Quinazolines and 1,4-Benzodiazepines LVII (1). 1*H*-1,4-Benzodiazepines

R. Ian Fryer, D. L. Coffen, J. V. Earley, and A. Walser

Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

Received January 22, 1973

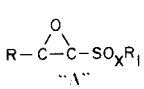
The preparation of the title compounds **3** and **4** using two different methods of synthesis is described. These compounds are readily reduced to 2,3-dihydro-1*H*-derivatives **5**. Oxidation of 2-alkylthio-1*H*-1,4-benzodiazepines leads to the corresponding sulfoxides and sulfones. The oxidative rearrangement of sulfones **9** to a 2*H*-1,4-benzodiazepin-2-one derivative **10** is also given. The "normal" addition of azodicarboxylate together with an unusual addition of two moles of acetylenedicarboxylate to the enamine double bond of 1*H* compounds is discussed.

The synthesis of two 1*H*-1,4-benzodiazepines has previously been reported in the literature. The first of these, a 3-carboxamido-1*H*-1,4-benzodiazepine was prepared by the intramolecular cyclization of a formamido diphenylmethyleneimino-*N*-methylacetamide (2) while the second, a 3-cyano compound, was prepared by the addition of sodium cyanide to a 5*H*-1,4-benzodiazepine-4-oxide (3).

It has been found that benzodiazepines of this type can be readily prepared by treatment of a 1-alkyl-1,4-benzodiazepine-2-thione with an alkyl halide in the presence of base. The 1*H* compounds are, as expected, base-stable, acid-sensitive compounds which readily hydrolyze to the corresponding 2,3-dihydro-1*H*-2-ones in mineral acid. The thiones **2a**, **b** were prepared from the corresponding 2-ones by treatment with phosphorus pentasulfide (4). The previously unknown benzodiazepin-2-one **1b** required for the preparation of **2b** was prepared by standard methods (5) from the known 2-amino-5-chloro-2′-fluorobenzophenone (**7**) (6) and is described in the experimental section.

Compound **3c** (Scheme I) was reduced to the 2,3-dihydrobenzodiazepine **5** simply by stirring with Raney nickel in acetone. The intermediate, the desulfurized 1*H*-benzodiazepine, compound **4**, could be isolated in low yield by carrying out the Raney nickel reduction in the presence of diethylamine and benzene. It was found that 1*H* compounds of type **4** were more readily prepared by dehydration of **6** with mesyl or tosyl chloride in pyridine. The 2-hydroxy derivative **6** was prepared by reduction of the corresponding 2-one **1a** with lithium aluminum hydride.

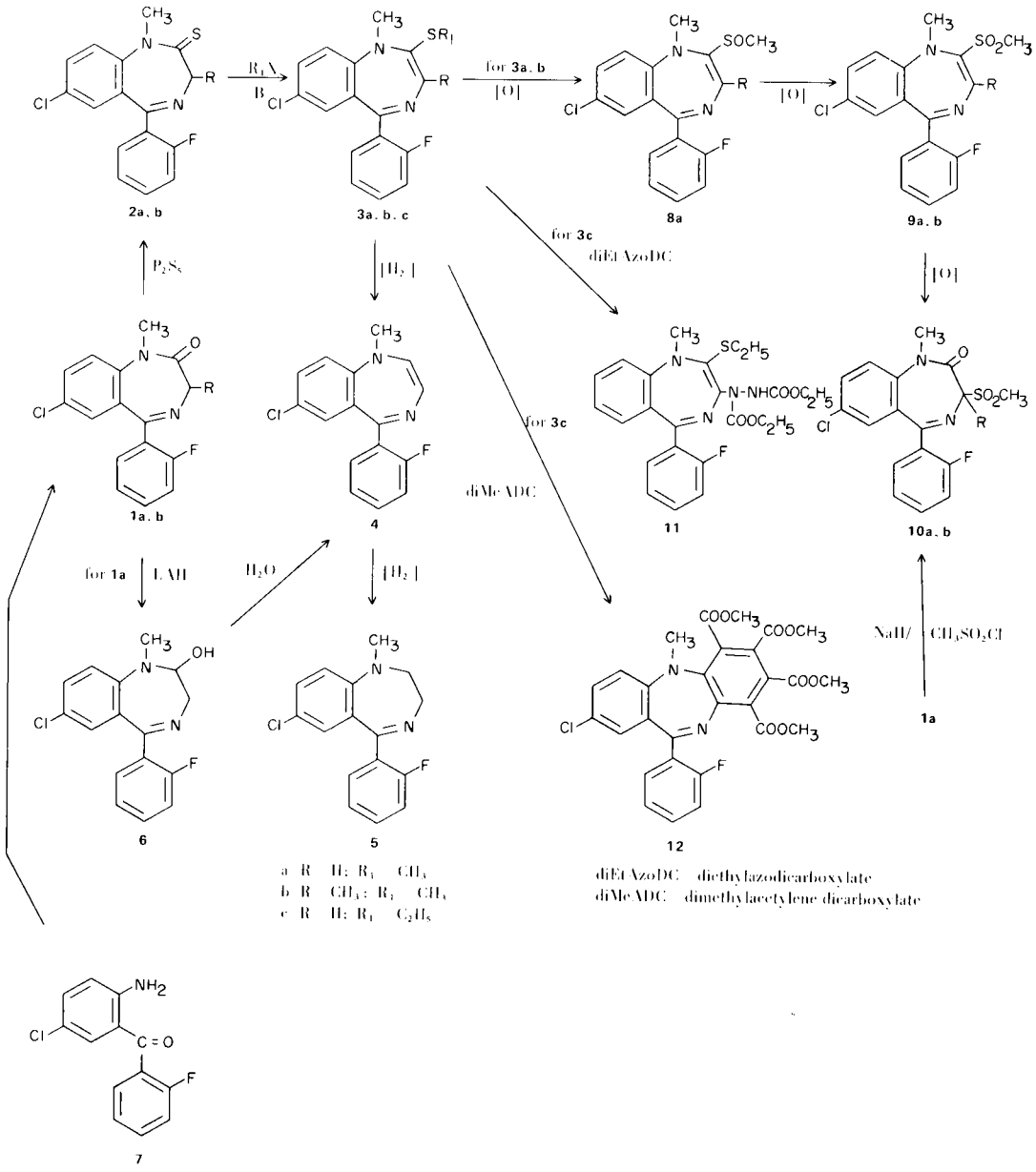
Oxidation of **3a** with *m*-chloroperbenzoic acid afforded, depending on the quantities of oxidant used, the expected sulfoxide or sulfone, **8a** and **9a**, respectively. Further oxidation of this sulfone **9a**, gave a rearranged oxidation product to which we have assigned structure **10a**. An alternate structure for **10a**, the unrearranged 3-one derivative was first ruled out on the basis of ir data (C=O 1670 cm^{-1} normal for 2-one: corresponding 2,3-dione, C=O at 1680 and 1730 cm^{-1}). Subsequent synthesis of the 3-methyl sulfone derivative **9b** and its oxidative rearrangement to **10b** excluded the possibility of an unusual type of Polonovski rearrangement and confirmed the postulated structure. Compound **10a** was later synthesized unequivocally by treatment of the 3-sodio derivative of **1a** with methane sulfonyl chloride. It is known that unsaturated sulfones can be oxidized to α,β epoxy sulfones and that α,β epoxy sulfoxides and sulfones of type "A" rearrange both thermally and catalytically (H^+) to the corresponding β-carboxyl sulfoxides and sulfones (7) (8).



Upon exposure to excess diethyl azodicarboxylate in boiling dioxane, compound **3c** forms an orange, crystalline 1:1 adduct. On the basis of reported results (9) from the reaction of enamines with this reagent, the anticipated product, compound **11**, was isolated. The spectral properties of the material obtained are fully in accord with the structure assigned.

The condensation of **3c** with dimethyl acetylenedicarboxylate in boiling dioxane afforded a yellow

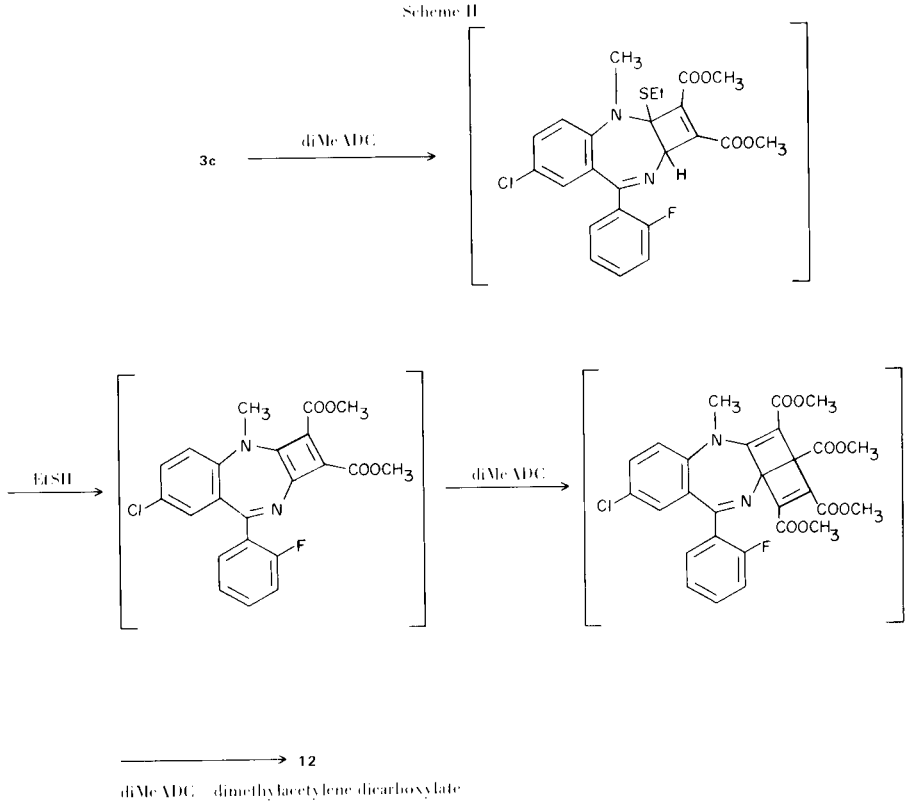
Scheme I



crystalline product formulated as **12** (42% yield). This structure was assigned on the basis of analytical and spectral data which established the molecular formula $C_{28}H_{22}ClFN_2O_8$. The most compelling evidence for this structural assignment was provided by the nmr spectrum which contains four separate methyl ester resonances at 3.81, 3.83, 3.87, and 4.03 ppm.

A reaction pathway different from that normally observed in the reaction of enamines with acetylenedicarboxylates is necessary to account for the formation of **12**. As proposed in Scheme II, the reaction proceeds in the normal manner to a cyclobutene derivative (10) but is diverted at this point due to the presence of the thioether function.

Scheme II



EXPERIMENTAL (11)

2-Bromo-4′-chloro-2′-(2-fluorobenzoyl)propionanilide.

A solution of 90 g. (0.362 mole) of 2-amino-5-chloro-2′-fluorobenzophenone (**7**) (6), in 650 ml. of benzene was treated with 77 g. (0.362 mole) of 2-bromopropionyl bromide and the reaction was refluxed and stirred for 2 hours. The reaction was made basic with a dilute solution of potassium carbonate, dichloromethane (300 ml.) was added and the organic layer was separated and washed with 300 ml. of water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized from a mixture of ether and petroleum ether and then recrystallized from methanol to give 120 g. (86%) of product as pale yellow rods, m.p. 74-77°.

Anal. Calcd. for $C_{16}H_{12}BrClFNO_2$: C, 49.96; H, 3.14; N, 3.64. Found: C, 49.87; H, 3.18; N, 3.44.

2-Amino-4′-chloro-2′-(2-fluorobenzoyl)propionanilide.

A solution of 115 g. (0.3 mole) of 2-bromo-4′-chloro-2′-(2-fluorobenzoyl)propionanilide and 5 g. (0.03 mole) of potassium iodide in 300 ml. of dichloromethane was added to 300 ml. of liquid ammonia, and the reaction was stirred for 24 hours using a dry ice condenser. After the ammonia was allowed to evaporate, the solution was washed with 2 x 250 ml. of water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in 200 ml. of benzene and filtered through 500 g. of Florisil. It was eluted with 1 l. of dichloromethane and 2 l. of ether to give 90 g. of an oil which still contained some starting material. Elution with 2 l. of ethyl acetate gave 15 g. of a 50/50 mixture of product and cyclized product. Elution with 1 l. of methanol gave 2.5 g. of oil which was crystallized from a mixture of ether and petroleum ether, and then recrystallized from a mixture of methanol, ether and petroleum ether to give 1.8 g. (1.9%) of yellow prisms, melting at 117-121°.

Anal. Calcd. for $C_{16}H_{14}ClFN_2O_2$: C, 59.91; H, 4.40; N, 8.73. Found: C, 60.18; H, 4.51; N, 8.56.

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-3-methyl-2*H*-1,4-benzodiazepin-2-one.

A solution of 15 g. (0.047 mole) of the 50/50 mixture obtained in the previous experiment in 100 ml. of ethanol was refluxed for 5 hours, cooled and filtered. The precipitate was recrystallized from a mixture of dichloromethane, ether and petroleum ether to give 11 g. (80%) of the product as white rods, m.p. 188-191°.

Anal. Calcd. for $C_{16}H_{12}ClFN_2O$: C, 63.48; H, 4.00; N, 9.25. Found: C, 63.71; H, 4.25, 4.26; N, 8.98, 8.96.

7-Chloro-1,3-dihydro-1,3-dimethyl-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one (**1b**).

A solution of 35.1 g. (0.115 mole) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-3-methyl-2*H*-1,4-benzodiazepin-2-one in 200 ml. of *N,N*-dimethylformamide was treated with 32.6 ml. of a 4.23 *N* solution of sodium methoxide in methanol and after 20 minutes, 24.4 g. (0.172 mole) of methyl iodide was added slowly with stirring. After 18 hours, the reaction was poured into 3 l. of ice and water, and made basic with dilute ammonium hydroxide. The precipitate obtained by filtration was recrystallized from methanol to give 24.8 g. (71.5%) of the product as white prisms, m.p. 122-127°.

Anal. Calcd. for $C_{17}H_{14}ClFN_2O$: C, 64.46; H, 4.46; N, 8.84. Found: C, 64.62; H, 4.58; N, 8.72.

7-Chloro-1,3-dihydro-1,3-dimethyl-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepine-2-thione (**2b**).

A solution of 41 g. (0.13 mole) of **1b** in 200 ml. of pyridine was treated with 34.6 g. (0.156 mole) of phosphorus pentasulfide and the reaction mixture was refluxed for 4 hours and then poured into 1 l. of ice and water. It was then made basic with ammonium hydroxide and extracted with dichloromethane (2 x 300 ml.) which was separated and washed with 300 ml. of water. The organic layer was dried over anhydrous sodium sulfate, concentrated and filtered through basic alumina. The product was eluted with 1.5 l. of dichloromethane to give 20 g. of oil. Elution with 1 l. of ether and 1.5 l. of ethyl acetate gave an additional 14 g. of crude oil. Everything was combined and crystallized from a mixture of ether and petroleum ether and recrystallized from the same solvents to give 25 g. (58%) of the product as white prisms, m.p. 104-109°.

Anal. Calcd. for $C_{17}H_{14}ClFN_2S$: C, 61.35; H, 4.24; N, 8.42. Found: C, 61.04; H, 4.31; N, 8.05.

7-Chloro-1-methyl-5-(2-fluorophenyl)-2-methylthio-1*H*-1,4-benzodiazepine (**3a**).

A solution of 50.0 g. (0.16 mole) of **2a** 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2*H*-1,4-benzodiazepine-2-thione (4) in 150 ml. of dry *N,N*-dimethylformamide was treated with 7.2 g. (0.176 mole) of a 57% dispersion of sodium hydride in mineral oil. The mixture was stirred for 1 hour, cooled in an ice bath and treated with 34 g. (0.24 mole) of methyl iodide added dropwise. The solution was stirred at room temperature for 1.5 hours and poured into ice water made slightly basic with ammonium hydroxide. The red precipitate was removed by filtration, dissolved in dichloromethane and the solution was washed with water, saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was crystallized from methanol to give 43.4 g. (83.5%) of **3a** as red prisms, m.p. 72-76°; nmr (deuteriochloroform) δ 2.25 (s, 3H, SCH_3), 3.17 (s, 3H, NCH_3) 6.60-7.78 (m, 8H, aromatic).

Anal. Calcd. for $C_{17}H_{14}ClFN_2S$: C, 61.35; H, 4.24; N, 8.42. Found: C, 61.14; H, 4.23; N, 8.32.

7-Chloro-1,3-dimethyl-5-(2-fluorophenyl)-2-methylthio-1*H*-1,4-benzodiazepine (**3b**).

A solution of 3.3 g. (0.01 mole) of **2b** in 15 ml. of *N,N*-dimethylformamide was treated with 4.8 ml. (0.02 mole) of a 4.23 *N* solution of sodium methoxide in methanol and after 30 minutes, it was cooled in an ice bath when 2.8 g. (0.02 mole) of methyl iodide was added dropwise with stirring. After 18 hours, the reaction mixture was poured into 150 ml. of cold water, filtered and the precipitate was dissolved in 75 ml. of dichloromethane. This was washed with dilute potassium carbonate solution (50 ml.), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized from methanol and recrystallized from methanol once more to give 2.6 g. (74%) of the product as orange prisms, m.p. 149-152°; nmr (deuteriochloroform) δ 2.17, 2.24 (s, 3H, 3H, SCH_3, CCH_3), 3.08 (s, 3H, $N\text{-}CH_3$), 6.75-7.78 (m, 7H, aromatic).

Anal. Calcd. for $C_{18}H_{16}ClFN_2S$: C, 62.33; H, 4.65; N, 8.08. Found: C, 62.14; H, 4.69; N, 7.93.

7-Chloro-2-ethylthio-5-(2-fluorophenyl)-1-methyl-1*H*-1,4-benzodiazepine (**3c**).

A solution of 16 g. (0.05 mole) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2*H*-1,4-benzodiazepine-2-thione (**2a**) (4), in 40 ml. of *N,N*-dimethylformamide was treated with 14.1 ml. (0.06 mole) of a 4.23 *N* solution of sodium methoxide in methanol, and after 1 hour, the mixture was cooled in an ice bath when 11.7 g. (0.075 mole) of ethyl iodide was added with stirring. The reaction mixture was then stirred at room temperature for 3 hours, when it was poured into 500 ml. of cold water. The precipitate was removed by filtration and was dissolved in 75 ml. of dichloromethane which was dried over anhydrous sodium sulfate and concentrated to 30 ml. Methanol was added and the remainder of the dichloromethane was removed on the steam bath. The solution was cooled and filtered. Recrystallization of the product from a mixture of dichloromethane and methanol gave 13.8 g. (79%) of **3c** as red prisms, m.p. 103-104°.

Anal. Calcd. for $C_{18}H_{16}ClFN_2S$: C, 62.33; H, 4.65; N, 8.07. Found: C, 62.11; H, 4.67; N, 8.03.

7-Chloro-5-(2-fluorophenyl)-1-methyl-1*H*-1,4-benzodiazepine (**4**).

A. From Compound **3c**.

A mixture of 1 g. of **3c**, 10 g. of Raney nickel, 20 ml. of diethylamine and 20 ml. of benzene was stirred at room temperature for 6 hours under nitrogen. The residue obtained after filtration and evaporation was chromatographed on 30 g. of silica gel treated with diethylamine in hexane. The red resin eluted with 10% ether in hexane was crystallized from ether/hexane to yield 0.11 g. of **4** as dark red crystals, m.p. 139-142°; uv (2-propanol): λ max 234 mμ (ε = 15,820) infl 285 (6420) infl 310 (3500) 417/9 (720); nmr (deuteriochloroform) δ 2.86 (s, 3H, NCH_3), 5.21 and 6.36 (AB, 2H, J = 6 Hz, C_2, C_3-H), 6.5-7.8 (m, 7H, aromatic H).

Anal. Calcd. for $C_{16}H_{12}ClFN_2$: C, 67.02; H, 4.22; N, 9.77. Found: C, 67.14; H, 4.12; N, 9.55.

B. From Compound **6**.

A mixture of 4.5 g. of **6** in 50 ml. of benzene, 30 ml. of pyridine and 3 ml. of mesyl chloride was refluxed for 10 minutes and then poured on 10% aqueous sodium carbonate solution. The benzene layer was separated, dried, and evaporated. The residue was dissolved in toluene, filtered through alumina and evaporated azeotropically to remove the pyridine. Crystallization of the residue from ether yielded 2.1 g. of red crystals which were further purified by chromatography on 150 g. of silica gel using 5% ethyl acetate in methylene chloride. Pure fractions were crystallized from ether to give 1.9 g. of **4**, m.p. 139-142°.

7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1-methyl-1*H*-1,4-benzodiazepine Hydrochloride (**5**).

A solution of 2.5 g. (0.0072 mole) of **2c** in 35 ml. of acetone was treated with one teaspoon of Raney nickel, and the mixture was stirred for 20 hours. The solution was filtered through Celite, which was then washed thoroughly with dichloromethane. The filtrates were combined, and evaporated to dryness. The residue was dissolved in 20 ml. of dichloromethane, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. Next, the residue was dissolved in 20 ml. of benzene and chromatographed over a basic alumina column. Elution with 1 l. of benzene and 1 l. of dichloromethane gave after evaporation of the solvents starting material. Using 2 l. of ethyl acetate as the eluent, gave after evaporation, 0.6 g. of an oil. This was crystallized as the hydrochloride by adding ethanolic hydrogen chloride followed by ether. Recrystallization from a mixture of methanol and ether gave the hydrochloride of **5** as orange rods, m.p. 243-245° dec. (sealed tube). A mixture melting point

with an authentic sample melted at 242-245° dec. (4).

7-Chloro-5-(2-fluorophenyl)-2-hydroxy-1-methyl-2,3-dihydro-1*H*-1,4-benzodiazepine (**6**).

A solution of 16.5 g. (55 mmoles) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2*H*-1,4-benzodiazepin-2-one (**1a**) (5) in 100 ml. of ether was added slowly to a suspension of 2.2 g. (55 mmoles) of lithium aluminum hydride in 200 ml. of ether cooled to -10°. After addition, the mixture was stirred for 15 minutes at -10° to 0°. The excess reagent was decomposed by careful addition of 11 ml. of water. The inorganic material was separated by filtration, the filtrate was dried over sodium sulfate and was evaporated. Crystallization of the residue from ether yielded 6 g. (37%) of **6** as white prisms, m.p. 142-143°. The analytical sample was recrystallized from tetrahydrofuran/ether, m.p. 143-146°; nmr (d-DMSO) δ 2.83 (s, 3H, N-CH_3), 3.07 (q, 1H, J_{AB} = 11 Hz, J_{AX} = 10 Hz, C_3-H), 4.03 (q, 1H J_{AB} = 11 Hz, J_{AX} = 4.5 Hz, C_3-H) 5.16 (m, 1H, CH-OH) 6.0 (d, 1H, J = 7 Hz, OH) 6.8-7.7 (m, 7H, aromatic).

Anal. Calcd. for $C_{16}H_{14}ClFN_2O$: C, 63.06; H, 4.62; N, 9.19. Found: C, 63.04; H, 4.68; N, 9.00.

7-Chloro-5-(2-fluorophenyl)-1-methyl-2-methylsulfinyl-1*H*-1,4-benzodiazepine (**8a**).

A solution of 5.0 g. (0.015 mole) of **3a** in 75 ml. of dichloromethane, cooled in an ice bath, was treated with 3.4 g. (0.02 mole) of 85% *m*-chloroperbenzoic acid over a 10 minute period with stirring. After standing at room temperature overnight, tlc indicated the presence of some starting material. An additional 0.6 g. of *m*-chloroperbenzoic acid was added and the mixture was stirred at room temperature for 1 hour. The reaction mixture was washed with dilute ammonium hydroxide (2 x 150 ml.), 100 ml. of saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness.

The residual oil was dissolved in 50 ml. of dichloromethane and filtered through 200 g. of basic alumina. The alumina was eluted with 500 ml. of dichloromethane, 800 ml. of ethyl acetate and then 500 ml. of methanol. The methanol fraction was evaporated and the residue was crystallized and recrystallized from methanol to give 2.5 g. (48%) of the sulfoxide as orange needles, m.p. 130-144° (sealed tube); nmr (deuteriochloroform) δ 2.78 (s, 3H, SCH_3), 3.22 (s, 3H, N-CH_3), 6.82-7.82 (m, 8H, aromatic).

Anal. Calcd. for $C_{17}H_{14}ClFN_2OS$: C, 58.54; H, 4.04; N, 8.03. Found: C, 58.59; H, 4.03; N, 7.91.

7-Chloro-5-(2-fluorophenyl)-1-methyl-2-methylsulfonyl-1*H*-1,4-benzodiazepine (**9a**).

A solution of 10 g. (0.03 mole) of **3a** in 150 ml. of dichloromethane was stirred in an ice bath and treated with 13.6 g. (0.08 mole) of 85% *m*-chloroperbenzoic acid over a period of 1 hour. The mixture was allowed to stand overnight. A tlc analysis showed the presence of some starting material and an additional 1.2 g. of *m*-chloroperbenzoic acid was added. The solution was stirred at room temperature for 4 hours, washed with 2-100 ml. portions of dilute ammonia, 100 ml. of brine, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was dissolved in dichloromethane and chromatographed over basic alumina using ether as the eluent. The forerun was discarded and the eluent changed to ethyl acetate. The ethyl acetate fraction was evaporated and the residue crystallized from a mixture of dichloromethane and methanol to give 6.1 g., (55%) of **9a** as orange prisms, m.p. 145-151°; nmr (deuteriochloroform) δ 3.01 (s, 3H, SCH_3), 3.27 (s, 3H, N-CH_3) 6.90-7.90 (m, 8H, aromatic).

Anal. Calcd. for $C_{17}H_{14}ClFN_2O_2S$: C, 55.97; H, 3.87; N, 7.68. Found: C, 55.78; H, 3.79; N, 7.81.

7-Chloro-1,3-dimethyl-5-(2-fluorophenyl)-2-methylsulfonyl-1*H*-1,4-benzodiazepine (**9b**).

A solution of 2.2 g. (0.00634 mole) of **3b** in 30 ml. of dichloromethane was cooled in an ice bath and then treated with 2.9 g. (0.017 mole) of 85% *m*-chloroperbenzoic acid. After 18 hours, the reaction mixture was poured into 100 ml. of dichloromethane which was washed with 75 ml. of 10% potassium carbonate solution, water (2 x 75 ml.), a saturated solution of brine (75 ml.) and dried over anhydrous sodium sulfate. The organic layer was then evaporated to dryness. The residue was crystallized and recrystallized from methanol to give 2 g. (83%) of **9b** as yellow prisms, m.p. 138-140°; nmr (deuteriochloroform) δ 2.39 (s, 3H, $\geqslant$C-CH_3), 3.02 (s, 3H, S-CH_3), 3.05 (s, 3H, N-CH_3).

Anal. Calcd. for $C_{18}H_{16}ClFN_2O_2S$: C, 57.07; H, 4.26; N, 7.39. Found: C, 56.84; H, 4.27; N, 7.27.

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-3-methylsulfonyl-2*H*-1,4-benzodiazepin-2-one (**10a**).

A. From **9a**.

A solution of 1.0 g. (0.0027 mole) of **9a** in 35 ml. of dichloromethane was cooled in an ice bath and treated with 0.6 g. (0.0029 mole) of *m*-chloroperbenzoic acid. After 24 hours at room temperature, the mixture was refluxed for 18 hours and then poured into water. The aqueous layer was made basic with ammonium hydroxide and the layers were separated. The organic layer was washed once with dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated to dryness.

The residue was dissolved in 15 ml. of dichloromethane, and chromatographed over a column of Florisil. The column was eluted first with benzene and then with a mixture of benzene and ether (10:1, v/v). These eluents were discarded, and the column was next eluted with ether and finally with ethyl acetate. The last two fractions were combined, evaporated and the residue was transferred to a silica gel thick layer plate. The plate was developed with a mixture of ethyl acetate and hexane (3:1).

The portion of silica gel corresponding to the product, at R_f 0.7 was scraped off the plate, and stirred with methanol. The methanol solution was filtered, and evaporated. The residue was dissolved in dichloromethane and purified as above on another thick layer plate. The product obtained was crystallized from a mixture of dichloromethane and ether to give **10a** as white prisms, m.p. 224-228°. A mixture m.p. with a sample of **10a** obtained from B was undepressed.

B. From **1a**.

A solution of 3 g. (0.00993 mole) of **1a** (5) in 25 ml. of dry *N,N*-dimethylformamide in an atmosphere of nitrogen was cooled in an ice bath and was treated with 1 g. (0.024 mole) of a 57% dispersion of sodium hydride in mineral oil. After 30 minutes, 5 g. (0.0435 mole) of methane sulfonyl chloride was added over a 5 minute period with stirring and the reaction was kept at room temperature for 3 hours. The reaction mixture was warmed at 70° for 30 minutes poured onto ice and filtered. The precipitate was dissolved in 50 ml. of dichloromethane which was then washed with 40 ml. of 5% potassium carbonate solution, dried over anhydrous sodium sulfate and

evaporated to dryness.

The residue was dissolved in 20 ml. of dichloromethane and chromatographed over Florisil. Elution with a 10% mixture of ether in benzene gave 0.4 g. of an oil. Elution with 1 l. of a 20% mixture of ether in benzene gave 0.4 g. of oil. These oils were crude mixtures of products and were discarded. Further elution of the column with the same solvent mixture gave 0.6 g. of an oil. This last fraction was transferred to a silica gel thick layer plate which was developed with a mixture of ethyl acetate and hexane (3:1). The material having an R_f of 0.7 was removed, stirred with methanol and filtered. The solution was evaporated, dissolved in dichloromethane, filtered and the product was precipitated with ether. Recrystallization from the same solvents gave **10a** as white prisms, m.p. 224-231°.

Anal. Calcd. for $C_{17}H_{14}ClFN_2O_3S$: C, 53.62; H, 3.71; N, 7.36. Found: C, 53.41; H, 3.77; N, 7.24.

7-Chloro-1,3-dihydro-1,3-dimethyl-5-(2-fluorophenyl)-3-methylsulfonyl-2*H*-1,4-benzodiazepin-2-one (**10b**).

A solution of 1.0 g. (0.00264 mole) of **9b** in 25 ml. of dichloromethane was treated with 2.0 g. (0.011 mole) of *m*-chloroperbenzoic acid. After 60 hours, the reaction mixture was poured into a dilute potassium carbonate solution (20 ml.), the layers were separated and the organic layer was washed with water (2 x 20 ml.), a saturated brine solution (20 ml.), and dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in benzene and chromatographed over a column of basic alumina (100 g.). Elution with ether (1.5 l.) gave 0.1 g. of an oil, and ethyl acetate (1.5 l.) gave 0.2 g. of crude product. This was crystallized from methanol and then recrystallized from a mixture of dichloromethane and petroleum ether to give 0.1 g. (10%) of the rearranged product **10b**, as white prisms, m.p. 226-229°; nmr (deuteriochloroform) δ 1.36 (s, 3H, C-CH_3), 3.21 (s, 3H, S-CH_3), 3.49 (s, 3H, N-CH_3).

Anal. Calcd. for $C_{18}H_{16}ClFN_2O_3S$: C, 54.75; H, 4.09; N, 7.09; S, 8.12. Found: C, 54.64; H, 4.20; N, 6.86; S, 8.32.

2-[7-Chloro-5-(2-fluorophenyl)-2-ethylthio-1-methyl-1*H*-1,4-benzodiazepin-3-yl]bicarbamic Acid Diethyl Ester (**11**).

A solution of compound **3c** (0.5 g.) and diethyl azodicarboxylate (1 ml.) in dioxane (20 ml.) was heated under reflux for 16 hours. The solvent was evaporated and the orange component of the resulting product mixture was isolated by a combination of column (alumina/benzene-ethyl acetate) and preparative layer (silica gel/benzene) chromatography. This product crystallized from ether-hexane as orange prisms, m.p. 118-120°; ir (Nujol) 3200, 1740, 1710, and 1590 cm^{-1}; nmr (deuteriochloroform) δ 1.20 (m, 9H, C-CH_3 overlapping triplets), 2.63 (m, 2H, S-CH_2), 3.20 (s, 3H, N-CH_3), 4.21 (m, 4H, O-CH_2), and 6.8-7.7 (m, 7H, aromatic), ms 520 (M^+).

Anal. Calcd. for $C_{24}H_{26}ClFN_4O_4S$: C, 55.32; H, 5.03; N, 10.75. Found: C, 55.21; H, 5.10; N, 10.60.

2-Chloro-11-(2-fluorophenyl)-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]-diazepine-6,7,8,9-tetracarboxylic Acid Tetramethyl Ester (**12**).

A solution of compound **3c** (6.3 g.) and dimethyl acetylenedicarboxylate (6.4 g.) in dioxane (150 ml.) was heated under reflux for 16 hours. The solvent was then evaporated and the residue taken up in a small volume of methanol and chilled. The product was filtered out and washed with methanol giving 4.5 g. (42%) of **12** as yellow prisms, m.p. 220-225°; ir (chloroform): 1745, 1710, 1580, 1530, 1500 cm^{-1}; nmr (deuteriochloroform) δ 3.46 (s, 3H, N-CH_3), 3.81 (s, 3H, O-CH_3), 3.83 (s, 3H, O-CH_3), 3.87 (s, 3H, O-CH_3), 4.03 (s, 3H, O-CH_3), 6.68-7.44 (m, 6H, aromatic) and 8.11 (d, 1H, aromatic); ms 568 (M^+).

Anal. Calcd. for $C_{28}H_{22}ClFN_2O_8$: C, 59.11; H, 3.90; N, 4.92; Cl, 6.23. Found: C, 58.69; H, 3.89; N, 4.82; Cl, 6.35.

Acknowledgement.

We are indebted to the following members of our Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. W. Benz, Dr. F. Scheidl, Dr. W. Toome, Mr. S. Traiman, and Dr. T. Williams for spectral and elemental analysis.

REFERENCES

(1) R. Jaunin, W. E. Oberhänsli, and J. Hellerbach, *Helv. Chim. Acta*, 55, 2975 (1972).

(2) R. Ian Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, 32, 3798 (1967).

(3) G. F. Field and L. H. Sternbach, U. S. Patent, 3,492,290 (1970) assigned to Hoffmann-La Roche, Inc.

(4) G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, **29**, 231 (1964).

(5) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

(6) L. H. Sternbach, R. Ian Fryer, W. Metlesics, G. Sach, and A. Stempel, *ibid.*, **27**, 3781 (1962).

(7) T. Durst and K. C. Tin, *Tetrahedron Letters*, 2369 (1970).

(8) D. F. Tavanes, L. E. Estepard, M. Blezard, *ibid.*, 2373 (1970).

(9) A. Risaliti and L. Marchetti, *Ann. Chim.* (Rome) **55**, 635 (1965); A. Risaliti, S. Fatutta, and M. Forchiassin, *Tetrahedron*, **23**, 1451 (1967); A. Risaliti, M. Forchiassin, and E. Valentin, *ibid.*, **24**, 1889 (1968); K. Schenker, *Angew. Chem.*, **72**, 638 (1960); N. J. Leonard, K. Conrow, and R. R. Sauers, *J. Am. Chem. Soc.*, **80**, 5158 (1958).

(10) A. G. Cook, "Enamines," Marcel Dekker, New York, N. Y., 1969, p. 230.

(11) Melting points were taken microscopically on a hot stage and are corrected. Spectra of all compounds were taken and compared in order to confirm or exclude structural changes. Only significant spectra are reported. The uv spectra were taken on a Cary Model 14 spectrophotometer, nmr spectra with a Varian A-60 instrument; ir spectra on a Beckman IR-9 spectrophotometer and mass spectra using a CEC-21-110B instrument at 70 eV by direct insertion. Basic alumina refers to Woelm basic aluminum oxide activity grade I.