Preparation of two acidic metabolites of timolol

PATRICE C. BÉLANGER

Department of Medicinal Chemistry, Merck Frosst Laboratories, P.O. Box 1005, Pointe Claire – Dorval, P.Q., Canada H9R 4P8

Received October 17, 1977

PATRICE C. BÉLANGER. Can. J. Chem. **56**, 722 (1978).

The preparation of two acidic metabolites of timolol, 2-[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yloxy]acetic acid and *d,l*-3-[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yloxy]lactic acid is reported using 3-chloro-4-(4-morpholinyl)-1,2,5-thiadiazol as starting material.

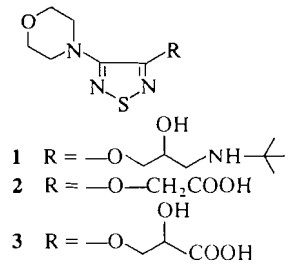
PATRICE C. BÉLANGER. Can. J. Chem. **56**, 722 (1978).

La préparation de deux métabolites acides de timolol, l'acide [(morpholinyl-4)-4-thiadiazol-1,2,5-yl-3-oxy]-2-acétique et l'acide *d,l*-[(morpholinyl-4)-4-thiadiazol-1,2,5-yl-3-oxy]-3-lactique y est rapporté en employant comme produit de départ le chloro-3-(morpholinyl-4)-4-thiadiazole-1,2,5.

Introduction

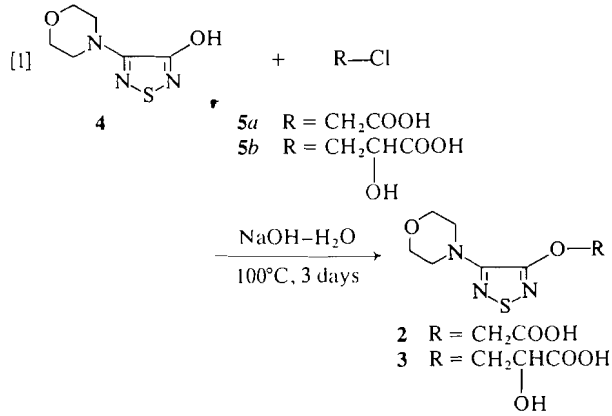
Timolol **1**, (*S*)-1[(1,1-dimethylethyl)amino]-3-{[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy}-2-propanol is a β-adrenergic blocking agent (1, 2) with antihypertensive (3) and antianginal properties (4). It is rapidly absorbed, metabolized, and excreted in man, rats, and dogs (5). The two most important sites of metabolic attack are the amine side chain and the morpholinyl group, respectively. Degradation of the (1,1-dimethylethyl)amino-2-hydroxypropoxy chain leads to the acidic metabolites **2** and **3**. Structural assignment for the metabolites was based primarily on mass spectral evidence (5) and on electrophoresis.

In this paper, syntheses of the two acidic metabolites formed by the degradation of the amine side chain, 2-[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yloxy]-acetic acid **2** and 3-[(4-morpholinyl)-1,2,5-thiadiazol-3-yloxy]lactic acid **3** are reported. The latter, while presumably an optically active metabolite, was prepared as the racemate.



Results and Discussion

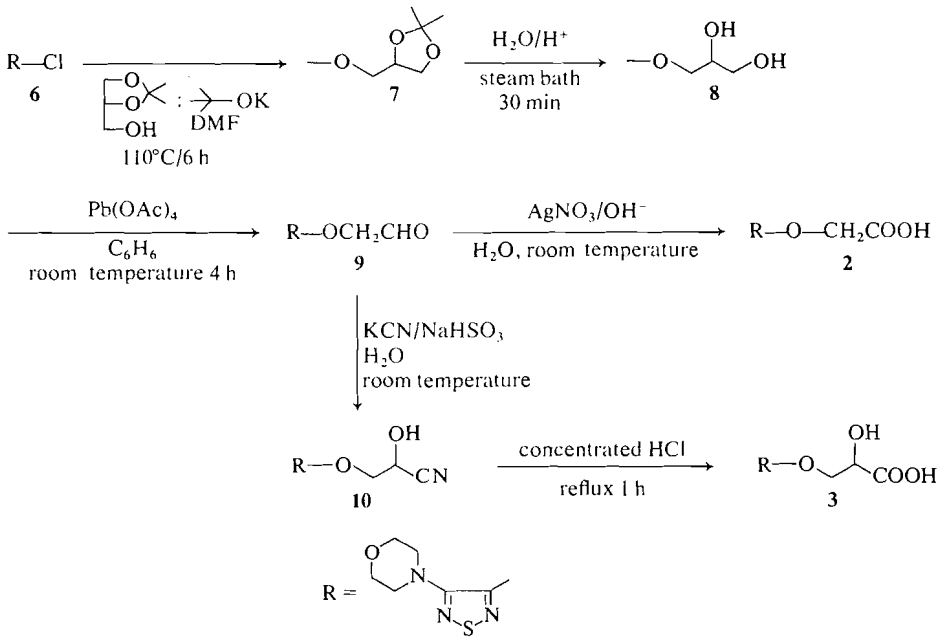
Initially for the preparation of **2** and **3**, condensation of the anion of 3-hydroxy-4-(4-morpholinyl)-1,2,5-thiadiazole **4** with either chloroacetic **5***a* or β-chlorolactic acid **5***b* was attempted, using procedures previously reported for substituted phenols (6) or for metabolites of propanolol (7). The best conditions were found to be heating equimolar amounts of **4** with the corresponding halo acid **5** and 2 equiv. of aqueous sodium hydroxide for several days. Reaction (as monitored by disappearance of starting material **4**) was slow and extensive decomposition occurred. Yields of the corresponding acidic metabolites **2** and **3** were only 2 and 4%, respectively.



The low yields are probably explicable based on the reduced reactivity of the chloro substituted carboxylic acids in the anion form and on the tautomeric nature of the 4-(4-morpholinyl)-1,2,5-thiadiazol-3(2*H*)one which permits alkylation to occur on either the oxygen or the nitrogen atom. Other examples of low yields on alkylation of a hydroxy-1,2,5-thiadiazole are known.[1]

In an alternative approach, treatment of 3-chloro-4-(4-morpholinyl)-1,2,5-thiadiazole **6** with 2,2-dimethyl-1,3-dioxolane-4-methanol in DMF with potassium *tert*-butoxide as base at 110°C for 6 h led to good yields of **7**. Hydrolysis of the resulting acetonide **7** in dilute hydrochloric acid gave crystalline diol **8** in nearly quantitative yield. Cleavage of the diol **8** to the aldehyde **9** was achieved with lead tetraacetate in benzene at room temperature (8) in nearly quantitative yield. Sodium metaperiodate was

[1]Merck Frosst Laboratories. Unpublished results.



SCHEME 1

also effective for the cleavage but the yields were much lower and less reproducible. The conversion of **9** to metabolite **2** occurred smoothly in 47% yield by silver oxide oxidation (9). Transformation of **9** to the racemic metabolite **3** was done through the cyanohydrin reaction followed by hydrochloric acid hydrolysis. These reactions are summarized in Scheme 1; the mass spectra of synthetic **2** and **3** and the electrophoretic behavior were identical with those of metabolites **2** and **3**.

The synthetic compounds **2** and **3** were found to be inactive as β-adrenergic blocking agents or antihypertensive agents.

Experimental

Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer. A Varian EM-360 instrument was used to record nmr spectra in deuteriochloroform using tetramethylsilane as an internal standard. Elemental analyses were performed by Dr. C. Daesslé. The low resolution mass spectral analyses were performed on a AEI MS 902 mass spectrometer and on an LKB 900 gc–ms spectrometer.

All reactions as well as column chromatography were monitored by tlc using precoated 0.25 mm silica gel plates (Eastman Kodak) with visualization of spots either by uv or by exposure to iodine vapors.

2-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]acetic Acid (2)

3-Hydroxy-4-(4-morpholinyl)-1,2,5-thiadiazole **4** (6.2 g, 33 mmol) and chloroacetic acid (3.2 g, 34 mmol) in 40 ml 1 *N* sodium hydroxide were heated for 3 days on a steam bath. The reaction mixture was acidified and unreacted **4** (1.7 g), mp 190°C, was recovered. On evaporation of the filtrate to half volume, crude **2** was obtained which on recrystallization from water afforded 70 mg, mp 174–176°C, homogeneous by tlc, R_f: 0.6 (chloroform–methanol–ammonia 8:4:0.5 by volume); ir: COOH 1765 cm^{-1}; ^1H nmr δ: 4.95 (2, s, CH_2CO), 3.68 (4H, m, CH_2—N—CH_2), 3.80 (4H, m, CH_2—O—CH_2); ms: M^+ 245. *Anal.* calcd. for $C_8H_{11}N_3O_4S$: C 39.18, H 4.52, N 17.14, S 13.07; found: C 39.27, H 4.74, N 17.01, S 12.93.

d,l-*3-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]lactic Acid (3)*

Similarly, the reaction of **4** with β-chlorolactic acid led to 3.0 g of unreacted **4** and to a residue after evaporation of the filtrate to dryness. This residue was dissolved in ethanolic HCl and refluxed 3 h. On evaporation to dryness, 2.4 g of an oil was obtained and tlc analysis showed it to be a mixture of seven components. Silica gel chromatography with chloroform elution was performed, taking fractions of 10 ml. The desired ester was found to be between tubes 41 and 61. These fractions were combined and 342 mg of an oil was obtained. This ester was hydrolysed with sodium hydroxide in methanol. The residue after evaporation was acidified with aqueous HCl and the mixture extracted several times with chloroform to yield 196 mg of **3**, mp 134–135°C after crystallization from chloroform–hexane (1:5 v/v); tlc, R_f: 0.5 (chloroform–methanol–ammonia 8:4:0.5 by volume); ir: COOH, 1732 cm^{-1}; ^1H nmr δ: 3.52 (4H, m, CH_2NCH_2), 3.72 (4H, m, CH_2OCH_2), 4.60 (3H, m, CHO and CH_2O); ms: M^+ 275. *Anal.* calcd. for $C_9H_{13}N_3O_5S$: C 39.27, H 4.76, N 15.26, S 11.65; found: C 39.63, H 5.01, N 15.13, S 11.91.

4-[4-(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]-3-(4-morpholinyl)-1,2,5-thiadiazole (7)

3-Chloro-4-(4-morpholinyl)-1,2,5-thiadiazole (10) (41 g, 0.21 mol), 2,2-dimethyl-1,3-dioxolan-4-ylmethanol (11) (28 g, 0.21 mol), and potassium *tert*-butoxide (30 g, 0.26 mol) in 200 ml dimethyl formamide were heated in an oil bath at 110°C for 6 h. The mixture was poured into water (1000 ml) and extracted twice with ethyl acetate (2 × 1000 ml). The extract after washing with water, drying over magnesium sulfate was concentrated under vacuum to give 39.6 g (66%) of **7** as an oil

that distilled at 165–170°C/1 Torr; tlc, R_f: 0.7 (ethyl acetate); ^{1}H nmr δ: 1.37 and 1.43 (6H, s, CH_3), 3.60 (4H, m, CH_2NCH_2), 3.72 (4H, m, CH_2OCH_2), 4.50 (5H, m, CH_2O, CHO); ms: M^+ 301. *Anal.* calcd. for $C_{12}H_{19}N_3O_4S$: C 47.83, H 6.37, N 13.94, S 10.64; found: C 47.41, H 6.67, N 14.08, S 10.54.

3-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]-1,2-propanediol (8)

4-[4-(2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy]-3-(4-morpholinyl)-1,2,5-thiadiazole (**7**) (37.3 g, 0.125 mol), water (100 ml), and concentrated hydrochloric acid (3 ml) were heated on a steam bath for 30 min until a one-phase system was obtained. The water was removed under vacuum and the yellow solid residue after trituration in 200 ml benzene gave compound **8** (31.1 g, 95.6%), mp 95–96°C; tlc, R_f: 0.2 (ethyl acetate); ir:—OH, 3380 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 3.50 (4H, m, CH_2NCH_2), 3.70 (4H, m, CH_2OCH_2), 4.40 (5H, m, CHO— and CH_2O—); ms: M^+ 261. *Anal.* calcd. for $C_9H_{15}N_3O_4S$: C 41.37, H 5.79, N 16.08, S 12.27; found: C 41.19, H 5.95, N 15.99, S 12.02.

2-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]acetaldehyde (9)

3-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]-1,2-propanediol (**8**) (8.7 g, 33 mmol) and lead tetraacetate (15.5 g, 35 mmol) in 200 ml benzene were stirred at room temperature for 4 h. The solids were filtered and the filtrate washed with water, dried over magnesium sulfate, and concentrated under vacuum to yield 7.5 g of **9** as a yellow oil, homogeneous by tlc, R_f: 0.2 (ethyl acetate); ir: C=O, 1735 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 3.57 (4H, m, CH_2NCH_2), 3.75 (4H, m, CH_2OCH_2), 5.00 (2H, s, CH_2O), 9.80 (1H, s, CHO); ms: M^+ 229. *Anal.* calcd. for $C_{14}H_{15}N_7O_6S$: C 41.08, H 3.69, N 23.95, S 7.83; found: C 40.88, H 3.90, N 23.84, S 7.63.

2-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]acetic Acid (2)

2-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]acetaldehyde **9** (6.7 g, 29 mmol) was suspended in 100 ml water and freshly made silver oxide, prepared from 25 g silver nitrate and 100 ml 2 *N* sodium hydroxide, was added. After stirring for 20 min, the solids were removed by filtration and the filtrate evaporated to 75 ml. Following refiltration and acidification with 6 *N* HCl, compound **4** was obtained, which after washing with water and air drying, weighed 3.2 g (47%), mp 180–181°C.

(D,L)-*3-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]lactonitrile (10)*

2-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]-acetaldehyde **9** (7.9 g, 34.5 mmol) was suspended in 100 ml water. Potassium cyanide (3 g, 45 mmol) was added, followed by sodium bisulfite (5 g, 48 mmol). After stirring 10 min at room temperature, a solid precipitated, which was filtered, washed with cold water, and air dried. 3-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]lactonitrile **12**, (5.7 g, 65%), mp 70–71°C, was obtained. This was probably a hydrate as a dried sample melted at 101°C; tlc, R_f: 0.5 (ethyl acetate – benzene 1:1); ir: OH, 3190 cm^{-1}, CN not detected; ^{1}H nmr ($CDCl_3$) δ: 3.50 (4H, m, CH_2NCH_2), 3.82 (4H, m, CH_2OCH_2), 4.60 (2H, m, CH_2O), 4.85 (1H, m, CHO); ms: M^+ 256, base peak 229 (loss of HCN). *Anal.* calcd. for $C_9H_{12}N_4O_3S$: C 42.18, H 4.72, N 21.86, S 12.51; found: C 42.11, H 5.04, N 22.32, S 12.89.

(D,L)-*3-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]lactic Acid (3)*

(D,L)-3-[4-(4-Morpholinyl)-1,2,5-thiadiazol-3-yloxy]lactonitrile **12** (4.1 g, 16 mmol) in concentrated hydrochloric acid (25 ml) was refluxed for a period of 1 h. The solution was poured into water (50 ml) and extracted twice with ethyl acetate (75 ml). The ethyl acetate extract was washed with water, dried over magnesium sulfate, and concentrated under vacuum to yield an oil that crystallized when triturated in petroleum ether. On filtration compound **3** was obtained (2.7 g, 61%), mp 137–138°C.

Acknowledgements

The author extends his appreciation to Mr. R. E. Rhodes of Merck Sharp & Dohme Research Laboratories, West Point, PA and to Dr. W. J. A. Vanden Heuvel for the mass spectra measurements, to Dr. D. Mulvey, Merck Sharp & Dohme Research Laboratories, Rahway, NJ, and to Dr. C. S. Rooney, Merck Frosst Laboratories for useful discussions on thiadiazole chemistry. The author is also grateful to Dr. A. Scriabine and his colleagues of Merck Sharp & Dohme Research Laboratories, West Point, PA for the biological testing of the metabolites.

1. B. K. Wasson, W. K. Gibson, R. S. Stuart, H. W. R. Williams, and C. H. Yates. J. Med. Chem. **15**, 651 (1972).
2. M. Ulryck, J. A. Franciosa, and J. F. Conway. Clin. Res. **19**, 343 (1971).
3. M. Ulryck, J. A. Franciosa, and J. F. Conway. Clin. Pharmacol. Ther. **13**, 232 (1972).
4. D. Brailovsky. *In* Beta-adrenergic blocking agents in the management of hypertension and angina pectoris. *Edited by* B. Magnani. Raven Press, New York, NY. 1974. p. 117.
5. D. J. Tocco, A. E. W. Duncan, F. A. Deluna, H. B. Hucker, V. F. Gruber, and W. J. A. Vanden Heuvel. Drug Metab. Dispos. **3**, 361 (1975).
6. I. Csiba, L. Krasmed, and M. Stuchlik. Cesk. Farm. **17**, 28 (1968); Chem. Abstr. **69**, 67041g (1968).
7. P. A. Bond. Nature, **213**, 721 (1967).
8. F. J. Walf and J. Weijland. Org. Synth. Coll. **4**, 124 (1963).
9. E. Campaigne and W. M. LeSuer. Org. Synth. Coll. **4**, 919 (1963).
10. L. M. Weinstock, P. Davis, B. Handelsman, and R. Tull. J. Org. Chem. **32**, 2823 (1967).