Quinazolines and 1,4-Benzodiazepines LXVIII (1). 5-Heterocyclic-substituted Benzodiazepinones

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The synthesis of a number of new 1,4-benzodiazepin-2-ones containg the 2-thiazolyl, 5-isothiazolyl, 1-methyl-2-imidazolyl, 1-methyl-5-pyrazolyl, and 3,5-dimethyl-4-isoxazolyl groups in the 5-position of the benzodiazepine ring are described.

Although the 1,4-benzodiazepines represent one of the most important classes of drugs in current use (3), relatively few such compounds possessing a heterocyclic ring in the 5-position of the benzodiazepine ring are known (4). As a continuation of our search for medicinally useful benzodiazepines, we have synthesized a variety of 5-(2-thiazolyl)-, 5-(5-isothiazolyl)-, 5-(1-methyl-2-imidazolyl)-, 5-(1-methyl-5-pyrazolyl)-, and 5-(3,5-dimethyl-4-isoxazolyl)-1,4-benzodiazepinones.

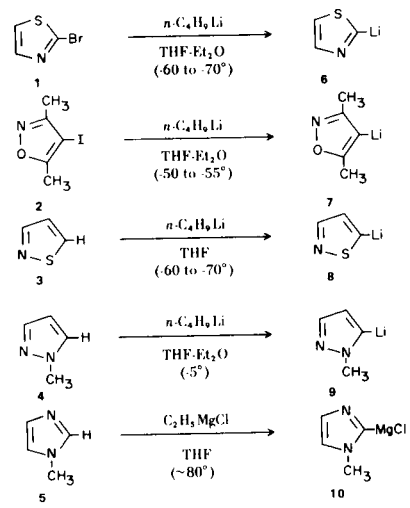
Although there are many routes for the synthesis of benzodiazepinones (5), considerations of reactivity, compound availability, and synthetic economy led us to favor the general route depicted in Schemes I and II.

The first two steps in this synthetic scheme, the *in situ* formation of organometallic derivatives of the desired heterocycles and their subsequent addition to various 2-nitrobenzaldehydes to give the requisite alcohols, were, in practice, the most difficult to effect in good yield.

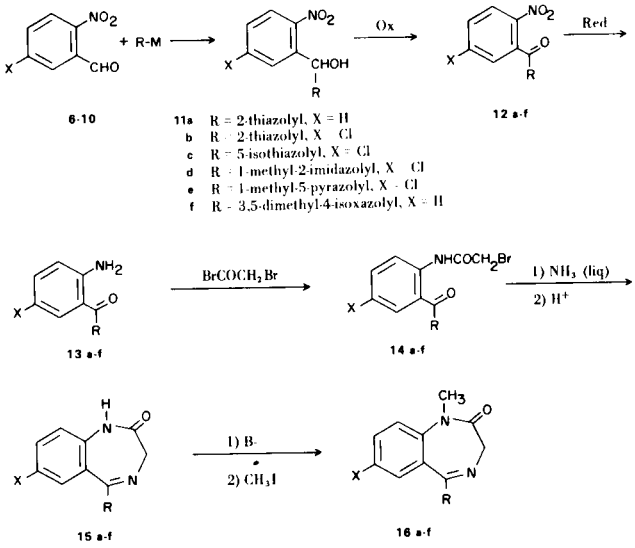
The desired organometallic derivatives **6-10** were prepared either by halogen-metal interchange or by metallation (hydrogen-metal interchange) of the parent heterocycles (Scheme I). Thus, 2-thiazolyllithium (**6**) was prepared from 2-bromothiazole by treatment with *n*-butyllithium at -70° (6), and 3,5-dimethylisoxazolyllithium (**7**) was prepared similarly by treatment of 4-iodo-3,5-dimethylisoxazole with *n*-butyllithium at -55°. 5-Isothiazolyllithium (**8**) and 1-methyl-5-pyrazolyllithium (**9**) were prepared by metalation of the corresponding heterocycles with *n*-butyllithium at -60° and -5°, respectively (7,8). Finally, 1-methyl-2-imidazolylmagnesium chloride (**10**) was obtained by metalation of 1-methyl-2-imidazole with ethylmagnesium chloride at *ca.* 80° (9).

Reaction of these metallated heterocycles with the appropriate aldehydes at low temperature (-30 to -60°) afforded the desired alcohols **11a-f**. The yields in these

Scheme I



Scheme II

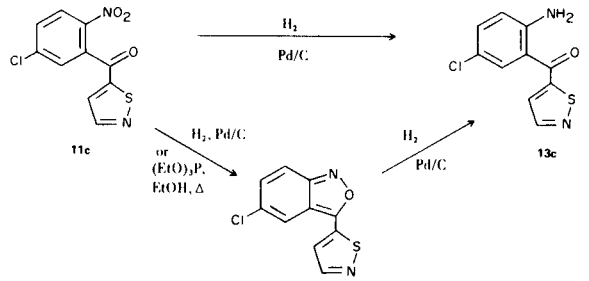


11a R = 2-thiazolyl, X = H
b R = 2-thiazolyl, X = Cl
c R = 5-isothiazolyl, X = Cl
d R = 1-methyl-2-imidazolyl, X = Cl
e R = 1-methyl-5-pyrazolyl, X = Cl
f R = 3,5-dimethyl-4-isoxazolyl, X = H

heterogeneous reactions were greatly dependent upon (a) the maintainance of the proper reaction temperature, (b) the effectiveness of the stirring, and (c) the volume of the solvent used. If the reaction mixtures were allowed to become too concentrated, the yields of the alcohols were greatly diminished presumably because of both precipitation of the metallated heterocycles and the increased solution viscosity with concommitant decrease in the stirring efficiency.

The heterocyclic nitroalcohols synthesized in this fashion were oxidized to the corresponding ketones **12a-f** in excellent yield with chromium trioxide in glacial acetic acid. The 2-nitrophenylketones thus produced were then reduced in good yield to the corresponding 2-aminophenylketones. Reduction of isothiazolylnitroketone **11c** gave either the desired amino ketone **13c** or the corresponding 2,1-benzisoxazole **17** which in turn, could be reduced to **13c** (Scheme III). While no products resulting from hydrogenolysis of the S-N bond were obtained in this system, the isoxazolylnitroketone **12f** was very susceptible to over-reduction *via* cleavage of the oxygen-nitrogen bond (10).

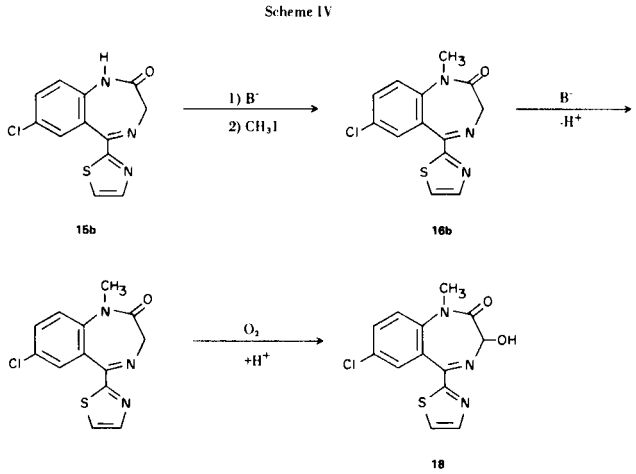
Scheme III



Elaboration of the benzodiazepinones form the 2-aminophenylketones was accomplished in the standard fashion *via* bromoacetylation, conversion of the resulting 2-bromoacetanilides to the corresponding (uncharacterized) 2-aminoacetanilides with liquid ammonia, acid-catalyzed cyclization to the corresponding benzodiazepinones, and, finally, *N*-methylation to give the 1-methylbenzodiazepinones (Scheme IV). Only the last step in this sequence, the *N*-methylation of the 1*H*-benzodiazepinones, was troublesome. In practice, the choice of the base and solvent system used to form the *N*-anion prior to methylation was critical and the yields of the 1-methylbenzodiazepinones thus obtained were quite dependent on the base and solvent system used (see Experimental).

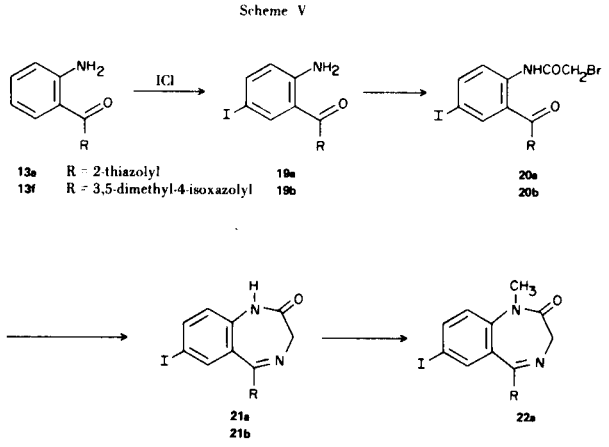
The methylation of benzodiazepinone **15b** in the presence of air (*in lieu* of an inert atmosphere) resulted in the formation of the 3-hydroxy-1-methylbenzodiazepinone **18** as a major by-product (Scheme IV). This reaction, which probably involves the initial formation of benzodiazepinone **16b**, removal of a proton from the 3-position, and attack by oxygen on the resulting carbanionic center, was not further investigated (11).

Scheme IV



The preparation of the 7-iodobenzodiazepinones **21a**, **21b**, and **22a** required the iodoaminoketones **19a** and **19b** which were prepared from the aminoketones **13a** and **13f** by direct iodination with iodine monochloride. In each instance only the desired monoiodo isomer (in which iodination occurred *para* to the amino group) was isolated (Scheme V).

Scheme V



EXPERIMENTAL

All new compounds possess infrared, ultraviolet, nmr, and mass spectral data in agreement with their assigned structures. Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected.

Reactions involving moisture- and/or oxygen-sensitive compounds were carried out in dry glassware under an argon atmosphere. Tetrahydrofuran (THF) was reagent grade (Fisher Scientific Co.) and was dried over type 5A molecular sieves. Diethyl ether (ether) was Mallinckrodt analytical reagent and was used without additional drying. *N,N*-dimethylformamide (DMF) was reagent grade (Fisher) and was dried over type 4A molecular

sieves. 1,2-Dimethoxyethane (DME) was distilled from sodium prior to use. *n*-Butyllithium (1.6*M* in hexane, Foote Mineral Company) and ethylmagnesium chloride (3*M* in THF, Alfa Inorganics-Ventron) were used as received.

All solutions were dried over powdered calcium sulfate (Drierite), and all solvent removal or concentration was done on a Büchi Rotavapor-R using aspirator vacuum (15-25 mm). Column chromatography was done on 70-325 mesh, neutral silica gel 60 (E. Merck). Thin layer chromatography (tlc) was done on precoated plates of silica gel F-254 (layer thickness 0.25 mm, E. Merck) which were equilibrated with atmospheric moisture prior to use.

Because of the similarity of many of the experimental procedures used in the preparation of the various benzodiazepinones and their precursors, only representative experimental procedures will be presented in full except in those instances in which marked variations from the normal experimental procedures were employed.

α-(2-Nitrophenyl)-2-thiazolemethanol (**11a**).

A cooled (-70°) vigorously stirred solution of 164 g. (1.0 mole) of 2-bromothiazole (12) in *ca.* 2.5 l. of ether was treated with 625 ml. (1.0 mole) of 1.6*M* *n*-butyllithium in hexane over a 1 hour period; the temperature was maintained at -65 to -60° during the addition. The resultant tan suspension was stirred at -70° for 30 minutes, and a solution of 121 g. (0.8 mole) of 2-nitrobenzaldehyde in 500 ml. of THF was added at -70 to -65° over a 1 hour period. After an additional 1.5 hours at -70° and 15 minutes at -55°, the reaction mixture was poured, with stirring, into a mixture of 2 l. of water containing 200 g. of ammonium chloride and 2 l. of methylene chloride. The *p*H was adjusted to 7-8, and the methylene chloride layer was removed. The aqueous phase was extracted with four 500 ml. portions of methylene chloride, and the combined organic extracts washed with water and brine, dried, and concentrated. The residue was slurried in ether, filtered, and dried yielding 138.3 g. of off-white product, m.p. 127-130°. A second crop of product weighing 7.3 g., m.p. 126-128°, was collected by further concentration of the filtrate for a combined yield of 145.6 g. (77%).

An analytical sample, m.p. 129-131°, was obtained by recrystallization from benzene.

Anal. Calcd. for $C_{10}H_8N_2O_3S$: C, 50.84; H, 3.41; N, 11.86. Found: C, 50.81; H, 3.36; N, 12.15.

2-Nitrophenyl 2-Thiazolyl Ketone (**12a**).

A solution of 74.8 g. (0.316 mole) of **11a** in 400 ml. of glacial acetic acid was heated to 60° and treated in portions with 63 g. (0.63 mole) of chromium trioxide; the temperature of the reaction mixture was allowed to rise to 90-100° and was maintained at 100° for 15 minutes after the completion of the addition of the oxidant. The solution was cooled to 20° and poured, with stirring, into 2 l. of water and 500 ml. of methylene chloride. The methylene chloride layer was separated and the aqueous phase extracted with three 500 ml. portions of methylene chloride. The combined organic extracts were washed with 2*N* sodium hydroxide, and water, dried, and concentrated; filtration afforded 64.3 g. (87%) of product as an off-white solid, m.p. 123-126°.

An analytical sample, m.p. 125-127°, was prepared by recrystallization from methanol.

Anal. Calcd. for $C_{10}H_6N_2O_3S$: C, 51.27; H, 2.58; N, 11.96. Found: C, 50.89; H, 2.52; N, 12.13.

2-Aminophenyl 2-Thiazolyl Ketone (**13a**)

Catalytic hydrogenation (Parr apparatus) of a solution of 70.3 g. (0.3 mole) of **12a** in *ca.* 1.5 l. of THF over 10.0 g. of 10% palladium-on-charcoal (autogeneous temperature, *ca.* 50 psig, 16 hours) followed by removal of the catalyst and the THF gave an oil which was dissolved in the minimum amount of methylene chloride; addition of hexane gave a yellow precipitate which was filtered, washed with hexane, and dried affording 50.3 g. of product, m.p. 77-81°. Cooling of the filtrate gave an additional 9.2 g. of product, m.p. 77-81°, for a total yield of 59.5 g. (98%).

An analytical sample, m.p. 80-82°, was prepared by recrystallization from benzene-hexane.

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.81; H, 3.95; N, 13.71. Found: C, 58.80; H, 3.84; N, 13.54.

2-Bromoacetamidophenyl 2-Thiazolyl Ketone (**14a**).

A stirred mixture of 10.3 g. (0.05 mole) of **13a** in 250 ml. of methylene chloride, 100 ml. of 2*N* sodium carbonate, and 250 ml. of saturated sodium bicarbonate was cooled to 5° and treated over a 10 minute period with 20.2 g. (0.10 mole) of bromoacetyl bromide while the temperature was maintained at 5-7°. The mixture was stirred for an additional 2 hours and poured into 200 ml. of water and 200 ml. of methylene chloride. The methylene chloride phase was removed, the aqueous phase was washed with two 100 ml. portions of methylene chloride, and the combined methylene chloride extracts were washed with water and brine and then dried. Removal of the solvent under reduced pressure afforded 15.2 g. (94%) of yellow product, m.p. 90-93°.

An analytical sample, m.p. 91-93°, was prepared by recrystallization from ether-hexane.

Anal. Calcd. for $C_{12}H_9BrN_2O_2S$: C, 44.32; H, 2.79; N, 8.61. Found: C, 44.01; H, 2.50; N, 8.56.

1,3-Dihydro-5-(2-thiazolyl)-2*H*-1,4-benzodiazepin-2-one (**15a**).

A solution of 13.0 g. (0.04 mole) of **14a** in 100 ml. of methylene chloride was added, with stirring, to 200 ml. of liquid ammonia (maintained at -78°) over a 20 minute period. The solution was stirred at reflux for 6 hours, the cooling bath was removed, and the ammonia was allowed to evaporate overnight. The methylene chloride solution was filtered, the solvent was removed, and the residue was dissolved in 150 ml. of methanol containing 4.6 ml. of glacial acetic acid. The solution was heated at reflux for 4 hours, cooled, treated with 25 ml. of saturated sodium bicarbonate, and poured, with stirring, into 750 ml. of water giving, after filtration and drying, 8.8 g. (91%) of white product, m.p. 243-246° dec.

An analytical sample, m.p. 247-248° dec. was prepared by recrystallization from chloroform-hexane.

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.02; H, 3.64; N, 17.16.

1,3-Dihydro-1-methyl-5-(2-thiazolyl)-2*H*-1,4-benzodiazepin-2-one (**16a**).

A stirred, cooled (-5°) solution of 6.1 g. (0.025 mole) of **15a** and 1.9 g. of 2-methoxyethanol in 20 ml. of DMF and 200 ml. of DME was treated with 1.2 g. (0.028 mole) of sodium hydride (57% dispersion in mineral oil). The resulting yellow solution was stirred at 0° for 2 hours, treated with 3.9 g. (0.028 mole) of methyl iodide, and then stirred at 0° for 0.5 hour and at 10° for 20 hours.

The reaction mixture was concentrated, and the crude product was purified by chromatography on 75 g. of silica gel (benzene elution) followed by recrystallization from methylene chloride ether to give 2.1 g. (33%) of white product, m.p. 185-188°.

An analytical sample, m.p. 187-190°, was prepared by recrystallization from methylene chloride-ether.

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.90; H, 4.31; N, 16.34. Found: C, 60.84; H, 4.19; N, 16.21.

α-(5-Chloro-2-nitrophenyl)-2-thiazolemethanol (**11b**).

This material was prepared in the same fashion as was alcohol **11a**. From 164 g. (1.0 mole) of 2-bromothiazole, 1.0 mole of *n*-butyllithium, and 152 g. (0.82 mole) of 5-chloro-2-nitrobenzaldehyde, 153 g. (69%) of yellow product, m.p. 130-136° was obtained.

An analytical sample, m.p. 137-139°, was prepared by recrystallization from benzene-hexane.

Anal. Calcd. for $C_{10}H_7ClN_2O_3S$: C, 44.37; H, 2.61; N, 10.35. Found: C, 44.17; H, 2.33; N, 10.17.

5-Chloro-2-nitrophenyl 2-Thiazolyl Ketone (**12b**).

Oxidation of 92.3 g. (0.34 mole) of **11b** with 68 g. (0.68 mole) of chromium trioxide in 500 ml. of glacial acetic acid yielded 76.9 g. (84%) of yellow product, m.p. 129-133°.

An analytical sample, m.p. 131-133°, was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_5ClN_2O_3S$: C, 44.70; H, 1.87; N, 10.42. Found: C, 44.83; H, 1.71; N, 10.39.

2-Amino-5-chlorophenyl 2-Thiazolyl Ketone (**13b**).

Catalytic hydrogenation of 32.2 g. (0.12 mole) of **12b** in 350 ml. of THF over 3.2 g. of 10% palladium-on-charcoal (autogeneous temperature; *ca.* 50 psig, 20 hours) followed by removal of the catalyst and solvent afforded an orange semi-solid which was slurried with 300 ml. of ether-hexane (2:1 v/v) and filtered to give 20.3 g. (71%) of red-orange product, m.p. 158-162° dec.

An analytical sample, m.p. 166-167° dec., was prepared by recrystallization from benzene-hexane.

Anal. Calcd. for $C_{10}H_7ClN_2OS$: C, 50.32; H, 2.96; N, 11.73. Found: C, 50.20; H, 2.80; N, 11.64.

2-(2-Bromoacetamido)-5-chlorophenyl 2-Thiazolyl Ketone (**14b**).

Bromoacetylation of 22.5 g. (0.094 mole) of **13b** with 38.4 g. (0.19 mole) of bromoacetyl bromide afforded 23.5 g. (70%) of yellow product, m.p. 140-141°.

An analytical sample, m.p. 141-142°, was prepared by recrystallization form benzene-hexane.

Anal. Calcd. for $C_{12}H_8BrClN_2O_2S$: C, 40.08; H, 2.24; N, 7.79. Found: C, 40.02; H, 2.16; N, 7.74.

7-Chloro-1,3-dihydro-5-(2-thiazolyl)-2*H*-1,4-benzodiazepin-2-one (**15b**).

A solution of 46 g. (0.13 mole) of **14b** in 1 l. of methylene chloride was added, with stirring, to 600 ml. of liquid ammonia (maintained at -78°) over a 2 hour period. After an additional 1 hour at -70°, the cooling bath was removed, and the ammonia was allowed to evaporate overnight. The suspension was poured into a mixture of 1 l. of water and 1 l. of methylene chloride, and the methylene chloride layer was removed, washed with water and brine, dried, and concentrated under reduced pressure.

The resultant solid was filtered, washed with ether, and dissolved in 1.5 l. of pyridine containing 30 g. of pyridine hydrochloride. The solution was stirred at 25° for 16 hours, diluted with 150 ml. of toluene, and the solvent removed under reduced pressure. The resultant solid was partitioned between methylene chloride and water, and the methylene chloride layer was removed, washed with water and brine, dried, concentrated to a volume of *ca.* 200 ml., and cooled to -25°. The precipitate thus obtained was filtered, washed with ether, and dried to give 25 g. (70%) of white product, m.p. 253-256°.

An analytical sample, m.p. 259-260°, was prepared by recrystallization from ethyl acetate-hexane.

Anal. Calcd. for $C_{12}H_8ClN_3OS$: C, 51.89; H, 2.90; N, 15.13. Found: C, 51.96; H, 2.76; N, 14.94.

7-Chloro-1,3-dihydro-1-methyl-5-(2-thiazolyl)-2*H*-1,4-benzodiazepin-2-one (**16b**).

A vigorously stirred, cooled (0°) solution of 22.3 g. (0.08 mole) of **15b** in 600 ml. of DME, 80 ml. of DMF, and 3.1 g. of 2-methoxyethanol was treated, in portions, with 5.1 g. (0.12 mole) of sodium hydride (57% dispersion in mineral oil). The yellow suspension was stirred at 0° for 2 hours and was then treated with a solution of 17.1 g. (0.12 mole) of methyl iodide in 200 ml. of DME over a period of 45 minutes. After 1 hour at 0° and 12 hours at 20°, the suspension was diluted with 100 ml. of water and concentrated to a volume of *ca.* 200 ml. One liter of water was added to the concentrate, and the aqueous solution was extracted with five 500 ml. portions of methylene chloride. The combined organic extracts were washed with water and brine, dried, and the solvent removed. The residue was washed with ether and then recrystallized from methylene chloride-methanol to give 19.9 g. (85%) of product as a white solid, m.p. 204-206°.

An analytical sample, m.p. 205-206°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{13}H_{10}ClN_3OS$: C, 53.51; H, 3.45; N, 14.40. Found: C, 53.22; H, 3.53; N, 14.36.

7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-(2-thiazolyl)-2*H*-1,4-benzodiazepin-2-one (**18**).

Benzodiazepine **15b** (1.35 g.) was methylated as described in the preparation of **16b** except that the reaction was carried out in air *in lieu* of an argon atmosphere. The crude product (a brown oil) thus obtained was crystallized from ether-benzene to give 0.50 g. (33%) of product as an off-white solid, m.p. 221-224° dec; ir (chloroform): 3460 (OH) and 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.43 (3H, s, NCH_3), 4.75 (1H, d, J = 9.5 Hz, exchangeable with D_2O, CHO*H*), 5.05 (1H, d J = 9.5 Hz, C*H*OH), and 7.26-7.93 (5H, m aromatic and thiazole H).

An analytical sample, m.p. 224-225° dec., was prepared by recrystallization from THF-hexane.

Anal. Calcd. for $C_{13}H_{10}ClN_2OS$: C, 50.73; H, 3.27; N, 13.65. Found: C, 50.59; H, 3.39; N, 13.85.

2-Amino-5-iodophenyl 2-Thiazolyl Ketone (**19a**).

A solution of 75.0 g. (0.462 mole) of iodine monochloride in 120 ml. of chloroform was added to a vigorously stirred, cooled (-10°) solution of 47.1 g. (0.231 mole) of **13a** in 300 ml. of THF, 450 ml. of methanol, and 250 ml. of chloroform over a period of 45 minutes while the temperature was maintained at -10°. The dark solution was stirred at -10° for an additional 70 minutes and then poured into a stirred mixture of 1 l. of ice-water and 600 ml. of chloroform. The resultant mixture was treated with a solution of 30 g. of sodium sulfite in 200 ml. of water. The chloroform layer was removed; washed with 1*N* sodium hydroxide (300 ml.), water, and brine; dried; and concentrated under reduced pressure affording 45.9 g. of russet product, m.p. 139-141°. Three additional crops of product (12.0 g., m.p. 139-141°; 4.7 g., m.p. 139-140°; and 5.1 g., m.p. 137-139°) were obtained from the filtrate by successive cooling and concentration for a total yield of 67.7 g. (89%).

An analytical sample, m.p. 140-141°, was prepared by recrystal-

lization form emthylene chloride-hexane.

Anal. Calcd. for $C_{10}H_7IN_2OS$: C, 36.38; H, 2.14; N, 8.48. Found: C, 36.17; H, 2.23; N, 8.48.

2-(2-Bromoacetamido)-5-iodophenyl 2-Thiazolyl Ketone (**20a**).

Bromoacetylation of 44.6 g. (0.136 mole) of **19a** with 40.4 g. (0.20 mole) of bromoacetyl bromide yielded 55.9 g. (92%) of product, m.p. 151-154°.

An analytical sample, m.p. 152-154°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{12}H_8BrIN_2O_2S$: C, 31.95; H, 1.79; N, 6.21. Found: C, 32.16; H, 1.69; N, 6.16.

1,3-Dihydro-7-iodo-5-(2-thiazolyl)-2*H*-1,4-benzodiazepin-2-one (**21a**).

Treatment of 33.8 g. (0.075 mole) of **20a** with liquid ammonia followed by cyclization in methanol-acetic acid yielded 16.3 g. (95%) of product as a yellow solid, m.p. 265-267° dec.

An analytical sample, m.p. 269-271° dec., was prepared by recrystallization from methanol-methylene chloride.

Anal. Calcd. for $C_{12}H_8IN_3OS$: C, 39.04; H, 2.18; N, 11.38. Found: C, 39.01; H, 2.09; N, 11.36.

1,3-Dihydro-7-iodo-1-methyl-5-(2-thiazolyl)-2*H*-1,4-benzodiazepin-2-one (**22a**).

A vigorously stirred, cooled (0°) suspension of 16.1 g. (0.044 mole) of **21a** in 225 ml. of THF containing 18 ml. of 2-propanol was treated, in portions, with 5.4 g. (0.048 mole) of potassium *t*-butoxide; the temperature was maintained at 3-4° during the addition (*ca.* 15 minutes). The resultant yellow solution was stirred at 0° for 1 hour and treated with 7.1 g. (0.05 mole) of methyl iodide in 50 ml. of THF over 15 minutes. The reaction mixture was stirred at 25° overnight and then treated with 5 ml. of concentrated ammonium hydroxide in 45 ml. of water. The mixture was concentrated to *ca.* 100 ml., 500 ml. of water was added, and the suspension was extracted with three 400 ml. portions of methylene chloride. The combined extracts were washed with water and brine, dried, and concentrated giving a yellow residue which was recrystallized from methylene chloride-ether giving, in two crops, 11.4 g. (69%) of product, m.p. 198-199° dec.

An analytical sample, m.p. 201-202° dec., was prepared by recrystallization from methylene chloride-ethanol.

Anal. Calcd. for $C_{13}H_{10}IN_3OS$: C, 40.75; H, 2.63; N, 10.97. Found: C, 40.76; H, 2.39; N, 11.01.

α-(5-Chloro-2-nitrophenyl)-5-isothiazolemethanol (**11c**).

A cooled (-70°), vigorously stirred solution of 127.5 g. (1.5 mole) of isothiazole in 2 l. of THF was treated with 940 ml. (1.51 mole) of 1.6*M* *n*-butyllithium over a 1.5 hour period; the temperature was maintained at -70 to -65° during the addition. The resultant brown mixture was stirred at -70° for 1 hour, and a solution of 185.5 g. (1 mole) of 5-chloro-2-nitrobenzaldehyde in 500 ml. of THF was added dropwise at -70 to -65° over a 45 minute period. After an additional 2.5 hours at -70 to -60°, the reaction mixture was poured, with stirring, into a solution of 500 g. of ammonium chloride in 2 l. of water. The *p*H was adjusted to 7-8, 1 l. of methylene chloride was added, and the organic layer was removed. The aqueous phase was extracted with six 500 ml. portions of methylene chloride, and the combined organic extracts were washed with water and brine, dried, and concentrated. The resultant amber oil was triturated with ether and allowed to crystallize; filtration, washing with ether, and drying afforded 125 g. (46%) of tan product, m.p. 112-115°.

An analytical sample, m.p. 115-116°, was prepared by recrystallization from methylene chloride-ether-hexane.

Anal. Calcd. for $C_{10}H_7ClN_2O_3S$: C, 44.37; H, 2.60; N, 10.35. Found: C, 44.50; H, 2.54; N, 10.29.

5-Chloro-2-nitrophenyl 5-Isothiazolyl Ketone (**12c**).

Oxidation of 128.9 g. (0.48 mole) of **11c** with 96 g. (0.96 mole) of chromium trioxide gave 111 g. (87%) of **23** as a light green solid, m.p. 109-112°.

An analytical sample, m.p. 111-113°, was prepared by recrystallization from chloroform-hexane.

Anal. Calcd. for $C_{10}H_5ClN_2O_3S$: C, 44.70; H, 1.88; N, 10.43. Found: C, 44.74; H, 1.72; N, 10.31.

3-(5-Isothiazolyl)-5-chloro-2,1-benzisoxazole (**17**).

A stirred solution of 26.9 g. (1 mole) of **12c** and 100 ml. of triethyl phosphite in 300 ml. of ethanol was heated at reflux, under argon, for 4 hours and allowed to stand at 0° overnight. The precipitated yellow solid was filtered, washed with ethanol, and dried yielding 22.8 g. (97%) of product, m.p. 184-187°.

An analytical sample, m.p. 185-187°, was prepared by recrystallization from DMF-ethanol.

Anal. Calcd. for $C_{10}H_5ClN_2OS$: C, 50.75; H, 2.13; Cl, 14.98; N, 11.84; S, 13.55. Found: C, 50.63; H, 1.89; Cl, 14.99; N, 11.85; S, 13.35.

2-Amino-5-chlorophenyl 5-Isothiazolyl Ketone (**13c**).

Catalytic hydrogenation of 40 g. (0.15 mole) of **12c** in 1.5 l. of ethanol over 6.7 g. of 10% palladium-on-charcoal (autogeneous temperature, *ca.* 50 psig, 18 hours) followed by removal of the catalyst and the solvent gave, in two crops, 33 g. (93%) of orange product, m.p. 116-119°.

An analytical sample, m.p. 118-120°, was prepared by recrystallization from ethanol-hexane.

Anal. Calcd. for $C_{10}H_7ClN_2OS$: C, 50.32; H, 2.96; Cl, 14.85; N, 11.74; S, 13.43. Found: C, 50.22; H, 2.80; Cl, 14.76; N, 11.90; S, 13.50.

Alternatively, **13c** can be prepared by catalytic hydrogenation of benzisoxazole **17**. Reduction of a solution of 1.5 g. (0.063 mole) of **17** in 250 ml. of THF over 0.15 g. of 10% palladium-on-charcoal (autogeneous temperature, *ca.* 50 psig, 18 hours) followed by filtration, removal of the solvent, and trituration of the residue with ether-hexane afforded 1.1 g. (73%) of product, m.p. 116-118°.

2-(2-Bromoacetamido)-5-chlorophenyl 5-Isothiazolyl Ketone (**14c**)

Bromoacetylation of 11.9 g. (0.05 mole) of **13c** with 18.2 g. (0.09 mole) of bromoacetyl bromide yielded 15.2 g. (85%) of light yellow product, m.p. 108-112°.

An analytical sample, m.p. 109-112°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{12}H_8BrClN_2O_2S$: C, 40.08; H, 2.24; Br, 22.22; Cl, 9.86; N, 7.79; S, 8.91. Found: C, 40.00; H, 2.01; Br, 22.44; Cl, 9.96; N, 7.77; S, 8.89.

7-Chloro-1,3-dihydro-5-(5-isothiazolyl)-2*H*-1,4-benzodiazepin-2-one (**15c**).

Treatment of 8.0 g. (0.022 mole) of **14c** with liquid ammonia followed by cyclization with acetic acid in methanol yielded 5.4 g. (88%) of yellow product, m.p. 108-112°.

An analytical sample, m.p. 109-112°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{12}H_8ClN_3OS$: C, 51.90; H, 2.90; Cl, 12.77; N, 15.15; S, 11.15. Found: C, 51.98; H, 2.75; Cl, 12.78; N, 15.05; S, 11.51.

7-Chloro-1,3-dihydro-5-(5-isothiazolyl)-1-methyl-2*H*-1,4-benzodiazepin-2-one (**16c**).

A stirred, cooled (0-5°) solution of 5.0 g. (0.018 mole) of **15c** in 100 ml. of DMF was treated with 1.0 g. (0.024 mole) of sodium hydride (57% suspension in mineral oil). The suspension was stirred at 25° for 1 hour and then treated with 6.2 ml. (14.1 g., 0.1 mole) of methyl iodide. After 3 hours the reaction mixture was poured into 1 l. of cold water giving a yellow solid which, after filtration, water-wash, and drying, yielded 4.6 g. (88%) of crude product, m.p. 159-165°.

Analytically pure material (m.p. 189-191°) was prepared by recrystallization from ethanol followed by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{13}H_{10}ClN_3OS$: C, 53.51; H, 3.45; Cl, 12.15; N, 14.40; S, 10.99. Found: C, 53.30; H, 3.26; Cl, 12.29; N, 14.41; S, 10.77.

α-(5-Chloro-2-nitrophenyl)-1-methylimidazole-2-methanol (**11d**).

A vigorously stirred, refluxing solution of 370 ml. (1.1 moles) of 3 *M* ethylmagnesium chloride in THF was treated with 91.1 g. (1.1 moles) of freshly distilled *N*-methylimidazole over a 15 minute period. After the addition of 800 ml. of additional THF, the solution was heated at reflux for 16 hours, cooled to -60°, and treated dropwise with a solution of 204.9 g. (1.1 moles) of 5-chloro-1-nitrobenzaldehyde in 300 ml. of THF; the reaction temperature was maintained between -70 and -60° throught the addition.

The pale yellow mixture was allowed to warm to ambient temperature over a 3 hour period and was stirred at 25° for an additional hour. The suspension then was poured into a stirred mixture of 300 ml. of 3 *N* hydrochloric acid and ice, and the pale yellow product was filtered, washed with ether, and dried yielding 128.5 g. (43%) of product, m.p. 206-211°.

An analytical sample, m.p. 226-228°, was prepared by recrystallization from pyridine.

Anal. Calcd. for $C_{11}H_{10}ClN_3O_3$: C, 49.36; H, 3.76; Cl, 13.24; N, 15.70. Found: C, 49.43; H, 3.90; Cl, 12.93; N, 15.64.

5-Chloro-2-nitrophenyl 1-Methyl-2-imidazolyl Ketone (**12d**).

Oxidation of 60.4 g. (0.23 mole) of **11d** with 46 g. (0.46 mole) of chromium trioxide in 500 ml. of glacial acetic acid yielded 80.1 g. (67%) of product, m.p. 175-176°.

An analytical sample, m.p. 175-177°, was prepared by recrystallization from methanol.

Anal. Calcd. for $C_{11}H_8ClN_3O_3$: C, 49.73; H, 3.03; N, 15.81. Found: C, 49.91; H, 2.99; N, 15.76.

2-Amino-5-chlorophenyl 1-Methyl-2-imidazolyl Ketone (**13d**).

A hot (60°) solution of 5.3 g. (0.02 mole) of **12d** in 50 ml. of methanol containing 10 ml. of concentrated hydrochloric acid was treated, in portions, with 4.2 g. (0.076 mole) of iron powder (13). The dark suspension was heated at 60-65° for 2 hours, filtered while still hot, and the filter cake washed with hot methanol. The combined methanol filtrates were concentrated and the resultant oil was treated with 1.5 l. of water. The aqueous solution was extracted with six 300 ml. portions of ether, and the combined etheral extracts were washed with water and brine, dried, and concentrated. The oil thus obtained was dissolved in the minimum amount of chloroform and chromatographed on a 10 x 5 cm column of silica gel; elution with chloroform followed by concentration of the filtrate and addition of hexane gave a gummy yellow soild.

The crude product was further purified *via* its hydrochloride salt; the material was dissolved in ether, treated with dry hydrogen chloride, and the precipitate thus formed was removed and treated with 100 ml. of 2*N* sodium carbonate. Extraction with chloroform, washing with water and brine, drying, and removal of the solvent gave an amber oil which was crystallized from ether-hexane to give 4.2 g. (90%) of yellow product, m.p. 85-90°.

An analytical sample, m.p. 89-91°, was obtained by recrystallization from ether-hexane.

Anal. Calcd. for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; N, 17.83. Found: C, 56.01; H, 4.29; N, 17.69.

2-(2-Bromoacetamido)-5-chlorophenyl 1-Methyl-2-imidazolyl Ketone (**14d**).

Bromoacetylation of 10 g. (0.043 mole) of **13d** with 17.2 g. (0.085 mole) of bromoacetyl bromide afforded 11.3 g. (75%) of yellow product, m.p. 152-156°.

An analytical sample, m.p. 152-154°, was prepared by recrystallization from chloroform-hexane.

Anal. Calcd. for $C_{13}H_{11}BrClN_3O_2$: C, 43.78; H, 3.11; N, 11.78. Found: C, 44.02; H, 3.22; N, 11.78.

7-Chloro-1,3-dihydro-5-(1-methyl-2-imidazolyl)-2*H*-1,4-benzodiazepin-2-one (**15d**).

A solution of 42.4 g. (0.12 mole) of **14d** in 1 l. of methylene chloride was added dropwise, with stirring, to 400 ml. of liquid ammonia (maintained at -78°) over a period of 2 hours. After an additional hour at -70°, the cooling bath was removed and the ammonia was allowed to evaporate overnight. The resultant suspension was diluted with 500 ml. of methylene chloride, washed with water (1 l.) and brine, dried, and concentrated. The resultant residue was dissolved in 700 ml. of pyridine containing 60 g. of pyridine hydrochloride, and the solution was stirred at 25° for 12 hours and at 50° for 18 hours. Removal of the pyridine afforded a solid which was partitioned between water and methylene chloride. The methylene chloride extract was washed with water and brine and then concentrated. The crude product thus obtained was recrystallized from acetone-hexane to give 18.8 g. (58%) of white product, m.p. 242-244° dec.

An analytical sample, m.p. 243-244° dec., was prepared by recrystallization from acetone-hexane.

Anal. Calcd. for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 56.89; H, 4.09; N, 20.51.

7-Chloro-1,3-dihydro-1-methyl-5-(1-methyl-2-imidazolyl)-2*H*-1,4-benzodiazepin-2-one (**16d**).

A stirred, cooled (5°) solution of 11.0 g. (0.04 mole) of **15d** in 200 ml. of DMF was treated with 5.0 g. (0.04 mole) of potassium *t*-butoxide. The resultant orange solution was stirred at 5° for 30 minutes and then treated with 7.1 g. (0.05 mole) of methyl iodide in 15 ml. of DMF. The reaction mixture was stirred at 25° for 2 hours and poured into 1 l. of water. The aqueous suspension was extracted with six 500 ml. portions of methylene chloride, and the combined organic extracts were washed with water and brine, dried, and the solvent removed under reduced pressure. Recrystallization of the crude product from methylene chloride-hexane afforded 7.6 g. (66%) of white product, m.p. 159-162°.

An analytical sample, m.p. 169-170°, was prepared by two recrystallizations from chloroform-hexane.

Anal. Calcd. for $C_{14}H_{13}ClN_4O$: C, 58.44; H, 4.20; N, 19.47. Found: C, 58.30; H, 4.44; N, 19.50.

α-(5-Chloro-2-nitrophenyl)-2-Methylpyrazole-3-methanol (**11e**).

A cooled (-5°), vigorously stirred solution of 90 g. (1.1 mole) of freshly distilled *N*-methylpyrazole (14) in 3 l. of ether was treated with 625 ml. (1.0 mole) of 1.6*M* *n*-butyllithium in hexane over a 30 minute period while the reaction temperature was maintained at -5°. The tan suspension was stirred at 5° for an additional 4 hours, and a solution of 178 g. (0.96 mole) of 5-chloro-2-nitrobenzaldehyde in 1 l. of dry THF was added at -5° over a 30 minute period. After 1 hour at 0° the reaction mixture was poured into a stirred mixture of 200 g. of ammonium chloride, 1.5 l. of water, and 1.5 l. of methylene chloride. The *p*H was adjusted to 7-8, the methylene chloride layer was removed, and the aqueous phase was washed with four 700 ml. portions of water, dried, and concentrated. The resultant solid was treated with ether and hexane, filtered, and dried affording 50.9 g. (20%) of product, m.p. 189-193°.

An analytical sample, m.p. 192-194°, was prepared by recrystallization from ethyl acetate-hexane.

Anal. Calcd. for $C_{11}H_{10}ClN_3O_3$: C, 49.36; H, 3.77; N, 15.70. Found: C, 49.37; H, 3.77; N, 15.81.

5-Chloro-2-nitrophenyl 1-Methyl-5-pyrazolyl Ketone (**12e**).

Oxidation of 50.9 g. (0.19 mole) of **11e** with 38 g. (0.38 mole) of chromium trioxide in 400 ml. of acetic acid yielded 42.5 g. (85%) of light yellow product, m.p. 147-151°.

An analytical sample, m.p. 149-151°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{11}H_8ClN_3O_3$: C, 49.23; H, 3.03; N, 15.81. Found: C, 49.55; H, 3.02; N, 15.54.

2-Amino-5-chlorophenyl 1-Methyl-5-pyrazolyl Ketone (**13e**).

A hot (55°) solution of 32.0 g. (0.12 mole) of **12e** in 1 l. of methanol containing 60 ml. of concentrated hydrochloric acid was treated, in portions, with 27.0 g. (0.48 mole) of iron powder. The suspension was heated at reflux for 2 hours, and, while hot, filtered through a pad of celite. The methanol solution was cooled and poured, with stirring, into 2 l. of water. Filtration of the precipitated solid followed by washing with hexane afforded 26.6 g. (93%) of yellow product, m.p. 116-118° dec.

An analytical sample, m.p. 117-119° dec., was prepared by recrystallization from ether-hexane.

Anal. Calcd. for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; N, 17.83. Found: C, 55.92; H, 4.32; N, 17.75.

2-(2-Bromoacetamido)-5-chlorophenyl 1-Methyl-5-pyrazolyl Ketone (**14e**).

Bromoacetylation of 43.5 g. (0.19 mole) of **13e** with 75 g. (0.38 mole) of bromoacetyl bromide afforded 60.2 g. (87%) of yellow product, m.p. 127-130°.

An analytical sample, m.p. 128-130°, was prepared by recrystallization from chloroform-hexane.

Anal. Calcd. for $C_{13}H_{11}BrClN_3O_2$: C, 43.78; H, 3.11; N, 11.78. Found: C, 44.03; H, 2.92; N, 12.01.

7-Chloro-1,3-dihydro-5-(1-methyl-5- pyrazolyl)-2*H*-1,4-benzodiazepin-2-one (**15e**).

A solution of 60.2 g. (0.17 mole) of **14e** in 400 ml. of methylene chloride was added, with stirring to 500 ml. of liquid ammonia (maintained at -78°) over a period of 1 hour. The cooling bath was removed and the ammonia was allowed to evaporate overnight. The suspension was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 600 ml. of pyridine containing 40 g. of pyridine hydrochloride, and the solution was stirred at 60° for 6 hours. Removal of the solvent under reduced pressure afforded a red oil which was partitioned between saturated sodium bicarbonate and chloroform. The chloroform layer was removed, washed with water and brine, dried, treated with activated charcoal, and concentrated under reduced pressure until cyrstallization began. The suspension was diluted with hexane, cooled, and filtered to afford 32.5 g. (70%) of white product, m.p. 194-196°.

An analytical sample was prepared by recrystallization from chloroform-hexane.

Anal. Calcd. for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 56.93; H, 4.10; N, 20.66.

7-Chloro-1,3-dihydro-1-methyl-5-(1-methyl-5-pyrazolyl)-2*H*-1,4-benzodiazepin-2-one (**16e**).

A stirred, cooled (-5°) solution of 17.9 g. (0.065 mole) of **15e** in 600 ml. of DME, 50 ml. of DMF, and 5 g. of 2-methoxyethanol was treated with 3.3 g. (0.08 mole) of sodium hydride (57% dispension in mineral oil). The yellow solution was stirred at 0° for 4 hours and was then treated with a solution of 12 g. (0.084 mole) of methyl iodide in 75 ml. of DME over a 15 minute period. The suspension was stirred at 25° overnight, diluted with 50 ml. of water, and concentrated under reduced pressure to a volume of 100 ml. The concentrate was treated with 1.2 l. of water and extracted with three 500 ml. portions of chloroform. The combined chloroform extracts were washed with water and brine, dried, and the solvent removed under reduced pressure. Recrystallization of the residue from chloroform-hexane afforded 10.5 g. (50%) of white product, m.p. 144-146°.

An analytical sample, m.p. 145-147°, was prepared by recrystallization from chloroform-hexane.

Anal. Calcd. for $C_{14}H_{13}ClN_4O$: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.17; H, 4.53; N, 19.50.

3,5-Dimethyl-α-(2-nitrophenyl)-4-isoxazolemethanol (**11f**).

A cooled (-55 to -50°), vigorously stirred solution of 167.9 g. (0.75 mole) of 4-iodo-3,5-dimethylisoxazole (15) in 2.5 l. of ether was treated with 470 ml. (0.75 mole) of 1.6*M* *n*-butyllithium in hexane over a 25 minute period; the temperature was maintained at -55 to -50° during the addition. The resultant tan suspension was stirred at -55 to -50° to 5.5 hours and a solution of 90.6 g. (0.60 mole) of 2-nitrobenzaldehyde in 400 ml. of THF was added at -55 to -50° over a 30 minute period. After an additional 1 hour at -50°, the reaction mixture was poured, with stirring, into 2 l. of water. The ether layer was separated, the aqueous phase extracted with two 500 ml. portions of ether, the combined organic extracts dried, and the ether removed under reduced pressure yielding 163 g. of crude product which was dissolved in 1 l. of hot methylene chloride. The methylene chloride solution was treated with 400 ml. of hexane; cooling and concentration of the solution afforded 105.5 g. of white solid; m.p. 101-130°. Further concentration of the mother liquor afforded an additional 111 g. of product, m.p. 96-100°, for a total yield of 116.6 g. (78%).

An anlytical sample, m.p. 101.5-103°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 57.90; H, 4.80; N, 11.31.

3,4-Dimethyl-4-isoxazolyl 2-Nitrophenyl Ketone (**12f**).

Oxidation of 62 g. (0.25 mole) of **11f** with 50 g. (0.50 mole) of chromium trioxide in 500 ml. of glacial acetic acid at 65-70° yielded 58 g. (93%) of white product, m.p. 90.5-92.5°.

An analytical sample, m.p. 92-94°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38.

Found: C, 58.43; H, 4.07; N, 11.32.

2-Aminophenyl 3,5-Dimethyl-4-isoxazolyl Ketone (**13f**).

A solution of 49.2 g. (0.2 mole) of **12f** in *ca.* 2.5 l. of glacial acetic acid was hydrogenated at autogeneous temperature over 10.0 g. of 10% palladium-on-charcoal at *ca.* 3-4 psig for 20 minutes. Removal of the catalyst and the acetic acid gave 58 g. of an oil.

The crude product was dissolved in 400 ml. of benzene-ethyl acetate (2:1 v/v), the solution vacuum filtered through 150 g. of silica gel, and the silica gel washed with 1 l. of benzene-ethyl acetate (2:1 v/v). The combined benzene-ethyl acetate filtrates were evaporated to dryness, and the tacky yellow solid thus produced (39.1 g.) was dissolved in 200 ml. of methylene chloride. The methylene chloride solution was washed with saturated sodium bicarbonate, water, and brine; dried; and concentrated to give 32.1 g. (74%) of product as a yellow powder, m.p. 51-62°.

An analytical sample, m.p. 69-70.5°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.81; H, 5.72; N, 12.98.

2-(2-Bromoacetamido)-henyl 3,5-Dimethyl-4-isoxazolyl Ketone (**14f**).

Bromoacetylation of 13.6 g. (0.063 mole) of **13f** with 17.7 g. (0.087 mole) of bromoacetyl bromide afforded 20.2 g. (95%) of light yellow product, m.p. 98-101.5°.

An analytical sample, m.p. 104.5-105.5° was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{14}H_{13}BrN_2O_3$: C, 49.87; H, 3.89; Br, 23.70; N, 8.31. Found: C, 49.71; H, 3.83; Br, 23.95; N, 8.22.

1,3-Dihydro-5-(3,5-Dimethyl-4-isoxazolyl)-2*H*-1,4-benzodiazepin-2-one (**15f**).

Treatment of 20.3 g. (0.06 mole) of **14f** with liquid ammonia followed by cyclization in methanol-acetic acid afforded 10.3 g. (67%) of white product, m.p. 274.5-275° dec.

An analytical sample, m.p. 276-277° dec., was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.70; H, 5.10; N, 16.61.

1,3-Dihydro-5-(3,5-dimethyl-4-isoxazolyl)-1-methyl-2*H*-1,4-benzodiazepin-2-one (**16f**).

A stirred, cooled (0-5°) solution of 3.2 g. (0.013 mole) of **15f** in 200 ml. of DMF was treated with 0.58 g. (0.014 mole) of sodium hydride (57% dispersion in mineral oil). The solution was stirred for 0.5 hour at 5°, 2 hours at 25°, and then treated with 1.3 ml. (2.9 g., 0.02 mole) of methyl iodide. After 2 hours the reaction mixture was poured into 1.5 l. of water containing 100 g. of sodium chloride. The DMF-water solution was extracted with six 100 ml. portions of methylene chloride and the combined methylene chloride extracts were washed with water and brine and dried. Removal of the solvent gave an oily solid which was recrystallized from methylene chloride-hexane to give 2.8 g. (84%) of white product, m.p. 207-208°.

An analytical sample, m.p. 208.5-209.5°, was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.98; H, 5.68; N, 15.74.

2-Amino-5-iodophenyl 3,5-Dimethyl-4-isoxazolyl Ketone (**19b**).

A stirred solution of 3.2 g. (0.015 mole) of **13f** in 50 ml. of THF, 75 ml. of methanol, and 40 ml. of chloroform was treated, in portions, at -11 to -9° with a solution of 10.3 g. (0.064 mole) of iodine monochloride in 75 ml. of chloroform over a 30 minute period. The solution was stirred at -10 to -5° for an additional 40 minutes and then poured, with stirring, into a mixture of 200 ml. of ice-water and 100 ml. of chloroform. Sodium sulfite (11 g.) was added in portions, and the organic layer was separated; washed with 50 ml. of 1*N* sodium hydroxide, water, and brine; dried; and the solvent removed to give 4.9 g. (97%) of product as a yellow solid, m.p. 97-108° dec. This crude product was used without further purification.

An analytical sample, m.p. 118.5-120.5° dec., was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{12}H_{11}IN_2O_2$: C, 42.13; H, 3.24; I, 37.09, N, 8.19. Found: C, 42.24; H, 3.12; I, 36.80; N, 8.07.

2-(2-Bromoacetamido)-4-iodophenyl 3,5-Dimethyl-4-isoxazolyl Ketone (**20b**).

Bromoacetylation of 4.6 g. (0.013 mole) of **19b** with 4.2 g. (0.021 mole) of bromoacetyl bromide yielded 5.7 g. (93%) of yellow product, m.p. 130-133° dec.

An analytical sample, m.p. 136.5-137.5° dec., was prepared by recrystallization from methylene chloride hexane.

Anal. Calcd. for $C_{14}H_{12}BrIN_2O_3$: C, 36.32; H, 2.62; Br, 17.26; I, 27.40; N, 6.05. Found: C, 36.35; H, 2.48; Br, 17.07; I, 27.10; N, 6.03.

1,3-Dihydro-7-iodo-5-(3,5-dimethyl-4-isoxazolyl)-2*H*-1,4-benzodiazepin-2-one (**21b**).

Treatment of 4.9 g. (0.011 mole) of **20b** with liquid ammonia followed by cyclization in methanol-acetic acid yielded 3.3 g. (81%) of off-white product, m.p. 247-254° dec.

An analytical sample, m.p. 253-254° dec., was prepared by recrystallization from methylene chloride-hexane.

Anal. Calcd. for $C_{14}H_{12}IN_3O_2$: C, 44.12; H, 3.17; I, 33.29; N, 11.02. Found: C, 43.83; H, 3.02; I, 33.35; N, 10.90.

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(10) The nature of the products resulting from this secondary reduction will be reported separately.

(11) The formation of 3-hydroxy-3-carboethoxy-1-methylbenzodiazepinones *via* the treatment of the corresponding 3-carboethoxybenzodiazepinones with base and oxygen is known: Netherlands Patent 68,11364 (1969). In a separate experiment, methylation of **16b** in the presence of oxygen was shown to give **18**.

(12) K. Ganapathi and A. Venkatarama, Proc. *Indian Acad. Sci., Sect A*, **22**, 343, 362 (1945).

(13) The yield in this reaction is greatly dependent upon the quality of the iron used. Only finely powdered, purified (hydrogen-reduced) iron gives reproducibily good yields.

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(15) N. K. Kochetkov, S. D. Sokolov, and N. M. Vagurtova, *J. Gen. Chem. USSR*, **31**, 2167 (1961).