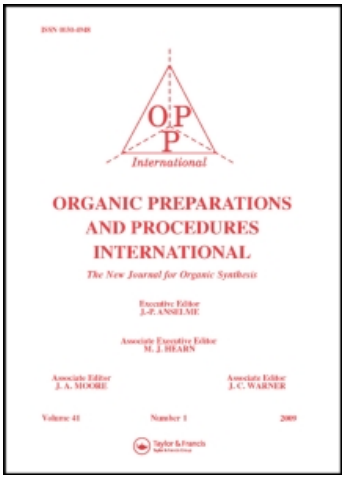

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A CONVENIENT PREPARATION OF N-DEMETHYLDILTIAZEM AND ITS CONVERSION TO A DILTIAZEM HOMOLOG

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A CONVENIENT PREPARATION OF N-DEMETHYLDILTIAZEM AND ITS CONVERSION TO A DILTIAZEM HOMOLOG

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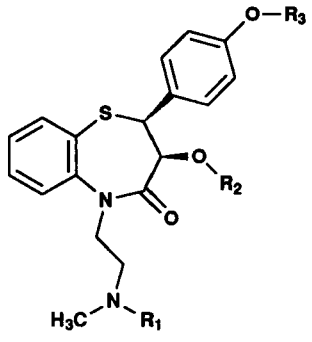
Diltiazem (**1a**), (2*S*,3*S*)-3-acetoxy-5-(2-dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one is a calcium channel blocker,[1] widely used for the treatment[2] of angina, hypertension and cardiac arrhythmias. It undergoes extensive metabolism *via* N- and O-demethylation, deacetylation, and N-oxidation, resulting in a variety of metabolites.[3] N-Desmethyldiltiazem (**1b**) accounts for approximately 50% of the unconjugated form excreted in 24 hrs human urine, about 45% being unchanged diltiazem.[4] In connection with the comparative performance evaluation of diltiazem tablets and extended release multiparticulate osmotic dosage forms,[5] and the subse-

quent human clinical evaluation of these osmotic devices, we needed samples of the major diltiazem metabolites in order to establish their identity in plasma samples.



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a) $R_1 = R_3 = Me$, $R_2 = Ac$
b) $R_1 = H$, $R_2 = Ac$, $R_3 = Me$
c) $R_1 = R_2 = H$, $R_3 = Me$
d) $R_1 = R_2 = R_3 = H$
e) $R_1 = Et$, $R_2 = Ac$, $R_3 = Me$
f) $R_1 = COOCH(Cl)CH_3$, $R_2 = Ac$, $R_3 = Me$

The conversion of diltiazem to the desacetyl-O-desmethyl derivative and to the corresponding N-oxide was reported by Miyazaka *et al.*[6] This group also reported the total synthesis of deacetylated N-desmethyl (**1c**) and N,O-bis-desmethyl (**1d**) derivatives. Most of the HPLC,[7] TLC densitometry[8] and GC-MS[4] determination of diltiazem metabolites in plasma in recent years, relied on the above source directly or indirectly for reference samples of these compounds. This report describes a convenient direct method for preparing N-desmethyldiltiazem (**1b**) by demethylation of diltiazem, as an alternative to total synthesis. The preparation of the N-methyl-N-ethyl analog (**1e**) is also reported. This compound, exhibiting a desirably longer retention time, served as a useful internal standard for the HPLC assay of diltiazem metabolites.[5]

N-Demethylation of diltiazem (**1a**) was carried out by reaction with α-chloroethyl chloroformate[9] in refluxing 1,2-dichloroethane. The resulting N-desmethyl-α-chloroethyl carbamate **1f** was converted to N-desmethyldiltiazem (**1b**) by refluxing in methanol. This step was accompanied by some O-deacetylation resulting in the formation of 5 to 10% of N-desmethyl-O-deacetyldiltiazem (**1c**) as a side product. Initial attempts to prepare the N-ethyl-N-methyl analog **1e** by reductive amination[10] of acetaldehyde using sodium cyanoborohydride was unsatisfactory because of deacetylation and incomplete dehydration/reduction of the intermediate carbinolamine. Alkylation with ethyl iodide and potassium carbonate in acetone was successful, but was accompanied by partial (8-15%) deacetylation. Although some amount of quaternized material was formed in this reaction, it was easily removed by water wash. A final acetylation using acetic anhydride and potassium acetate gave the N-ethyl-N-methyl analog **1e**, which was crystallized as the hydrochloride salt.

EXPERIMENTAL SECTION

The following spectrometers were used: IR, Mattson Galaxy 5020; NMR, Bruker AC200 operating at 200 MHz for proton and 50 MHz for carbon-13; MS, Riber R_{10}-10 interfaced with a PDP-8A computer or VG ZAB instrument with PDP11/250J computer. Chemical shifts are reported in parts per million relative to tetramethylsilane as internal reference. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Reagents and chemicals were

purchased from common commercial suppliers and were used as received. Yields were not optimized.

3-Acetoxy-5-(2-methylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one hydrochloride (Desmethyldiltiazem Hydrochloride, 1b).- Diltiazem (**1a**) (free base form, 10.88 g 26.2 mmol), which was pre-dried by azeotropic distillation of chloroform, was refluxed with 4.13 g (28.9 mmol) α-chloroethyl chloroformate in 150 mL of 1,2-dichloroethane for 4 hrs. The reaction mixture was cooled and washed with water, 1N hydrochloric acid, water and brine. The organic layer was dried over sodium sulfate and evaporated to furnish 12.46 g of a foamy solid. This product was dissolved in 50 mL chloroform and filtered through a column of silica gel (150 g). The pure chloroethyl carbamate was eluted with approximately 750 mL of ethyl acetate-chloroform (1:1) yielding 6.2 g of a foamy solid. ^{1}H NMR ($CDCl_3$): δ 1.76 (d, J = 7 Hz, 3 H), 1.93 (s, 3 H), 3.03 (d, 3 H), 3.3-3.8 (m, 2 H), 3.8 (s, 3 H), 3.9-4.6 (m, 2 H), 5.03 (d, J = 8 Hz, 1 H), 5.23 (d, J = 8 Hz, 1 H), 6.55 (q, J = 7 Hz, 1 H), 6.8-7.8 (m, 8 H); IR (KBr): 1725, 1681, 1514, 1475, 1445, 1406, 1252, 1097, 763 cm^{-1}; MS *m/e*: 509 (M^+), 507 (M^+), 471, 427, 367, 283.

The above desmethyl-α-chloroethyl carbamate (6.1 g), which tended to decompose on standing, was refluxed in 150 mL of methanol for 1.5 hr. The methanol was evaporated *in vacuum*, the thick sticky residue was dissolved in about 30 mL of ethyl acetate, ether was added to turbidity and allowed to stand. The white solid that deposited was collected and washed with anhydrous ether to yield 5.22 g of desmethyldiltiazem hydrochloride (**1b**). It was crystallized from chloroform to yield 4.3 g (38%) of the pure compound, mp. 192-193° (softened at 161-163° and resolidified before melting). ^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3 H, OAc), 2.76 (s, 3 H, NC*H*$_3$), 3.27 (m, 1 H, CONCH*H*), 3.49 (m, 1 H, CONC*H*H), 3.81 (s, 3 H, OC*H*$_3$), 4.2-4.6 (m, 2 H, MeNC*H*$_2$), 5.01 (d, J = 8 Hz, 1 H, SC*H*), 5.12 (d, J = 8 Hz, 1 H, C*H*OAc), 6.8-7.7 (m, 8 H, *ar*); ^{13}C NMR ($CDCl_3$): δ 20.37, 33.07, 46.25, 46.63, 54.18, 55.2, 71.24, 113.83, 124.61, 125.88, 127.71, 128.17, 129.39, 130.57, 131.81, 131.55, 144.48, 159.83, 168.41, 169.86; IR (KBr): 3422, 1744, 1680, 1513, 1469, 1252, 1025, 759 cm^{-1}; MS (*m/e*): 401 (M^++1), 343, 283, 161, 150.

Anal. Calcd for $C_{21}H_{25}ClN_2O_4S$•$CHCl_3$: C, 51.99; H, 5.17; N, 5.64; S, 6.45
Found: C, 52.23; H, 5.19; N, 5.67; S, 6.99

3-Acetoxy-5-[2-(N-ethyl-N-methylamino)ethyl]-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one hydrochloride (1e).- N-Demethyldiltiazem hydrochloride (**1b**) (5.97 g, 13.7 mmol) was stirred in 200 mL of dry acetone at room temperature with 10 g of potassium carbonate and 3 mL (19.2 mmol) of ethyl iodide for 20 h. The progress of the reaction was monitored by HPLC using a Brownlee Spheri-5 RP-18 column and a similar 3 cm guard column at ambient temperature. Acetonitrile-water (3:7) containing 4 mL/L of phosphoric acid and 4 mL/L of triethylamine was used as the mobile phase at a flow rate of 1.5 mL per min. The detector was set at 238 nm. Under these conditions **1b**, **1e** and **1c** had retention times of 6.5, 10 and 3.2 min, respectively. The deacetylated N-ethyl analog had a retention time of 4.8 min. The reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in ether and washed with water, aqueous sodium bisulfite,

water and brine. The ethereal layer was dried over sodium sulfate and evaporated. The residue (5.1 g) was a glassy solid containing approximately 10% of deacetylated material. It was stirred at room temperature with 10 mL of acetic anhydride and 1 g of potassium acetate. After 17 hrs, the reaction mixture was diluted with 100 mL of water and the pH was adjusted to 9 using solid sodium carbonate. It was extracted with ether and the ethereal extract was washed with water and brine. Evaporation of solvent gave 5 g of **1e** as an oil.

The above free base of the N-ethyl analog **1e** (8.79 g) was dissolved in a mixture of 150 mL of ether and 25 mL of chloroform and dry HCl gas was bubbled in. The white precipitate that formed was collected and dried, yielding 8.54 g of the hydrochloride salt. It was crystallized from chloroform-hexane to furnish 6.7 g (60%) of the pure hydrochloride salt, mp. 192-194°; ^{1}H NMR ($CDCl_3$): δ 1.47 (t, J = 7 Hz, 3 H), 1.89 (s, 3 H), 2.85 (br s, 3 H), 3.22 (m, 3 H), 3.5 (m, 1 H), 3.82 (s, 3 H), 4.45 (m, 2 H), 5.02 (d, J = 8 Hz, 1 H), 5.12 (d, J = 8 Hz, 1 H), 6.85-7.75 (m, 8 H); ^{13}C NMR ($CDCl_3$): δ 8.79, 20.24, 39.41, 44.54, 50.1, 51.39, 54.22, 55.13, 71.02, 113.74, 124.4, 125.9, 127.45, 128.16, 129.2, 130.44, 131.83, 135.51, 144.12, 159.72, 168.02, 169.66; IR (KBr): 3446, 2587, 1744, 1678, 1220, 1026 cm^{-1}; FAB MS (*m/e*): 429 (M^+).

Anal. Calcd. for $C_{23}H_{29}ClN_2O_4S$: C, 59.40; H, 6.28; N, 6.02; S, 6.89
Found: C, 59.05; H, 5.99; N, 5.74; S, 6.95

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THE ONE-STEP SYNTHESIS OF *p-tert*-BUTYLCALIX[5]ARENE

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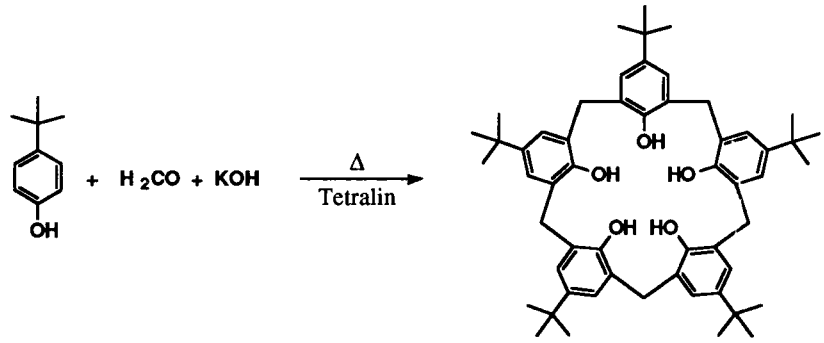
The one-step synthesis of *p-tert*-butylcalix[5]arene (**1**) from *p-tert*-butylphenol and formaldehyde was first reported in 1982 by Ninagawa and Matsuda[1], who isolated it in *ca* 6% yield. Regen and co-workers[2] repeated the synthesis in 1986 and, although using a different work-up procedure, obtained a similar yield. With the recent escalation in research in calixarene chemistry this less accessible member of the calixarene family is assuming increasing importance. The present communication provides details whereby it can be prepared in yields up to 15% which, while still low, nevertheless allows the easy accumulation of workable amounts of this potentially useful compound.



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EXPERIMENTAL SECTION

Caution: *The high temperature, the high flammability of the hot tetralin, and the large scale of the procedure described below make it a potentially dangerous preparation. Be certain to perform it in a fire-resistant fume hood with apparatus that has been carefully set up and checked before each stage of heating.*