 4 milliseconds. A single quaternary aliphatic signal was detected at 37.3 ppm. The proton decoupled ^{13}C-NMR

spectrum indicates a single diastereomer based on the number of carbon signals observed. Separate signals are observed for carbons b, c, d and e indicative of hindered rotation of the aromatic ring. Such steric crowding is supported by a molecular mechanics study which indicated a rotational energy barrier in excess of 200 kcal. The benzene ring is calculated to be at an angle of 83° to the mean plane of the piperidine ring at its lowest energy state.

Since 1) the hydrogenation step should not cause isomerization and 2) only one major HPLC peak is observed from reaction mixtures obtained in the preparation of each compound, a single diastereomer for 7 is indicated.
The proton NMR spectrum of 7H indicates it is the trans isomer, based on the large coupling constant observed for the benzylic proton (11.9 Hz).

Intermediate 6

The chloro derivative of ritodrine is indicated for this intermediate by the Cl cluster for MH^+ at m/z 306 and 308 in the FAB mass spectrum of the HCl residue. The FAB mass spectrum of the HBr residue contains the Br cluster at m/z 350 and 352 expected for the corresponding bromo analog. The ^{1}H-NMR spectrum of the chloro derivative in acetone - d_6 contains a doublet at 6.06 ppm (J=3.7 Hz) and one at 5.60 ppm (J=9.3 Hz) consistent with erythro and threo forms of this intermediate. [5] Integration indicates essentially equal amounts of each. The spectrum of this intermediate reverts to that of 7 after removal of acetone - d_6 and dissolution in D_2O.

Reaction of 6 and 7 with Methanol and Ethanol

Reaction of evaporate residues, 6, with methanol produces the α-methoxy analog as well as large proportions of 7; the latter converts to the α-methoxy analog when acid is added. The compound is primarily the threo enantiomers based on the coupling constant of the CHO proton in analogy with the ephedrines [6] as well as those of 5-E and 5-T.

The reaction product of the intermediate(s) with ethanol gives a new HPLC peak at a retention volume of 22 mL (mpC) and is believed by analogy to be the α-ethoxy derivative of 5-T. The corresponding retention volume for the α-methoxy analog is 13 mL, and for ritodrine is 7 mL.

EXPERIMENTAL

NMR spectra were recorded using Varian XL 300 and Varian FT-80A spectrometers. Chemical shifts are reported in ppm from TMS or DSS. Mass spectra were obtained using the Kratos MS-50 (+EI, 10,000 resolution, direct insertion probe) the Finnigan TSQ (FAB), the Finnigan Model 4500 (+CI/CH_4, +EI) and the Finnigan Model 1015 with Model 3300 electronics (+EI) mass spectrometers. IR spectra were recorded on the Perkin Elmer 521 and Beckman Model 4240 spectrometers using KBr discs and UV spectra were obtained on the Cary 17 and Hewlett Packard Model 8450A spectrophotometers. The Molecular Mechanics study was carried out using the Clark Still Interactive Molecular Modeling Program [7] which uses an Allinger MM2 forcefield. [8] The angle between planes was calculated using a program called XRA. [9] All HPLC except that used to isolate 7H and the threo form was performed on a Chromegabond C-8 column (4.6 mm x 30 cm) (ES Industries) using mobile phases A (mpA): 0.05M $C_7H_{15}SO_3Na$, 0.002M NH_4OAc and 0.235M AcOH in 30% MeOH, B: 0.01M NaOAc, pH 5/CH_3CN (4:1), and C: 0.1M NaOAc, pH 5/CH_3CN (77/23). Ultraviolet detection was used at 274 nm. Concentrations of 6 and 7 were calculated from HPLC data under the assumption that the response at 274 nm was equal to that of ritodrine .HCl. Isolation of 7H was carried out using a Bondapak C-18 column (0.8 x 60 cm) with a mobile phase of 0.1M NaOAc in 18% CH_3CN. Isolation of 5-T is described below.

5-E/5-T Epimerization

Typical conditions for the epimerization involved evaporating a solution of ritodrine .HCl (0.5 mg/mL in 1M HCl at 35-50°, 20 mm pressure) to dryness, redissolving the residue under acidic conditions and allowing to stand until intermediate 7 was completely converted to 5-T (threo form). The 5-T was isolated using a Bondapak C-18 column (0.8 x 60 cm) with a mobile phase of 0.5M NaOAc, 0.002M NH_4OAc, 0.2M AcOH and 0.005M $C_7H_{15}SO_3Na$ in 25% MeOH. Elution volumes of 5-E and 5-T were 69 and 81 mL, respectively. The isolated sulfonate salt was passed through a cation exchange column (Bio Rad AG 50W-X4) and eluted with 1M NH_4Cl in 50% MeOH to convert to the hydrochloride salt.

The residue from the eluent was extracted with CH_3CN. This material was further purified on the same HPLC column using a mobile phase of 0.1M NaOAc, pH 5.3/CH_3CN (7:3). The pooled fractions were adjusted to pH 3 with HCl, evaporated to dryness and the residue extracted with acetone. The acetone solution was filtered through anhyd. Na_2SO_4 and the filtrate evaporated to dryness. The product contained 90% 5-T , 3% 5-E and 6% unknowns by HPLC (mpA). Retention volume for 5-T is 32 mL (mpA). NMR (1 mg in 25 μL D_2O, 1.7 mm insert, FT-80A) 7.0-7.4 (4H, 2d overlapped, arom) 6.7-7.0 (4H, d, arom) 4.63 (1H,d, 8.8 Hz, CHO) 3.15-3.7 (3H, m, CH_2NCH) 2.7-3.1(2H, m, $ArCH_2$) 1.15 (3H, d, 6.5 Hz, CH_3). MS (+EI, m/z) 288 (0.1)MH^+, 269 (0.3) $(M-H_2O)^+$, 207 (0.2), 180 (1), 164 (66), 121 (100), 107 (23), 103 (23), 93 (16), 91 (23), 77 (64), 65 (9), 57 (28), 56 (53), 44 (16). IR (KBr) 2300-3700 (broad), 1620, 1590, 1520, 1440, 1380, 1260, 1220, 1170, 1120, 1040, 1010, 830 cm^{-1}. UV (MeOH) 226 nm (ε~20,000), 277 (ε~3400), 284s (ε~2800).

HPLC retention volume of 5-E is 28 mL (mpA), NMR (1 mg in 25 μL D_2O, 1.7 mm insert, FT-80A) 6.7-7.4 (8H, 4d, arom) 5.00 (1H, d, 4.3 Hz, CHO) 3.15-3.7 (3H, m, CH_2NCH) 2.7-3.15 (2H, m, $ArCH_2$) 1.21 (3H, d, 6.7 Hz, CH_3). MS (+EI, m/z) 288 (0.4) MH^+, 269 (0.1) $(M-H_2O)^+$, 207 (0.6), 180 (1), 164 (51), 121 (>100), 107 (44), 103 (34), 93 (28), 91 (50), 77 (>100), 65 (31), 57 (>100), 56 (58) 44 (61). IR (KBr) 2300-3700 (broad), 1610, 1590, 1510, 1440, 1380, 1340, 1260, 1220, 1170, 1040, 1010, 990, 830 cm^{-1}. UV (MeOH) 224 nm (ε=17,800), 278 (ε=3200), 284s (ε~2600).

The equilibration ratio between 5E and 5T was determined by refluxing a solution of ritodrine HCl (0.5 mg/mL in 0.1M H_2SO_4) for 120 hrs, removing aliquots periodically for HPLC analysis using mpA.

Intermediate 6

The residue from the evaporation of a 1M HCl solution of ritodrine .HCl was dissolved in acetone-d_6 to observe its NMR spectrum: δ6.06 (0.5H, d, 3.7 Hz, CHCl) 5.60 (0.5H, d, 9.3 Hz, CHCl) 1.2-1.6 (3H, 2d, 6.5 and 6.7 Hz, CH_3), MS (FAB) 306, 308 (MH^+), 270 $(MH-HCl)^+$. UV (CH_3CN) 226 nm (ε~16,600), 277 (ε~3700), 283s (ε~3300). The corresponding residue using 1M HBr gave: NMR (acetone-d_6) δ6.12 (0.4H, d, 5.4 Hz, CHBr) 5.83 (0.4H, d, 9.2 Hz, CHBr) 1.61 (1.2H, d, 6.5 Hz, CH_3) 1.43 (1.4H, d, 6.7 Hz, CH_3) 1.25 (0.6H, d, 6.6 Hz, CH_3). MS (FAB), m/z 350, 352 $(MH)^+$, 270 $(MH-HBr)^+$.

Intermediate 7

The residue from the evaporation of ritodrine .HCl in 1M HCl was dissolved in 0.01M NaOAc (~20 mg/mL), adjusted to pH~4 and fractionated on the Chromegabond C-8 column (mpB). The combined fractions were evaporated to dryness and the residue was extracted with acetone. The acetone solution was filtered through anh. Na_2SO_4 and the filtrate evaporated to dryness to give 4 mg. of intermediate 7, 94% pure by HPLC (retention volume of 19 mL, mpA), NMR (acetone-d_6):δ7.83 (1H, dd, 10.4 and 3.1 Hz, diene) 6.4-7.3 (m, arom + diene) 6.13 (1H, dd, 10.4 and 1.9 Hz, diene) 5.85 (1H, dd, 10.1 and 1.9 Hz, diene) 0.81 (3H, d, 6.0 Hz, CH_3. MS (+EI, m/z) 311 (0.1) acetyl derivative of M^+; 269 (0.7) M^+, 207 (3), 191 (15), 162 (90), 149 (12), 133 (24), 121 (>100), 107 (48), 103 (18), 91 (16), 77 (17), 56 (23), 45 (31), 43 (88). IR (KBr) 2200-3700 (broad), 1670, 1620, 1550, 1520, 1450, 1410, 1380, 1270, 1240, 1180, 1140, 1030, 860, 830 cm^{-1}. UV (CH_3CN) 227 nm (ε~23,000), 240s (ε~14,500), 277 (ε~2800), 286s (ε~2200).

Hydrogenation of Intermediate 7

No attempts have been made to optimize the yield of 7H. Satisfactory yields, however, can be obtained by the following procedure: Four g of ritodrine .HCl are dissolved in 75 mL of 2M HCl in 67% CH_3CN (for improved solubility). The solution is evaporated at 50°C and 5 mm Hg. The residue is reconstituted in 200 mL 50% CH_3CN and 10 mL saturated $NaHCO_3$. The solution is adjusted to pH 3 and hydrogenated over 300 mg 10% Pd/C catalyst in a Paar hydrogenator for 1 hour. The yield of 7H at this point is 17% based on HPLC analysis. After removal of catalyst, the solution is acidified to 2N with HCl and recycled 3 times through the evaporation and hydrogenation steps. Yield of 7H at this

point is 54% based on HPLC analysis. Isolation is accomplished by reversed phase chromatography using 0.1M NaOAc in 18% CH_3CN as the mobile phase. The eluate is acidified with HCl, reduced to dryness in vacuo and the product separated from NaCl by extraction with i-PrOH. The product traps i-PrOH but is freed of this material by dissolving in $MeOH/H_2O$, pumping to dryness, dissolving in MeOH, pumping to dryness and drying at 127° under high vacuum. High resolution MS (+EI, m/z) 273.1703 (M^+ calc. $C_{17}H_{23}NO_2$). Other fragments observed by normal EI: 258, (-CH3), 216, 202, 188, 166, 148, 134, 121, 107, 91, 77, 71, 70, 56, 42. CI/CH_4:274$(MH)^+$, 302 $(M+C_2H_5)^+$, 314 $(M+C_3H_5)^+$ 258, 180, 102, 69. ^{1}H-NMR (D_2O, XL300, structure 7H): 7.13-7.10 (1H, dd, $H_{d\ or\ e}$) 7.06-7.03 (1H, dd, $H_{e\ or\ d}$) 6.92-6.881 (1H, dd, $H_{b\ or\ c}$) 6.876-6.84 (1H, dd, $H_{c\ or\ b}$) 3.89-3.81 (1H, sextuplet-dq overlapped, on decoupling CH_3, collapses to doublet, 11.9 Hz,H_h) 3.5-3.3 (3H, m, H_i + MeOH) 2.73 (1H, d, 11.9Hz, H_g) 2.6-2.4 and 2.3-2.0 (6H, m, $H_{f,p}$) 1.8-1.4 (4H, m, $H_{m,n}$) 1.08 (3H, d, H_l)? ^{13}C-NMR (D_2O, XL300): 220.8 (C_q)? 157.7 (C_a) 137.0, 131.9 ($C_{d,e}$) 130.1 (C_c) 118.0, 117.6 (C_b) 58.3 (C_g) 53.8 (C_h) 42.7 (C_f) 39.1, 38.9, 38.5 ($C_{k,o,p}$) 37.3 (C_l) 31.5, 27.3 ($C_{m,n}$) 20.7 (C_i).IR[h](KBr) 2300-3700 (broad), 1705 ($\nu_{C=O}$), 1610, 1590, 1515, 1440, 1380, 1340, 1310, 1260, 1220, 1180, 1140, 1100, 1060, 1010, 840, 825 cm^{-1}. UV (MeOH) 226 nm (ε=9400), 275 (ε=1750).

Reaction of intermediates with methanol

The residue from the evaporation of ritodrine .HCl in 1M HCl (Intermediate 6) was reacted with MeOH to give the α-methoxy analog. HPLC retention volume 13 mL (mpC), purity by HPLC=89%. NMR (acetone-d_6) 5.4 (trace H, s, CHO-erythro) 4.42 (0.7H, d, 9.8 Hz, CHO-threo) 3.15 (s in midst of multiplet, OCH_3), 1.17 (3H, d, 6.7 Hz, CH_3). MS (EI, m/z) 302 (0.1) MH^+, 270 (0.3) $(M-OCH_3)^+$, 207 (0.5), 164 (>100), 137 (23), 121 (>100), 107 (22), 103 (19), 91 (20), 77 (40), 65 (17), 57 (47). Reaction of 7 with MeOH gave the same product based on its HPLC retention time and ^{1}H-NMR spectrum.

Acknowledgements

We acknowledge R. A. Farr for his suggestion for the structure of 7, J. P. Paolini for the molecular mechanics study, D. Zackett, P. J. Savickas and R. J. Barbuch for mass spectra, M. R. Whalon for NMR spectra (XL 300) and M. A. Rebman for typing the manuscript. We also appreciate the reviewer's comments.

REFERENCES

1. D. P. Venter and D. F. Greeff, Tetrahedron, 36, 305 (1980).
2. L. C. Schroeter and T. Higuchi, J. Am. Pharm. Assn., 47 426 (1958).
3. K. Florey, "Analytical Profiles of Drug Substances", Vol 1, Press, N.Y., 1972, p369.
4. J. Pospíšek, M. Písová and M. Souček, Coll, Czech, Chem. Comm., 40, 142 (1975).
5. 5.85 ppm for the CHCl proton of $C_6H_5CHClCH_2NMe_2$ .HCl: N. J. Leonard and J. A. Klainer, J. Heteroc. Chem. 8, 215 (1971).
6. P. S. Portoghese, J. Med. Chem., 10, 1057 (1967).
7. Program obtained through the courtesy of Prof. Clark Still, Columbia University.
8. N. L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977).
9. J. Paolini, Merrell Dow Research Institute.