The ether-extractable Dragendorff-positive components, bands 1 and 2 (Table II), were characterized with little difficulty. Band 1 which migrated as intact I (compare R_f with that of I in Table I) was found to be identical with I by further tlc and by high-resolution mass spectrometry (Table IV). Band 2, on purification by tlc, yielded a pattern of metabolites (and artifact) which was almost an exact duplicate of that obtained with band 4. Components $2A_1$, $2A_2$, 2B, and 2C analogous to the band 4 components (Table III) were obtained and each component was found by high-resolution mass spectrometry (Table IV) to be identical with the analogous band 4 component. Furthermore, components $2A_2$ and 2C were more readily identified as VII because they did not contain the extraneous *m/e* 302 fragment. It is evident from the above that nonconjugated II, III, and intact drug (I) were excreted in the urine.

The hydroxyl-bearing compounds IV, VI, and metabolite 3A (phenolic analog of V) would be expected to be excreted as glucosuronic acid and/or sulfate conjugates and were found as such. However, II and III were also found in the ethyl acetate extracts after treatment of the urine with Glusulase which suggests that these compounds were either conjugated in the enolate form with sulfate and/or glucuronate or were present in some other chemical form susceptible to modification upon treatment with Glusulase. Further work is required to clarify this unexpected finding.

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Quinazolines and 1,4-Benzodiazepines. XL.[1] The Synthesis of Metabolites of 7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

J. V. EARLEY, R. IAN FRYER, D. WINTER, AND L. H. STERNBACH

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

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The synthesis of a number of compounds related to the hypnotic, 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2**), is reported. These compounds were prepared as potential metabolites and many were found to be identical with the metabolites isolated and discussed in the preceding paper.[2]

In connection with the metabolic studies of the hypnotic, 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2**)[3] discussed in the preceding paper,[2] we have synthesized a number of related compounds designed as possible *in vivo* and/or *in vitro* metabolites. By means of direct comparison or by a comparison of mass spectra and the use of tlc techniques, many of these derivatives were shown by Schwartz, Vane, and Postma[2] to be identical with the metabolites of **2**.

Some of these compounds were synthesized after their initial tentative identification by an interpretation of mass spectral data while others were prepared based on our knowledge of the metabolism of other 1,4-benzodiazepines (*e.g.*, diazepam is known to yield a 3-hydroxy derivative[4]).

The synthesis of the monoethylamino derivative (**4**) was carried out by a von Braun degradation of the side chain of **2**. Thus treatment of **2** with cyanogen bromide gave the cyanamide **3** which on reaction with sulfuric acid gave the desired secondary amine **4** (Scheme I). By treating the cyanamide with base and with H_2O_2, the urea **5** could be obtained. The hydrolysis of **3** in concentrated H_2SO_4 under milder conditions than those used for the synthesis of **4** also gave the intermediate urea **5**. From both of these reactions, we also isolated the hydroxyethyl derivative **6**. This compound was synthesized in much better yield from **1** either by treatment with sodium methoxide and 2-bromoethanol, or by a direct condensation with ethylene oxide.

Another compound synthesized as a possible metabolite was the aminoethyl derivative **8**. Again the unalkylated compound **1** was used as the starting material and was treated first with sodium methoxide and then with carbobenzoxybromoethylamine to give **7**. Compound **7** was then treated with a solution of HBr in glacial acetic acid to give the free amino derivative **8**. The dehydration product **16** formed by heating **8** under reflux in ethanol[1] was found as an artifact of **8** in the metabolic studies carried out by Schwartz and Postma.[2]

The 3-hydroxy compound (**12**) was prepared in the conventional manner from **10** by a Polonovski rearrangement of the N-oxide to give **11** which was subsequently hydrolyzed to **12**. Compound **10** was synthesized from **1** in two steps. In the first step, **1** was oxidized with peracetic acid to give the nitrone **9**, and in the second step **9** was alkylated *via* the sodio

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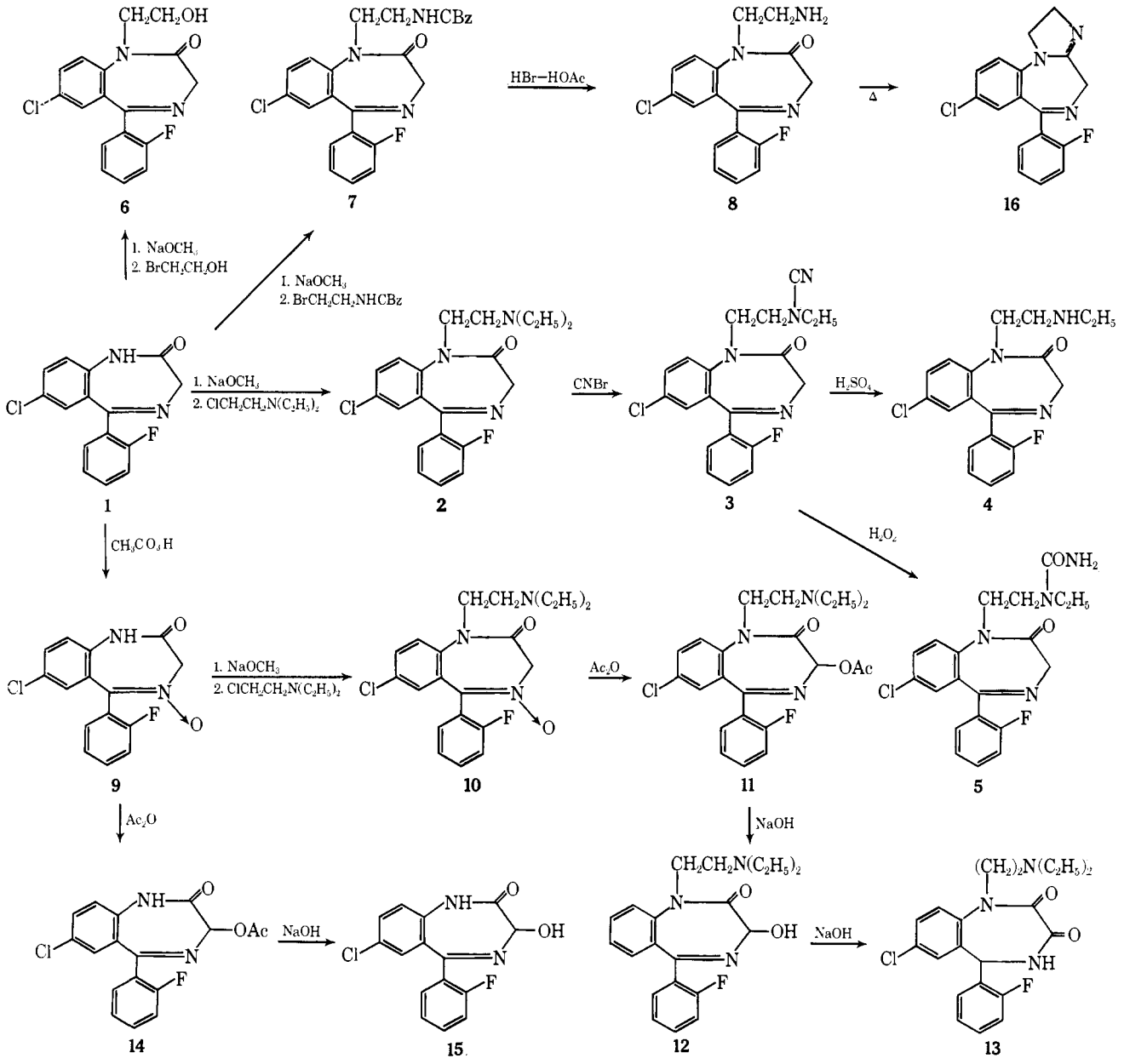
SCHEME I



CBz = carbobenzoxy

derivative with diethylaminoethyl chloride. The treatment of **12** with base gave the expected 2,3-dione (**13**). Similarly, the same Polonovski type of rearrangement of **9** gave the 3-acetoxy derivative **14** and alkaline hydrolysis of this compound afforded the 3-hydroxybenzodiazepine (**15**).

Experimental Section

All melting points were determined either microscopically on a hot stage or in a sealed capillary and are corrected. Reference spectra were taken on all compounds and where necessary were compared in order to confirm or exclude structural changes. Acceptable analytical data for C and H (±0.4% of the theoretical values) on all new compounds were obtained.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-[2-(N-cyano-N-ethylamino)ethyl]-2H-1,4-benzodiazepin-2-one (3).—To 4.0 g (0.0393 mole) of BrCN dissolved in 60 ml of $CHCl_3$ was added dropwise a solution of 10 g (0.0258 mole) of 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2**)[3a] in 90 ml of $CHCl_3$. The reaction mixture was refluxed for 4 hr under an air condenser and was then cooled to room temperature. The resulting solution was extracted with 50 ml of 2 *N* HCl. The chloroform layer was washed with 50 ml of dilute NH_4OH and 50 ml of saturated brine solution, dried (Na_2SO_4), and then evaporated to dryness. The residue was recrystallized twice from MeOH to yield 4.5 g of product. The filtrates were evaporated to dryness and dissolved in C_6H_6 and the insoluble tar was discarded. The benzene solution was filtered through Florisil which was eluted with EtOAc. Removal of solvents gave a residue which was recrystallized from MeOH to give an additional 2.0 g of product. The combined 6.5 g of product was recrystallized from a mixture of CH_2Cl_2–MeOH to give the pure compound as white rods, mp 132–134°.[5] *Anal.* ($C_{20}H_{18}ClFN_4O$) C, H.

7-Chloro-1,3-dihydro-1-(2-ethylaminoethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one Dihydrochloride (4).—Two grams (0.0052 mole) of **3** was dissolved in concentrated H_2SO_4 and heated at 175° for 2 hr. The solution was cooled to approximately 10°, made neutral with NH_4OH, and then reacidified (pH 6) with dilute H_2SO_4. The precipitate was recovered by filtration and the filtrates were extracted ($CHCl_3$, two 50-ml portions). The water layer was made basic with NH_4OH and the solution was reextracted ($CHCl_3$, two 50-ml portions). The organic layers were combined, dried (Na_2SO_4), and evapo-

(5) Starting material (1.5 g) was recovered from the aqueous acid layer and the total yield of product, based on 8.5 g of starting material, was 76%.

rated to dryness. The residual oil (1.1 g) contained about 15% of starting material (tlc, visual estimation). The oil was dissolved in a small amount of EtOH and an excess of ethanolic HCl was added. The solution of the salt was cooled and ether was added until the salt precipitated. The precipitate was obtained by filtration and was recrystallized from MeOH–Et_2O to yield 0.8 g (35%) of product as pale yellow rods, mp 215–217° (sealed tube). *Anal.* ($C_{19}H_{19}ClFN_3O \cdot 2HCl$) C, H. A solution of 2 g of the pure salt in 100 ml of H_2O was made basic (NH_4OH) (pH 8). The solution was extracted (CH_2Cl_2, three 50-ml portions). The organic layers were combined, washed (H_2O), dried (Na_2SO_4), and evaporated to an oil. The residual oil was crystallized and recrystallized from a mixture of ether and petroleum ether (30–60°) to give the pure base as white prisms, mp 80–85°.

1-Ethyl-1-{2-[7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2-oxo-1,4-benzodiazepin-1-yl]ethyl}urea (5). Method A.—To a solution of 0.2 g (0.00052 mole) of **3** in 15 ml of EtOH was added 1 ml of 1 *N* NaOH followed by 50 ml of a 3% solution of H_2O_2. The resulting mixture was stirred for 4 hr and was then extracted with two 50-ml portions of CH_2Cl_2. The organic layers were combined and washed with 40 ml of saturated brine solution, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from CH_2Cl_2–Et_2O to give 0.19 g (90% yield) of the product as white rods, mp 120–130° resets, mp 185–188°. *Anal.* ($C_{20}H_{20}ClFN_4O_2$) C, H.

Method B.—A solution of 0.1 g (0.00026 mole) of **3** in 4 ml of concentrated H_2SO_4 was heated at 95° for 5 hr, cooled, and poured onto ice. The solution was made basic (NH_4OH) and extracted with CH_2Cl_2 (two 40-ml portions). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. Recrystallization of the residue from CH_2Cl_2–Et_2O gave 0.06 g (57% yield) of crude product, mp 180–185°, mmp 183–187° with the product prepared by method A.

7-Chloro-1-(2-hydroxyethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one Hydrochloride (6).—A solution of 10 g (0.0346 mole) of **1**[6] in 25 ml of DMF was treated with 10.6 ml of a solution containing 0.0415 mole of NaOMe in MeOH. The solution was stirred at room temperature for 30 min and 8.7 g (0.0692 mole) of 2-bromoethanol was added. The reaction mixture was heated at 80° for 2 hr and then poured into H_2O (200 ml). The reaction products were removed by filtration, dissolved in 100 ml of CH_2Cl_2 which was then washed (H_2O, two 100-ml portions, and saturated brine), dried (Na_2SO_4), and evaporated. The residual oil (10.5 g) was crystallized from ether to give 4.5 g of starting material. The mother liquors were evaporated, dissolved in C_6H_6, and filtered over 200 g of silica. The silica was eluted with ether until all impurities had been removed and the product was then obtained by using MeOH as the eluent.

Removal of the solvent gave the base of **6** as an oil (4.5 g). An excess of ethanolic HCl was added, followed by ether to precipitate the salt. Three recrystallizations of the salt from MeOH–Et_2O gave the pure salt (3.2 g, 46%, based on 5.5 g of starting material consumed) as pale yellow prisms, mp 194–196° dec. *Anal.* ($C_{17}H_{14}ClFN_2O_2 \cdot HCl$) C, H.

1-[2-(Benzyloxycarbonylamino)ethyl]-7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (7).—A solution of 33.9 g (0.116 mole) of **1** in 150 ml of dry DMF was treated with 5.1 g (0.127 mole) of a 60% dispersion of NaH in mineral oil. The resulting solution was stirred at room temperature for 30 min and then treated with 30 g (0.116 mole) of carbobenzoxy-2-bromoethylamine.[7] The reaction mixture was then stirred at room temperature for 2 hr, poured into H_2O (500 ml), and extracted (CH_2Cl_2, three 200-ml portions). The combined organic layers were washed with H_2O (three 50-ml portions) and saturated brine, dried (Na_2SO_4), filtered, and evaporated to give 60.1 g of an amber oil. This oil was dissolved in 1.5 l. of ether and the product was allowed to crystallize slowly. Filtration gave 24.2 g (45%) of **7** as white prisms, mp 142–145°. *Anal.* ($C_{25}H_{21}ClFN_3O_3$) C, H.

1-(2-Aminoethyl)-7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one Dihydrochloride (8).—A suspension of 10 g (0.0214 mole) of **7** in 20 ml of glacial AcOH was treated at room temperature with 20 ml of a 33% (w/w) solution of HBr–AcOH. The reaction mixture was stirred for 2 hr and then diluted with 1 l. of ether. The product, as the dihydrobromide, was removed by filtration, washed (Et_2O, Me_2CO), and then recrystallized from (MeOH, Me_2CO) to give 10.0 g of the dihydrobromide with a wide melting range of 185–280°.

The salt was suspended in CH_2Cl_2 and treated with an excess of dilute NH_4OH. The mixture was shaken thoroughly and the layers were separated. The organic layer was washed (H_2O), dried (Na_2SO_4), filtered, and evaporated. The base, thus obtained, was then dissolved in a small amount of EtOH and treated with an excess of a solution of HCl in EtOH. The addition of ether caused the dihydrochloride to precipitate and the salt was obtained by filtration. Recrystallization from EtOH gave the pure salt **8** as white prisms, mp 218–221° dec. *Anal.* ($C_{17}H_{15}ClFN_3O \cdot 2HCl$) C, H.

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one 4-Oxide (9).—A solution of peracetic acid was prepared by cooling 25 ml of CH_2Cl_2 to 10°, adding 7.5 ml of 90% H_2O_2 (0.275 mole), 1 drop of concentrated H_2SO_4, followed by the dropwise addition of 33.6 g of Ac_2O (0.33 mole). The reaction mixture was stirred at 10° for 15 min and then at room temperature for 30 min. The peracetic acid solution was then added dropwise (25 min) to a solution of 72.2 g (0.25 mole) of **1** in 1.35 l. of CH_2Cl_2 at 10°. The mixture was then allowed to stand at room temperature for 4 days.

The reaction mixture was divided into three 460-ml portions, and each was worked up in the following manner. The aliquot was washed with H_2O (three 400-ml portions),[8] 10% NH_4OH (one 100-ml portion), H_2O (two 300-ml portions), 2 *N* HCl (one 250-ml portion), H_2O (two 300-ml portions), and a saturated brine solution. The organic layer was dried (Na_2SO_4) and tested for the presence of peroxides with a Zn-reduced solution of potassium thiocyanate, $FeSO_4 \cdot 7H_2O$, and dilute H_2SO_4. If the test proved negative, the solution was evaporated to near dryness and ether was added. The crystalline precipitate was obtained by filtration. The combined products were recrystallized from a mixture of Me_2CO, MeOH, and petroleum ether (30–60°) to give 51.0 g (67.0%) of **9** as white prisms, mp 220–223°. *Anal.* ($C_{15}H_{10}ClFN_2O_2$) C, H.

7-Chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one 4-Oxide (10).—A solution of 38.0 g (0.125 mole) of **9** in 100 ml of DMF was treated with a solution of NaOMe in MeOH (0.15 mole of NaOMe was added) and was stirred at room temperature of 1 hr. A toluene solution of 2-chloro-*N*,*N*-diethylethylamine[9] was then slowly added to the solution of the sodio derivative of **9**. An additional 100 ml of DMF was added, and the cloudy reaction mixture was stirred at 30° for 2 hr and then at 40° for 0.5 hr. The reaction mixture was filtered and evaporated to dryness under reduced pressure. The residual oil was then partitioned between 300 ml of H_2O and 300 ml of CH_2Cl_2. The layers were separated and the aqueous phase was extracted with 100 ml of CH_2Cl_2. The combined organic layers were washed (H_2O, four 300-ml portions, and saturated brine solution), dried (Na_2SO_4), and evaporated to dryness. The residual oil (52 g) was crystallized from a mixture of ether and petroleum ether (30–60°) to give 37.5 g (74.4%) of **10** as white prisms, mp 122–124°. *Anal.* ($C_{21}H_{23}ClFN_3O_2$) C, H.

3-Acetoxy-7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one Hydrochloride (11).—A solution of 41 g (0.1 mole) of **10** in 330 ml of Ac_2O was stirred and heated under reflux for 1 hr. The solution was evaporated to near dryness and the residue was dissolved in 200 ml of H_2O. A 50% K_2CO_3 solution was added to pH 9, and the resulting mixture was extracted into 200 ml of CH_2Cl_2. The extract was washed (H_2O, four 400-ml portions, and saturated brine solution), dried (Na_2SO_4), and evaporated to dryness to give 49.5 g of a dark oil. The oil was dissolved in a small amount of benzene and filtered over 250 g of silica gel using hexane as the eluent to give, after solvents were removed, 32 g of an oil. The silica was next eluted with EtOAc to give, after removal of the solvent, 6.1 g of an oil. The first fraction was triturated with two 100-ml portions of boiling hexane which were decanted from the residual

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(8) Part of the product sometimes precipitated at this point and could be separated by filtration.

(9) The solution of 2-chloro-*N*,*N*-diethylethylamine was prepared as follows: 17.1 g (0.25 mole) of the hydrochloride was added to 30 g of crushed ice. NaOH (10 *N*) was added until pH 11. The solution was then extracted with three 35 ml-portions of toluene. The combined toluene extracts were filtered over Celite, washed with two portions of a saturated brine solution, and dried (Na_2SO_4).

tars and were combined. The hexane solution was added to the second fraction and evaporated to dryness to give 38 g (84.0%) of the base of **11** as an oil.

A solution of 200 mg of the base in anhydrous Et_2O was treated with an excess of HCl gas. The ether solution was then evaporated to dryness and the residual oil was crystallized from Me_2CO–Et_2O to give pure **11**·HCl, white prisms, mp 214–218°. *Anal.* ($C_{23}H_{25}ClFN_3O_3$·HCl) C, H.

7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one (12).—A solution of 12.0 g (0.0248 mole) of **11** in 230 ml of EtOH was treated with 28.0 ml (0.028 mole) of 1 *N* NaOH. The reaction mixture was allowed to stand for 16 hr at room temperature and was then evaporated to dryness. The residual oil was partitioned between 200 ml of H_2O and 200 ml of CH_2Cl_2. A 50% K_2CO_3 solution was added until the pH of the aqueous layer was approximately 11. The layers were separated and the CH_2Cl_2 extract was washed (H_2O, four 200-ml portions, and saturated brine solution), dried (Na_2SO_4), and evaporated to dryness. The residual oil was dissolved in Et_2O and cooled in an ice bath, and gaseous HCl was bubbled into the solution. The ether solution of the salt was evaporated to dryness and the residual oil was crystallized from Me_2CO–Et_2O to give 8.0 g (73.0%) of the pure salt of **12** as white prisms, mp 196–203° dec. *Anal.* ($C_{21}H_{23}ClFN_3O_2$·HCl) C, H.

A solution of 1.5 g of the salt was dissolved in 30 ml of H_2O and 50% K_2CO_3 was added to pH 11. The mixture was extracted with 30 ml of CH_2Cl_2, the layers were separated, and the organic layers were washed (H_2O, three 50-ml portions, and saturated brine solution), dried (Na_2SO_4), and evaporated to dryness. The residual oil was crystallized from a mixture of ether and petroleum ether (30–60°) to give the pure base as white prisms, mp 118–121°. *Anal.* ($C_{21}H_{23}ClFN_3O_2$) C, H.

7-Chloro-1-(2-diethylaminoethyl)-4,5-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepine-2,3-dione (13).—A solution of 2.0 g (0.0045 mole) of the hydrochloride of **11** in 25 ml of EtOH was treated with 9 ml (0.009 mole) of 1 *N* NaOH. The reaction mixture was allowed to stand at room temperature for 16 hr and was then treated with 1 *N* HCl to pH 6. The solution was made basic again with 50% K_2CO_3 and the resulting mixture was evaporated to dryness. The residual oil was dissolved in 150 ml of CH_2Cl_2 which was washed (H_2O, three 150-ml portions, and saturated brine solution), dried (Na_2SO_4), and evaporated to dryness. The residual yellow oil (1.8 g) was crystallized from Me_2CO–petroleum ether (30–60°) to give 1.2 g (65.5%) of the pure product as white prisms, mp 169–171°. *Anal.* ($C_{21}H_{23}ClFN_3O_2$) C, H.

3-Acetoxy-7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (14).—A solution of 10 g (0.0328 mole) of **9** in 150 ml of Ac_2O was heated with stirring on a steam bath for 3.5 hr. Ac_2O was removed under reduced pressure and the residue was dissolved in 100 ml of CH_2Cl_2. The organic solution was washed with 75 ml of dilute NH_4OH, two 75-ml portions of H_2O, and 75 ml of saturated brine, dried (Na_2SO_4), and evaporated to dryness. The product was recrystallized from MeOH to give 8.6 g (76%) of **14** as white prisms, mp 239–247° (sealed tube). *Anal.* ($C_{17}H_{12}ClFN_2O_3$) C, H.

7-Chloro-5-(2-fluorophenyl)-3-hydroxy-1,3-dihydro-2H-1 4-benzodiazepin-2-one (15).—A solution of 5 g (0.0145 mole) of **14** in 200 ml of EtOH was treated with 36.3 ml (0.036 mole) of 1 *N* NaOH. After 5 min a white precipitate separated which was redissolved after an additional 10 min by the addition of 200 ml of H_2O. The solution was then acidified with AcOH and EtOH was removed under reduced pressure. The product separated as a white precipitate and was recrystallized from a mixture of THF and hexane to give 4.2 g (96%) of **15** as white rods, mp 197–200°.

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Tetrahydroisoquino[2,1-*d*][1,4]benzodiazepines. Synthesis and Neuropharmacological Activity

HANS OTT, GOETZ E. HARDTMANN, MAX DENZER, ALBERT J. FREY,

Medicinal Chemistry Research Department

JOHN H. GOGERTY, GEORGE H. LESLIE, AND JOSEPH H. TRAPOLD

Biological Research Department, Sandoz Pharmaceuticals, Hanover, New Jersey 07936

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The synthesis and neuropharmacological activities for a series of tetrahydroisoquinobenzodiazepines are described. These substances produce qualitatively similar pharmacological activities to the well-known benzodiazepines, although similar structure–activity relationships could not be developed. One significant difference between compounds of the present series and the standard benzodiazepines was obtained in the dihydroxyphenylalanine-potentiation test (indicating possible "antidepressant" activity residing in the isoquinobenzodiazepine molecule). The most active compound in the present series was the dextrorotatory isomer of 2-chloro-5-methyl-5,9,10,14b-tetrahydroisoquino[2,1-*d*][1,4]benzodiazepin-6(7H)-one. Only those substances possessing electronegative substituents at position 2 demonstrated significant CNS depressant effects.

The pharmacological and clinical spectra of 5-phenyl-1,4-benzodiazepines (**1**) have been well documented since the advent of chlordiazepoxide.[1-5] A review of reports in which attempts were made to modify the chemical structure of the parent molecule with no concomitant loss in biological activity has brought out the fact that the benzene ring in the 5 position is important for neuropharmacological activity.[6] One might assume that such a molecule combines with the enzyme at the receptor site in one specific rotational conformation. Based on this idea we became interested in the biological activities of 5-phenyl-1,4-benzodiazepines (**1**) in which the free rotation of the phenyl group is blocked by an ethylene bridge between position 2′ and 4. The resulting novel tetracyclic

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