The Base-promoted Dehydration of rac.-*trans*-Tetrahydro-6-hydroxy-4-[(2-(dimethylamino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one

Erno Mohacsi* and Jay P. O'Brien

Roche Research Center, Hoffmann-La Roche Inc.,
Nutley, NJ 07110

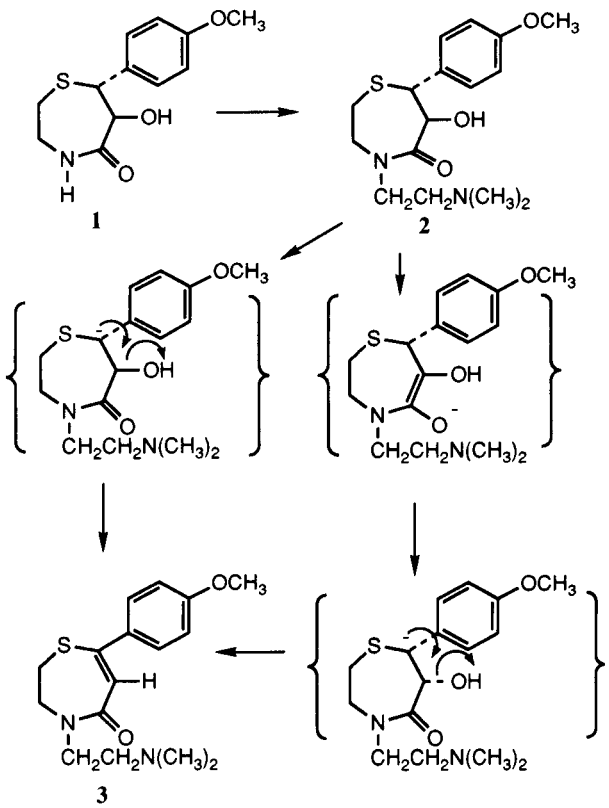
Received September 10, 1991

The base-catalyzed alkylation of rac.-*trans*-tetrahydro-6-hydroxy-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**1**) with dimethylaminoethyl chloride in dimethyl sulfoxide provided predominantly rac.-*trans*-tetrahydro-6-hydroxy-4-[(2-dimethylamino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**2**) and in addition, 2,3-dihydro-4-[2-(dimethylamino)-ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(4*H*)-one (**3**). A plausible mechanism is postulated for the dehydration of the rac.-*trans*-amide **2**.

J. Heterocyclic Chem., **28**, 2051 (1991).

As part of a pharmacologically oriented investigation concerning the preparation of potential calcium regulating agents we have previously described the synthesis of rac.-*trans*-tetrahydro-6-hydroxy-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**1**) [1] and its conversion to the title compound **2** [2]. In this connection we have observed that base-promoted alkylation of **1** with dimethylaminoethyl chloride in dimethyl sulfoxide at 50° for 1.5 hours yielded the desired amine **2**, starting material **1** and in addition a by-product **3** in a ratio of about 11:6:4 after chromatographic separation of the crude mixture (Scheme). The mass spectrum of **3** shows the molecular ion peak at m/e 306 and the infrared spectrum showed an amide carbonyl absorption at 1610 cm^{-1}. The ^1H nmr spectrum features an AA'BB' pattern at δ 7.56, 6.87 (J = 9.0 Hz) for the four aromatic protons, a one-proton singlet at 6.33 for the =CH proton, a two-proton multiplet at 3.86 for the NCH_2 protons and a three-proton singlet at 3.80 for the methoxy protons. Furthermore, this compound shows a two-proton triplet at δ 3.60 (J = 6.5 Hz) for the NCH_2 protons, a two-proton multiplet at 3.30 for the SCH_2 protons, a two-proton triplet at 2.52 (J = 6.5 Hz) for the NCH_2 protons and a six-proton singlet at 2.27 for the $N(CH_3)_2$ protons. On the basis of this spectral data structure **3** was assigned to the by-product. The formation of **3** presumably resulted from base-promoted dehydration of **2**, since at room temperature under basic conditions this compound can be converted in good yield to **3**.

Scheme



The detailed mechanism of the reaction is not clear. It is probable that **3** is formed from **2** by *cis* elimination, due to the enhanced acidity of the hydrogen attached to the carbon adjacent to the phenyl and sulfur groups. This reaction is analogous to the base-catalyzed dehydrohalogenation of *cis*-chlorocycloalkyl aryl sulfones that have been investigated previously [3,4]. However, it is also possible that in the presence of base enolization can occur leading to epimerization of the asymmetric center adjacent to the carbonyl group which would ultimately result in *trans* elimination.

EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were measured in 95% ethanol with a Carey Model 14 spectrophotometer. Infrared spectra were determined with a Beckman Model IR-9 spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian HA-100 spectrometer and recorded in δ values in deuteriochloroform as the solvent and tetramethylsilane as an internal reference. The proton signals are designated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (70 eV, direct inlet system) were determined with a CEC type 21-110 spectrometer.

rac.-*trans*-Tetrahydro-6-hydroxy-4-[(2-dimethylamino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**2**) and 2,3-Dihydro-4-[2-

(dimethylamino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(4*H*)-one (**3**).

A suspension of sodium hydride (0.620 g of 50% dispersion in mineral oil, 0.013 mole) in 80 ml of dry dimethyl sulfoxide under nitrogen was heated at 70° for one hour and cooled to room temperature. After 30 minutes stirring at room temperature with 3.0 g (0.012 mole) of rac.-*trans*-tetrahydro-6-hydroxy-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**1**) the mixture was treated with a solution of 1.5 g (0.013 mole) of 2-dimethylaminoethyl chloride in 5 ml of dimethyl sulfoxide and heated at 50° for 1.5 hours. The mixture was poured onto ice-water (100 ml) and acidified with 1*N* hydrochloric acid (180 ml). The aqueous suspension was extracted with ethyl acetate (3 x 100 ml) and the combined ethyl acetate solutions were washed with water and dried (magnesium sulfate). Removal of the solvent gave 1.2 g of crude starting material which after recrystallization from ethyl acetate yielded 0.7 g (23%) of pure rac.-*trans*-tetrahydro-6-hydroxy-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**1**) as a white solid, mp 172-174° (reported [2] mp 168-170°).

The acidic solution was chilled, made basic with 10*N* sodium hydroxide and extracted with ethyl acetate (3 x 75 ml). The combined ethyl acetate solutions were washed with brine, dried (magnesium sulfate) and concentrated to give 2.3 g of a residue which was chromatographed on a silica gel column. The column was eluted with 20 ml portions of chloroform. Fractions 1-7 were collected and the solvent was removed under reduced pressure to yield 1.6 g (42%) of rac.-*trans*-tetrahydro-6-hydroxy-4-[(2-dimethylamino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**2**) as a yellow solid, mp 92-94° (reported [2] mp 90-91°). Further elution of the column with acetonitrile/ammonium hydroxide (9:1, v/v; fractions 8-10) afforded 0.6 g (17%) of 2,3-dihydro-4-[2-(dimethylamino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(4*H*)-one (**3**) as a yellow oil. The analytical sample was distilled, bp 210-215° (0.05 mm); ir (chloroform): 1610 (lactam CO) cm^{-1}; uv (ethanol): λ max 277 mμ (ϵ 10940); ^{1}H nmr (deuteriochloroform): δ 7.56, 6.87 (AA'BB', J = 9.0 Hz, 4H, Arom), 6.33 (s, 1H, CH=), 3.86 (m, 2H, NCH_2), 3.80 (s, 3H, OCH_3), 3.60 (tr, J = 6.5 Hz, 2H, NCH_2), 3.30 (m, 2H, SCH_2), 2.52 (tr, J = 6.5 Hz, 2H, NCH_2) and 2.27 [s, 6H, $N(CH_3)_2$]; ms (70 eV): 306 (M^+).

Anal. Calcd. for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24; N, 9.14. Found: C, 61.90; H, 7.38; N, 8.92.

A sample of the above base **3** in ethanol was treated with hydrogen chloride (anhydrous) and the crude hydrochloride was recrystallized from ethanol to give **3** hydrochloride as the hydrate (white solid), mp 162-164°.

Anal. Calcd. for $C_{16}H_{22}N_2O_2S \cdot HCl \cdot H_2O$: C, 53.25; H, 6.98; N, 7.76. Found: C, 53.53; H, 7.06; N, 7.78.

Dehydration of rac.-*trans*-Tetrahydro-6-hydroxy-4-[(2-dimethylamino)amino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**2**).

A suspension of sodium hydride (0.038 g of 50% dispersion in mineral oil, 0.0008 mole) in 8 ml of dry dimethyl sulfoxide under nitrogen was heated at 70° for one hour and cooled to room temperature. To the mixture was added 0.2 g (0.0006 mole) of rac.-*trans*-tetrahydro-6-hydroxy-4-[(2-dimethylamino)ethyl]-7-(4-methoxyphenyl)-1,4-thiazepin-5(2*H*)-one (**2**) and after stirring at room temperature for 65 hours, the mixture was poured onto ice-water (75 ml) and the aqueous suspension was acidified with 1*N* hydrochloric acid (3 x 50 ml). The acidic solution was chilled, made basic with 10*N* sodium hydroxide and extracted with ethyl acetate (3 x 50 ml). The combined ethyl acetate solutions were washed with brine and dried (magnesium sulfate). Removal of the solvent gave a residue which was dissolved in ethanol and acidified with hydrogen chloride (anhydrous). The crude hydrochloride was recrystallized from ethanol to give 1.2 g (55%) of **3** hydrochloride, mp 162-164°, which was not depressed on admixture with a sample of **3** hydrochloride prepared above.

Acknowledgements.

We thank our Physical Chemistry Department and in particular, Dr. W. Benz for mass spectra, Dr. F. Scheidl for elemental analysis, Mr. M. Lanyi for ir spectra and Dr. T. Williams for the nmr spectra.

REFERENCES AND NOTES

[1] *Trans* nomenclature in this work refer to the relative orientation of the aryl and hydroxyl groups.

[2] E. Mohacsi and J. O'Brien, *J. Heterocyclic Chem.*, **27**, 1085 (1990).

[3] J. Weinstock, R. G. Pearson and F. G. Bordwell, *J. Am. Chem. Soc.*, **76**, 4748 (1954); **78**, 3468, 3473 (1956).

[4] H. L. Goering, D. I. Relyca and K. L. Howe, *J. Am. Chem. Soc.*, **79**, 2502 (1957).