Quinazolines and 1,4-Benzodiazepines. LXXIII. The Ring Expansion of 2-Chloromethylquinazoline 3-Oxides with Nitromethane

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The reaction of 2-chloromethylquinazoline 3-oxides (**3**) with the anion of nitromethane gave the 2-nitromethylene benzodiazepine oxides (**4**) as a result of ring expansion. Other nucleophiles led only to products derived from substitution of the halogen. The ring expansion of 2,2-dichloro-1,2-dihydroquinazolines with nitromethane anion is also described.

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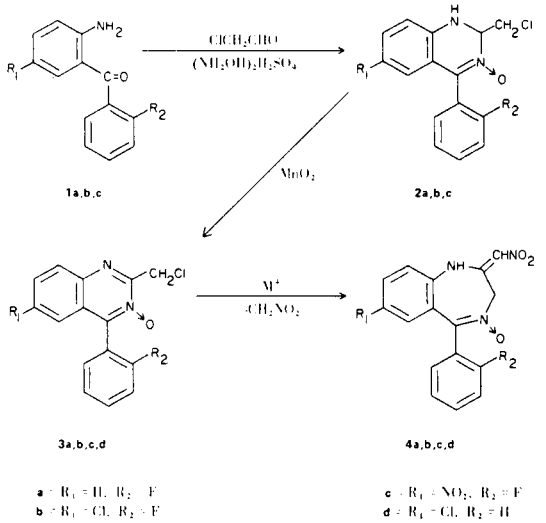
The ring expansion of 2-chloromethylquinazoline 3-oxides with heteroatom nucleophiles affording benzodiazepine amidines, amides, thioamides, imino ethers, and iminothioethers is well known (2), however, no examples of a carbon nucleophile causing ring expansion have been reported.

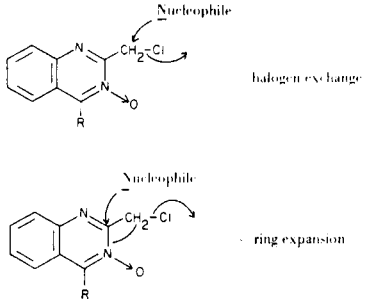
It has now been found that treatment of the quinazoline derivatives **3a, 3b, 3c** and **3d** with the anion derived from nitromethane, gives the 2-nitromethylene substituted benzodiazepine oxides **4a, 4b, 4c** and **4d** in high yield.

While a variety of bases and solvents were tried, the optimum yield of ring expanded product was obtained utilizing lithium amide in dimethyl sulfoxide solution.

The three quinazolines **3a, 3b, 3c,** previously unreported, were synthesized in two steps from the corresponding ketones **1a, 1b** and **1c** *via* the intermediate dihydroquinazolines **2a, 2b** and **2c** using essentially the procedures described by Field and co-workers (3) (4).



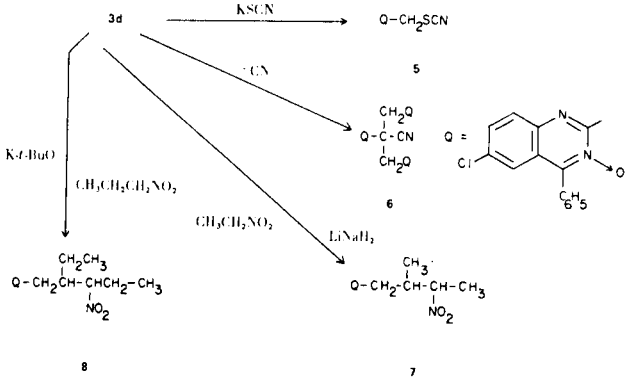
In an attempt to increase the utility of this reaction, the reaction of other nucleophiles with the quinazoline **3d** was investigated. The ring expansion, however, seems to be fairly specific for nitromethane since thiocyanate ion, cyanide ion, and the carbanions of nitroethane and 1-nitropropane gave products derived from halogen exchange rather than ring expansion. This is undoubtedly due to steric hinderance and has been noticed before with other series of nucleophiles (5).



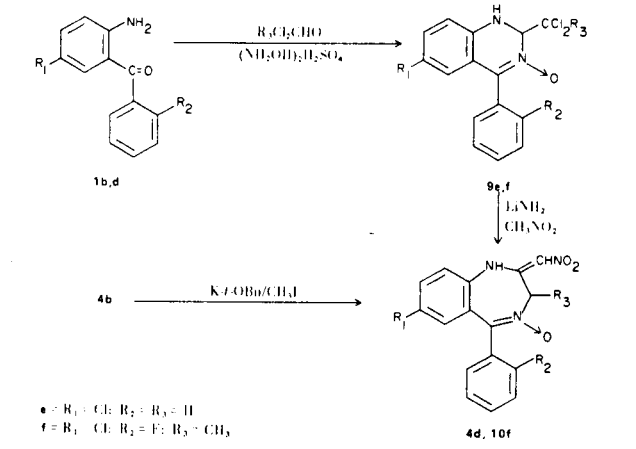
Thus treatment of **3d** with potassium thiocyanate gave compound **5**, cyanide ion gave the trimer **6** as the only isolable product while nitroethane and 1-nitropropane afforded **7** and **8** respectively derived from two moles of the anion.

Compound **6** was probably formed as outlined by M. Gordon and co-workers (6) who isolated a similar trimer from the reaction of 4-nitrophenylacetonitrile with cyanide

ion, while compounds **7** and **8** can be derived by an attack of a second mole of the anion on the first formed substitution product. The nmr spectrum of **7** indicated that this compound was a mixture of *erythro* and *threo* isomers (approximately 50/50). The signal for the $-CH_2-CH-CH_3$ methyl protons was split into two doublets, each integrating for 1.5 protons. As anticipated, this was not observed for compound **8** although this compound is undoubtedly also a mixture of the two diasteriomers. The use of other nucleophiles (^-OCN, $^-CH(CN)_2$, $RC{\equiv}C^-$) led to complicated reaction mixtures and were not studied further.



The ring expansion of 2,2-dichloro-1,2-dihydroquinazolines with amines has been reported by Field (7) and we have found that these compounds also undergo ring enlargement with nitromethane anion. Thus the dichlorodihydroquinazolines **9e, 9f** in the presence of three equivalents of base and one equivalent of nitromethane gave the benzodiazepines **4d** and **10** respectively in good yield.



Compound **10f** was also prepared from **4b** by direct alkylation using methyl iodide in the presence of potassium *t*-butoxide. Thus it would appear that in contrast to benzodiazepin-2-ones, the protons at the 3-position of 2-nitromethylene substituted 1,4-benzodiazepines are much more acidic than the proton on the 1-nitrogen.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus or on a Reichert hot stage (microscope). The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian A-60 or Varian T-60 instrument with TMS as internal standard. Ir spectra were determined on a Beckman 112-9 spectrometer and mass spectra on a CEC-110 B instrument. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying purposes. Spectra were obtained for all compounds, but are only reported where possible ambiguity existed.

2-Chloromethyl-4-(2-fluorophenyl)-1,2-dihydroquinazoline 3-Oxide (**2a**).

A solution of 100 g. (0.8 mole) of chloroacetaldehyde dimethylacetal and 100 ml. (0.15 mole) of 1.5 *N* hydrochloric acid was refluxed for 15 minutes, cooled to about 50°, and added to a mixture containing 109 g. (0.507 mole) of 2-amino-2′-fluorobenzophenone (9), 41 g. (0.25 mole) of hydroxylamine sulfate and 750 ml. of ethanol. After stirring for 18 hours, 500 ml. of a 10% potassium carbonate solution was added slowly. Ice (200 g.) was added, and after 30 minutes, the reaction mixture was filtered, and the precipitate was washed with 500 ml. of water. After drying, a portion of the precipitate (132 g., 91%) was recrystallized from a mixture of dichloromethane and ether, and again from dichloromethane to give **2a** as yellow prisms, m.p. 157-160°.

Anal. Calcd. for $C_{15}H_{12}ClFN_2O$: C, 61.97; H, 4.16; N, 9.64. Found: C, 61.83; H, 4.14; N, 9.63.

6-Chloro-2-chloromethyl-4-(2-fluorophenyl)-1,2-dihydroquinazoline 3-Oxide (**2b**).

A solution of 400 g. (3.2 moles) of chloroacetaldehyde and 400 ml. (0.6 mole) of 1.5 *N* hydrochloric acid was refluxed for 15 minutes, and added to a stirred mixture of 499 g. (2 moles) of 2-amino-5-chloro-2-fluorobenzophenone (10), 180 g. (1.1 moles) of hydroxylamine sulfate and 2.2 l. of ethanol. After 1.5 hours, 1 l. of water and 700 g. of ice was added, and the precipitate was filtered and washed with 2 l. of water to give 556 g. of product. The combined filtrates were evaporated and the residue was recrystallized from a mixture of dichloromethane and methanol to give an additional 48 g. of product for a total yield of 604 g. (93%). A sample was recrystallized from a mixture of dichloromethane and hexane to give **2b** as yellow prisms, m.p. 169-171°.

Anal. Calcd. for $C_{15}H_{11}Cl_2FN_2O$: C, 55.41; H, 3.41; N, 8.62. Found: C, 55.09; H, 3.75; N, 8.37.

2-Chloromethyl-4-(2-fluorophenyl)-6-nitro-1,2-dihydroquinazoline 3-Oxide (**2c**).

A mixture of 100 g. (0.8 mole) of chloroacetaldehyde dimethylacetal and 100 ml. of 1.5 *N* hydrochloric acid was heated under reflux for 15 minutes and then cooled and added to a solution of 130 g. (0.5 mole) of 2-amino-2′-fluoro-5-nitrobenzophenone (10) and 46 g. (0.28 mole) of hydroxylamine sulfate in 1 l. of ethanol. The mixture was stirred at room temperature for 2 hours and then heated to reflux for 1.5 hours. The mixture was cooled and filtered. Recrystallization of the precipitate from a mixture of chloroform and methanol gave 146 g. (87%) of the pure product as yellow prisms, m.p. 220-224°.

Anal. Calcd. for $C_{15}H_{11}ClFN_3O_3$: C, 53.66; H, 3.30; N, 12.52. Found: C, 53.49; H, 3.32; N, 12.40.

2-Chloromethyl-4-(2-fluorophenyl)quinazoline 3-Oxide (**3a**).

A mixture of 100 g. (0.344 mole) of **2a**, 100 g. of activated manganese dioxide, and 1.5 l. of dichloromethane was stirred and refluxed for 8 hours. Another 20 g. of activated manganese dioxide was added and after 3 hours the reaction was filtered hot through Celite, which was then washed with 500 ml. of a 50/50 (v/v) mixture of methanol and dichloromethane. The combined filtrates were evaporated and the residue was crystallized from a mixture of dichloromethane and ether. The filtrates were concentrated and the residue was crystallized from a mixture of ethyl acetate and ether to give a combined yield of 82 g. (82%) of **3a** as yellow prisms, m.p. 139-142°.

Anal. Calcd. for $C_{15}H_{10}ClFN_2O$: C, 62.41; H, 3.49; N, 9.70. Found: C, 62.40; H, 3.50; N, 9.73.

6-Chloro-2-chloromethyl-4-(2-fluorophenyl)quinazoline 3-Oxide (**3b**).

To 5 g. (0.0153 mole) of **2b** in 175 ml. of dichloromethane was added 15 g. of activated manganese dioxide, and the reaction was stirred and refluxed for 3 hours. The reaction mixture was filtered through Celite which was then washed with 150 ml. of a 50/50 (v/v) mixture of dichloromethane and methanol. The combined filtrates were evaporated and the product was crystallized from methanol. Recrystallization from a mixture of dichloromethane and hexane gave 4 g. (80%) of **3b** as off-white prisms, m.p. 154-158°.

Anal. Calcd. for $C_{15}H_9Cl_2FN_2O$: C, 55.75; H, 2.81; N, 8.67. Found: C, 55.95; H, 3.09; N, 8.66.

2-Chloromethyl-4-(2-fluorophenyl)-6-nitroquinazoline 3-Oxide (**3c**).

A solution of 142 g. (0.423 mole) of **2c** in 2.3 l. of dichloromethane was treated with 400 g. of manganese dioxide, and after stirring for 18 hours, the solution was filtered. The manganese dioxide was washed with 600 ml. of tetrahydrofuran and 600 ml. of dichloromethane. The combined filtrates were concentrated to 400 ml. and 1 l. of ether was added. This was cooled and filtered to give 115 g. (82%) of product. A sample was recrystallized from a mixture of dichloromethane and methanol to give the pure product as pale yellow prisms, m.p. 127-130°.

Anal. Calcd. for $C_{15}H_9ClFN_3O_3$: C, 53.99; H, 2.72; N, 12.59. Found: C, 53.80; H, 2.72; N, 12.42.

1,3-Dihydro-5-(2-fluorophenyl)-2-nitromethylene-2*H*-1,4-benzodiazepine 4-Oxide (**4a**).

To a stirring solution of 75 ml. (1.4 moles) of nitromethane in 250 ml. of dimethyl sulfoxide under nitrogen was slowly added 8.8 g. (0.0381 mole) of lithium amide. After 30 minutes, the reaction mixture was cooled to 5° in an ice bath, and 50 g. (0.173 mole) of **3a** was added slowly keeping the temperature below 8° After the addition was complete, the mixture was stirred for 10 minutes more in the ice bath and for 3.5 hours at room temperature. It was then added with stirring to 2 l. of an ice-water mixture containing 50 ml. of acetic acid. After 30 minutes, the solution was filtered and the precipitate was washed with water. The precipitate was refluxed with 300 ml. of ethanol for 15 minutes, cooled and filtered to give 45.6 g. (84%) of product. A sample was recrystallized from a mixture of tetrahydrofuran and hexane to give **4a** as yellow rods, m.p. 209-212° dec.

Anal. Calcd. for $C_{16}H_{12}FN_3O_3$: C, 61.34; H, 3.86; N, 13.41. Found: C, 61.41; H, 3.79; N, 13.58.

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

To a solution of 7.5 ml. (0.14 mole) of nitromethane in 25 ml. of dimethyl sulfoxide under nitrogen was added with stirring 0.78 g. (0.0341 mole) of lithium amide. After 30 minutes, the mixture was cooled in an ice bath to 5°, and 5 g. of **3b** (0.0155 mole) was added slowly keeping the temperature below 8°. After 10 minutes, the reaction mixture was removed from the ice bath, stirred for 3.5 hours at room temperature, and then poured into 140 ml. of ice and water containing 5 ml. of acetic acid. After 0.5 hours, the solution was filtered. The precipitate was first washed with water and then refluxed in 50 ml. of ethanol for 5 minutes, cooled and filtered to yield 5 g. (93%) of product. A sample was recrystallized from a mixture of *N,N*-dimethylformamide and water to give **4b** as pale yellow prisms, m.p. 240-243°.

Anal. Calcd. for $C_{16}H_{11}ClFN_3O_3$: C, 55.27; H, 3.19; N, 12.08. Found: C, 55.22; H, 3.20; N, 12.17.

1,3-Dihydro-5-(2-fluorophenyl)-7-nitro-2-nitromethylene-2*H*-1,4-benzodiazepine 4-Oxide (**4c**).

A mixture of 500 ml. of dimethylsulfoxide and 75 ml. (1.4 moles) of nitromethane was stirred under nitrogen and treated with 15.6 g. (0.678 mole) of lithium amide. After 30 minutes, the solution was cooled to 5° and 104 g. (0.31 mole) of **3c** was added slowly, keeping the temperature below 8°. After 68 hours at room temperature, the reaction was poured into a mixture of 2.5 l. of ice and water and 25 ml. of acetic acid, and the solution was filtered. The gummy precipitate was dissolved in 1 l. of dichloromethane which was washed with dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from ethyl acetate to give 20 g. of product. The filtrates were evaporated and the residue was dissolved in dichloromethane. The solution was filtered through a sintered glass funnel containing 200 g. of Florisil. The Florisil was eluted with dichloromethane (600 ml.), ether (600 ml.) and ethyl acetate (1.2 l.). The ether and ethyl acetate fractions were combined and concentrated to give an additional 20 g. of product for a total yield of 40 g. (36%). A sample was recrystallized from a mixture of tetrahydrofuran and hexane to give the pure product as yellow prisms, m.p. 216-220°.

Anal. Calcd. for $C_{16}H_{11}FN_4O_5$: C, 53.64; H, 3.09; N, 15.64. Found: C, 53.77; H, 3.32; N, 15.62.

7-Chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-1,4-benzodiazepine 4-Oxide (**4d**).

Method A from Compound **3d**.

To a solution of 1 ml. (0.0193 mole) of nitromethane in 13 ml. of dimethyl sulfoxide under nitrogen was added 0.17 g. (0.00722 mole) of lithium amide, and the reaction was stirred for 30 minutes and then cooled to 15°. To the reaction was added 1 g. (0.00328 mole) of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (**3d**) (11) and after 18 hours at room temperature, the solution was poured onto 5.0 g. of ice, treated with charcoal and filtered through Celite. The charcoal was washed with water and the combined filtrates were acidified with acetic acid and filtered. Recrystallization of the precipitate from methanol gave 0.62 g. (57%) of **4d** as yellow rods, m.p. 251-254°. A mixture melting point with an authentic sample synthesized by an alternate route (12) showed no depression.

Method B from Compound **9e** (7).

A solution of 9.5 ml. of nitromethane in 100 ml. of dimethylformamide was stirred under nitrogen and treated with 5.0 g. (0.045 mole) of potassium *t*-butoxide at 0.10°. The resulting mixture was stirred at room temperature for 1 hour. The mixture was then cooled in an ice bath and 5.1 g. (0.015 mole) of 6-chloro-2-dichloromethyl-1,2-dihydro-4-phenylquinazoline 3-oxide (**9e**) (7) added slowly at a temperature $<9°$. The reaction mixture was

stirred at room temperature for 17 hours.

The mixture was poured into a mixture of ice water and dichloromethane and then made slightly acid with glacial acetic acid. The aqueous phase was extracted three times with dichloromethane. The organic layers were combined, washed with water and brine, dried, filtered and concentrated to dryness *in vacuo* giving an amber residue. Crystallization from boiling ethanol afforded 1.4 g. (29%) of **4d** as yellow prisms, m.p. and m.m.p. with an authentic sample 245-248° dec.

6-Chloro-4-phenyl-2-thiocyanatomethylquinazoline 3-Oxide (**5**).

To a solution of 6.12 g. (20 mmoles) of **3d** in 50 ml. of DMSO stirred at room temperature was added dropwise a solution of 4.0 g. (40 mmoles) of potassium thiocyanate. After stirring overnight, the mixture was poured into ice water, and the resulting precipitate filtered. After recrystallization from methanol, 5.6 g. (85%) of **5** was obtained as yellow prisms, m.p. 153-155°. The analytical sample was obtained by recrystallization from the same solvent, m.p. 154.5-156°; uv max (ethanol): 235 nm (ε, 25,000), 269 34,400), shoulder 310 (5,700), and shoulder 370 (4, 950); ir (potassium bromide): 2160 cm^{-1} (SCN); nmr (DMSO-d_6): δ 4.75 (2H, s, CH_2), 7.37-8.27 (8H, m, C_6H_5 and C_6H_3); mass spectrum: m/e 327 (M^+), 310 (M^+-OH), 255 (M^+-CH_2SCN), and 239 (M^+-CH_2SCNO).

Anal. Calcd. for $C_{16}H_{10}ClN_3OS$: C, 58.63; H, 3.08; N, 12.82. Found: C, 58.58; H, 3.08; N, 13.03.

2-Cyano-1,2,3-tris(6-chloro-4-phenylquinazoline-2-yl)propane 3-Oxide (**6**).

A solution of 1.18 g. (24 mmoles) of sodium cyanide in 12 ml. of water and 12 ml. of DMSO was added dropwise to a solution of 7.2 g. (23.5 mmoles) of **3d** in 100 ml. of DMSO. After stirring overnight at room temperature, the precipitate which had formed was filtered, washed with water and allowed to air-dry. The yellow solid was filtered through a short column of silica gel using ethyl acetate as the eluent. The crude product obtained upon removal of solvent was recrystallized from acetone-hexane to give 3.7 g. (57%) of **6** as a yellow powder, m.p. 248-251°. The analytical sample was prepared by recrystallization from the same solvent, m.p. 250-252°; uv max (ethanol): 234 nm (ε, 23,100), max 267 (25,320), shoulder 310 (8,700), and shoulder 360 (5,100); ir (chloroform): 3000, 1595, 1540, 1465, 1345, 1310, 1280, 1150, 1070, 820 and 685 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 4.68 (4H, bs. CH_2), and 7.27-7.97 (24 H, m, 3 x C_6H_5 and 3 x C_6H_3); mass spectrum: m/e 799 (M^+-O_2), 783 (M^+-O_3), 548, 531, 254 and 77.

Anal. Calcd. for $C_{46}H_{28}Cl_3N_7O_3$: C, 66.32; H, 3.39; N, 11.79. Found: C, 66.43, 66.27; H, 3.39, 3.33; N, 11.66, 11.61.

6-Chloro-2-[(3-nitro-2-butyl)methyl]-4-phenylquinazoline 3-Oxide (**7**).

A solution of 10 ml. of nitroethane in 50 ml. of dimethyl sulfoxide under nitrogen was treated with 0.8 g. (0.0348 mole) of lithium amide. The mixture was stirred for 30 minutes, cooled to 10° and then 5 g. (0.0163 mole) of **3d** was added. After 20 hours at room temperature, the reaction mixture was poured onto ice, acidified with acetic acid and filtered. The precipitate was dissolved in 100 ml. of dichloromethane, which was washed with 75 ml. of water, saturated solution of brine (50 ml.), and dried. The solution was concentrated and chromatographed over 100 g. of Florisil. It was eluted with 1 l. of dichloromethane and 500 ml. of ether which were combined and evaporated. The residual oil was crystallized from a mixture of ether and petroleum ether and recrystallized from a mixture of dichloromethane and hexane to give 1.0 g. (17%) of **7** as off-white rods, m.p. 109-111°; ir (chloroform): 1550, 1360 cm^{-1} (NO_2); nmr (deuteriochloroform): δ 1.15 (3H, d, CH_3CH), 1.61, 1.65 (3H, 2d. CH_3CH), 3.33 (3H, m, CH_2CH), 4.83 (1H, m, $CHNO_2$), 7.63-8.03 (8H, m, aromatic); mass spectrum: m/e 371 (M^+), 345 (M^+-O), 325 (M^+-NO_2), 254 (M^+, $C_5H_{10}NO_2$).

Anal. Calcd. for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30. Found: C, 61.36; H, 4.75; N, 11.40.

6-Chloro-2-[4-nitro-3-hexyl)methyl]-4-phenylquinazoline 3-Oxide (**8**).

A solution of 5 ml. of 1-nitropropane and 50 ml. of dimethyl sulfoxide under nitrogen was treated with 3.9 g. (0.0348 mole) of potassium *t*-butoxide. The solution was stirred for 30 minutes, cooled to 16° and treated with 5.0 g. (0.0164 mole) of **3d**. After 5 hours at room temperature, the reaction mixture was poured over ice and extracted with 100 ml. of dichloromethane, which was washed with 100 ml. of water, 75 ml. of a saturated brine solution and dried. The solution was concentrated and filtered through 100 g. of Florisil in a sintered glass funnel using dichloromethane (750 ml.) as the eluent. The filtrates were evaporated, and the residue crystallized from a mixture of ether and hexane. Recrystallization from the same solvents gave 1.1 g., 16% of **8** as off-white prisms, m.p. 115-118°; uv max (2-propanol): 231 nm (ε, 26,000), 266 (ε, 27,000), shoulder 310 (5,500), 370 (4.500); ir (chloroform): 1550 and 1360 cm^{-1} (NO_2); nmr (deuteriochloroform): δ 0.98 (6H, t, 2 CH_3CH_2), 1.59 (2H, quintet, CH_2CH_3), 2.08 (2H, m, CH_2CH_3), 2.87 (1H, m, $CHCHNO_2$), 3.35 (2H. m, CH_2Ar), 4.68 (1H. m, $CHNO_2$), 7.42-7.93 (8H, m, aromatic); mass spectrum: m/e 398 (M^+), 388 (M^+-O), 382 (M^+-OH), 369 (M^+-NO) and 353 (M^+-NO_2).

Anal. Calcd. for $C_{21}H_{22}ClN_3O_3$: C, 63.07; H, 5.55; N, 10.51. Found: C, 63.11, 63.09; H, 5.77, 5.54; N, 10.54, 10.48.

6-Chloro-2-(1,1-dichloroethyl)-1,2-dihydro-2-(2-fluorophenyl)quinazoline 3-Oxide (**9f**).

A mixture of 49.9 g. (0.2 mole) of **1b**, 38.0 g. (0.3 mole) of 2,2-dichloropropanal (13), 18.0 g. (0.11 mole) of hydroxylamine sulfate and 500 ml. of 2B ethanol was stirred at room temperature for 2 days. The mixture was diluted with 200 ml. of 10% aqueous sodium carbonate solution with vigorous agitation. A gummy material precipitated from solution and the solution was diluted with 1.0 l. of ice-water. The solution was extracted with dichloromethane (3 x 100 ml.). The extracts were combined, dried, filtered and concentrated to dryness *in vacuo*. The residue was crystallized from dichloromethane and petroleum ether giving 32.0 g. (43%) of **9f** as yellow prisms, m.p. 199-201° dec.

Anal. Calcd. for $C_{16}H_{12}Cl_3FN_2O$: C, 51.43; H, 3.24; N, 7.50. Found: C, 51.67; H, 3.39; N, 7.50.

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-3-methyl-2-nitromethylene-2*H*-1,4-benzodiazepine 4-Oxide (**10f**).

Method A from Compound **4b**.

Potassium *t*-butoxide, 3.37 g. (0.03 mole) was added to a stirred suspension of 3.5 g. (0.01 mole) of **4b** in 100 ml. of dimethylformamide cooled to -20°. After stirring under nitrogen for 10 minutes at this temperature, 2.13 g. (0.015 mole) of methyl iodide was added and stirring was continued for 10 minutes. The reaction mixture was neutralized by the addition of glacial acetic acid and was partitioned between water and dichloromethane. The organic phase was separated, dried over sodium sulfate and evaporated. The residue was crystallized from methylene chloride/ethyl acetate to yield 3.1 g. (87%) of **10f** as yellow crystals with m.p. 215-218°. The analytical sample was recrystallized from the same solvents,

m.p. 216-218°.

Anal. Calcd. for $C_{17}H_{13}ClFN_3O_3$: C, 56.44; H, 3.62; N, 11.62. Found: C, 56.69; H, 3.67; N, 11.89.

Method B from Compound **9f**.

Nitromethane (3.8 ml.) was added to 50.0 ml. of dimethylformamide with stirring and under an atmosphere of nitrogen. The solution was chilled to 0° and 1.3 g. (0.012 mole) of potassium *t*-butoxide was added in portions. The temperature was maintained at 0° to 10° by means of an ice water bath. The mixture was stirred at room temperature for 1 hour.

The mixture was chilled to 5° with stirring and 2.2 g. (0.006 mole) of the quinazoline **9f** was added at 5°-9° in portions. After the addition had been completed, the mixture was stirred at room temperature for 17 hours.

The reaction mixture was poured into ice water and dichloromethane. The mixture was neutralized with glacial acetic acid. The dichloromethane was washed with water, brine and dried. After concentration an amber residue was obtained which was crystallized with ethyl acetate. The crystals were collected and dried giving 0.8 g. (39%) of **10f** as yellow prisms, m.p. 198-200° dec. Recrystallization from a mixture of dichloromethane and ethyl acetate gave pure **10f**; m.p. and m.m.p 216-218°dec.

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REFERENCES AND NOTES

(1) Paper LXXII, N. W. Gilman, J. F. Blount, and R. I. Fryer, *J. Org. Chem.*, **41**, No. 4, 737 (1976).

(2) See for example G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).

(3) G. F. Field and L. H. Sternbach, U. S. patent 3,515,724, January 2, 1970.

(4) G. F. Field, W. Zally and L. H. Sternbach, *J. Org. Chem.*, **30**, 3957 (1965).

(5) L. H. Sternbach, *Angew. Chem.*, **83**, 70 (1971).

(6) M. Gordon, M. L. DePamphilis and C. E. Griffin, *J. Org. Chem.*, **28**, 698 (1963).

(7) G. F. Field and L. H. Sternbach, U. S. patent 3,594,364, July 20, 1971.

(8) R. I. Fryer, J. V. Earley and L. H. Sternbach, *J. Org. Chem.*, **34**, 649 (1969).

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

(10) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

(11) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(12) Prepared by Dr. A. Walser, unpublished.

(13) C. R. Dick, *J. Org. Chem.*, **27**, 272 (1962).