31 (100). After removal of this product, the ether mother liquor was chilled at −70 °C, giving 1.2 g of a yellow solid. This was dissolved in carbon tetrachloride, to remove a small amount of the insoluble dimer **9**. The solvent was removed, and the solid was purified further by HPLC (eluting with a mixture of 20% cyclohexane in chloroform), giving white, crystalline **29:** mp 135–137 °C (from ether and a little methylene chloride at −70 °C); IR (KBr) 2250 (CN), 1725 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.18 (s, 2, aromatic H), 4.00 (s, 6, $CH_3$); mass spectrum *m/e* (rel intensity) 244 (3.5), 213 (100).

**Registry No.**—**1,** 19652-57-4; **2** isomer 1, 64784-29-8; **2** isomer 2, 64784-30-1; **3,** 64760-88-9; **4,** 64760-90-3; **5,** 64760-91-4; **6,** 64760-89-0; **7,** 64760-92-5; **8,** 3716-97-0; **9,** 41793-19-5; **10,** 53399-95-4; **11,** 64760-93-6; **12,** 64760-95-8; **13,** 64760-94-7; **15,** 64760-97-0; **16,** 64760-98-1; **17,** 64760-99-2; **18,** 64761-00-8; **19,** 64760-80-1; **20** isomer 1, 64760-81-2; **20** isomer 2, 64760-96-9; **21,** 64760-82-3; **22,** 64760-83-4; **23,** 64760-84-5; **24,** 64760-86-7; **25,** 64760-85-6; **26,** 64760-87-8; **27,** 64760-79-8; **19,** 64754-35-4; diazomethane, 334-88-3; ethyl diazoacetate, 623-73-4; maleic anhydride, 108-31-6; *N*-ethylmaleimide, 128-53-0; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; 1-cyanovinyl acetate, 3061-65-2; styrene, 100-42-5; ethyl vinyl ether, 109-92-2; divinyl ether, 109-93-3; 1-methoxycyclohexene, 931-57-7; furan, 110-00-9; TCNE, 670-54-2; dimethylisobutenylamine, 6906-32-7; 1-dimethylaminocyclohexene, 13815-46-8; *N*-methylpyrrole, 96-54-8; dimethyl acetylenedicarboxylate, 762-42-5.

## References and Notes


(1) R. L. Cobb and J. E. Mahan, *J. Org. Chem.*, **42,** 2601 (1977).
(2) C. A. Uraneck, J. E. Burleigh, and R. L. Cobb, U.S. Patent 3 998 998 (1976).
(3) R. L. Cobb, V. C. Vives, and J. E. Mahan, *J. Org. Chem.*, preceding paper in this issue.
(4) D. Belluš, K. von Bredow, H. Sauter, and C. D. Weis, *Helv. Chim. Acta*, **56,** 3004 (1973).
(5) (a) D. Wollweber, "Diels-Alder Reaktionen", Georg Thieme Verlag, Stuttgart, 1972, p 66; (b) P. Beltrame in "Comprehensive Chemical Kinetics", Vol. 9, C. H. Bumford and C. F. H. Tipper, Ed., Elsevier Scientific Publishing Co., New York, N.Y., 1973, Chapter 2; (c) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, 16 (1967).
(6) The origin of **6** is obscure. It could have arisen from reaction of the dimer of **1** with diazomethane,[1] but this dimer was not normally present in the samples of **1** utilized in this study. Alternatively, reaction of **1** with **4** or its pyrazoline precursor is also a plausible route to **6**. No further study of these possibilities was made.
(7) Isomerization of initially-formed 1-pyrazolines was noted also with similar products from cyclobutene-1,2-dicarbonitrile[8] and *cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile.[1]
(8) R. L. Cobb and J. E. Mahan, *J. Org. Chem.*, **42,** 2597 (1977).
(9) D. Belluš and C. D. Weis, *Tetrahedron Lett.*, 999 (1973).
(10) (a) Diene **1,** the valence tautomer of **8,** is prepared conveniently by thermolysis of **8**[4] (see ref 1 for further comments on the conversion of **8** to **1** in hot solvents). (b) A study that would clarify the observed differences in the reactivity of **1** and **8** was not made. However, as a referee also noted, the rate of diene formation from **8** in hot xylene may be slow enough so that the amount of **1** produced at any one time is small relative to the concentration of the dienophile. Cycloaddition rather than polymerization is thus favored. No attempt to effect reactions of **1** itself with dienophiles above ca. 140 °C was made, since self-dimerization to **9** and **10** is a major process under these conditions. Optimum reaction conditions were not determined, and, except for the example noted (preparation of **21**), the reactions of **8** were also carried out at or below ca. 140 °C.
(11) Cyanovinyl acetate has been used as a probe in determining the dual reactivity occasionally observed in diene cycloadditions, i.e., (2 + 2) processes to cyclobutanes or (2 + 4) processes to cyclohexenes; see, e.g., J. C. Little, *J. Am. Chem. Soc.*, **87,** 4020 (1965), and P. D. Bartlett and K. E. Schueller, *ibid.*, **90,** 6077 (1968).
(12) The thermal dimerization of $\alpha$-chloroacrylonitrile to 1,2-dichlorocyclobutane-1,2-dicarbonitrile has apparently not been previously observed.
(13) For example, the furan adduct of *cis,trans*-1,5-cyclooctadiene-1,2,5,6-tetracarbonitrile underwent reaction with TCNE.[1]
(14) A (2 + 2) cycloaddition from equimolar amounts of **1** and the enamine would give a product with NMR resonances at $\delta$ ca. 6–7. The resonance at $\delta$ ca. 6.4 for **1** completely disappeared, and this region became and remained essentially clear of even trace (at 70× amplification) resonances.
(15) (a) I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 2165 (1964); (b) K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **29,** 801 (1964).
(16) Melting points, uncorrected, were obtained in a Mel-Temp apparatus; IR spectra were recorded on a Perkin-Elmer Model 137 Infracord; NMR spectra (vs. internal $Me_4Si$) were obtained on Varian T60, XL100, and CFT20 instruments; mass spectra were determined on a CEC 110B spectrometer (70 eV).
(17) Meaningful elemental analyses could not be obtained because of the slight instability of the product. However, spectral data adequately confirmed the structure.
(18) The complexity of the NMR spectrum suggests that this might be the meso product. Intuitively, a less complicated spectrum would be expected for the *d,l* isomer pair.
(19) Calcd. for $C_{18}H_{13}N_5O$: C, 65.64; H, 3.98; N, 25.52.
(20) Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. The impurity in this product was not either of the dimers **9** or **10** (by IR and VPC) and remains unknown.


# Quinazolines and 1,4-Benzodiazepines. 84.[1] Synthesis and Reactions of Imidazo[1,5-*a*][1,4]benzodiazepines


Armin Walser,* Louis E. Benjamin, Sr., Thomas Flynn, Carl Mason, Robert Schwartz, and R. Ian Fryer

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


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Condensation of 1,4-benzodiazepines having a *N*-nitrosomethylamino group in the 2 position with a primary nitroalkane led to the nitroalkylidene derivatives **3** and **4**. These nitro compounds were converted to imidazo[1,5-*a*][1,4]benzodiazepines by a sequence of steps involving catalytic reduction, condensation with triethyl orthoacetate, and oxidation with activated manganese dioxide. A variety of chemical transformations of the imidazobenzodiazepine **9** and the nitromethylene derivative **3** are described.


The synthesis of the pharmacologically active triazolo[4,3-*a*][1,4]benzodiazepines[2] revived interest in benzodiazepines with a heterocyclic ring fused to the 1,2 position and a review of such compounds has recently been published.[3] We report the synthesis and reactions of imidazo[1,5-*a*][1,4]benzodiazepines, compounds which differ in their ring fusion from their more easily accessible isomers described in the literature.[4]

The synthesis of the title compounds was facilitated by the discovery of the carbon–carbon bond forming reaction of the nitrosoamidines **2** with carbanions.[5] Thus, the condensation of the nitrosoamidine **2** (Scheme I), obtained by nitrosation of the corresponding amidines **1**, with the anion of a nitroalkane led to the 2-nitroalkylidene benzodiazepines **3a–c** and **4**. Other methods of preparing compounds **3** have subsequently been developed in our laboratories and were published recently.[6,7]

The stereochemistry assigned to the nitroalkylidenes is based on NMR data and in particular on the large chemical shift ($\delta$ 11–12 ppm) of the proton in the 1 position which may be due to intramolecular hydrogen bonding.

Catalytic hydrogenation of the nitro compounds **3b** or **3d** over Raney nickel afforded the 2-aminomethylbenzodiazepine **5**, characterized as a dimaleate salt. Heating the amine **5** with

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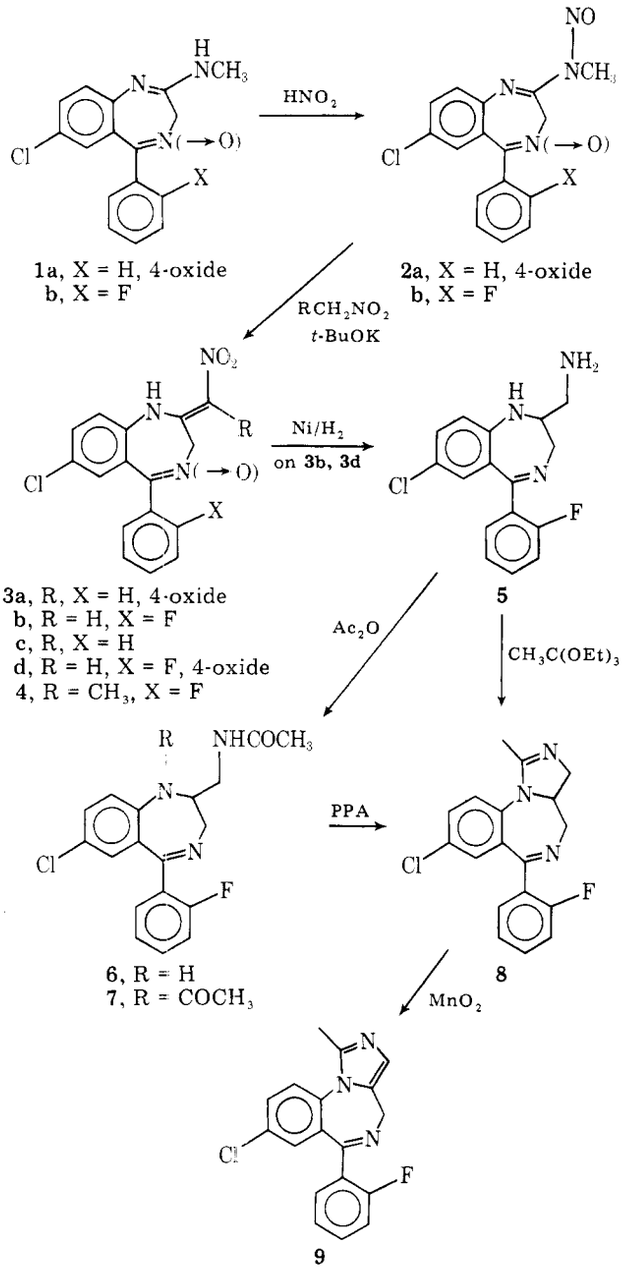
Scheme I




1a, X = H, 4-oxide
b, X = F

2a, X = H, 4-oxide
b, X = F

3a, R, X = H, 4-oxide
b, R = H, X = F
c, R, X = H
d, R = H, X = F, 4-oxide
4, R = $CH_3$, X = F

5

6, R = H
7, R = $COCH_3$

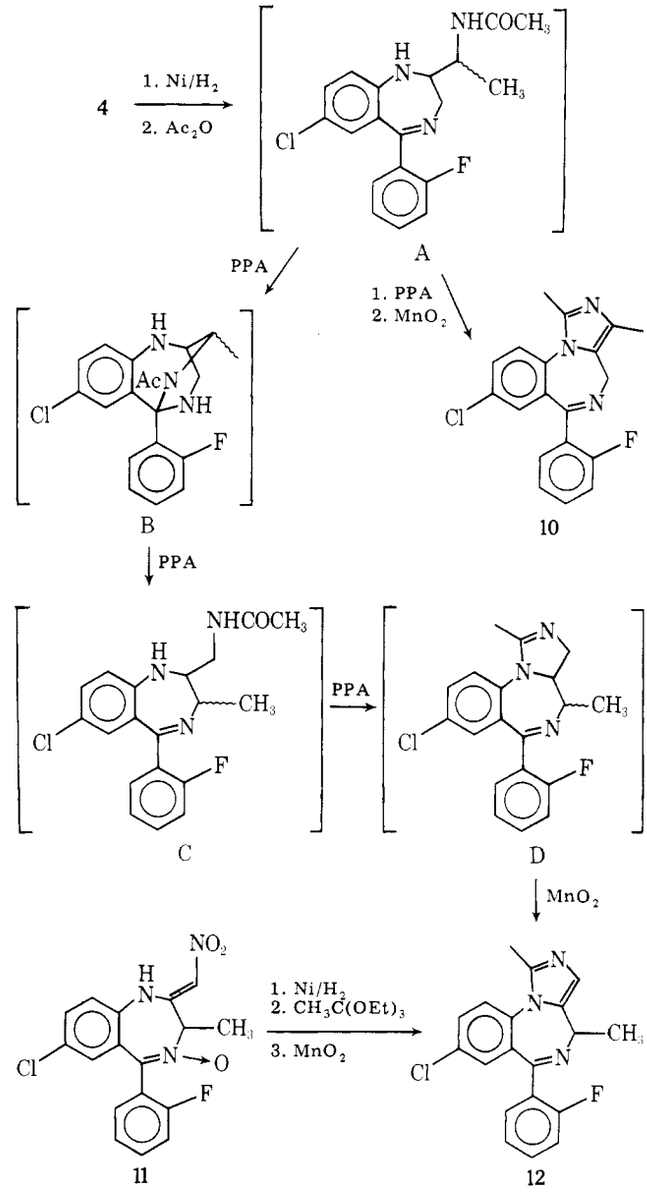
8

9

triethyl orthoacetate in boiling xylene gave the crystalline imidazoline **8** in good yield. The same imidazoline could also be obtained by cyclization of either the monoacetyl derivative **6** or the diacetate **7** by heating in polyphosphoric acid. The selective acetylation of the primary amino group of **5** was accomplished by reaction with acetic anhydride in methanol or in a two-phase system consisting of methylene chloride and aqueous sodium bicarbonate solution. The diacetate **7** was formed by acetylation of **5** with acetic anhydride in pyridine. The conversion of the imidazoline **8** to the desired imidazole **9** was carried out by oxidation with activated manganese dioxide.

When compound **4** was subjected to the same sequence of steps as described above for **3**, the expected imidazole **10** was obtained only as the minor product (Scheme II). The major product, separated by careful chromatography, was the 4-methylimidazobenzodiazepine **12**. The 4-methyl group of **12** appeared in the NMR spectrum as a doublet with $J$ = 6.5 Hz at $\delta$ 1.85 ppm. The formation of **12** from **4** implies that the seven-membered ring was opened and reclosed with participation of the 2-aminoethyl moiety. Since no ring opening was

Scheme II




A

B

10

C

D

11

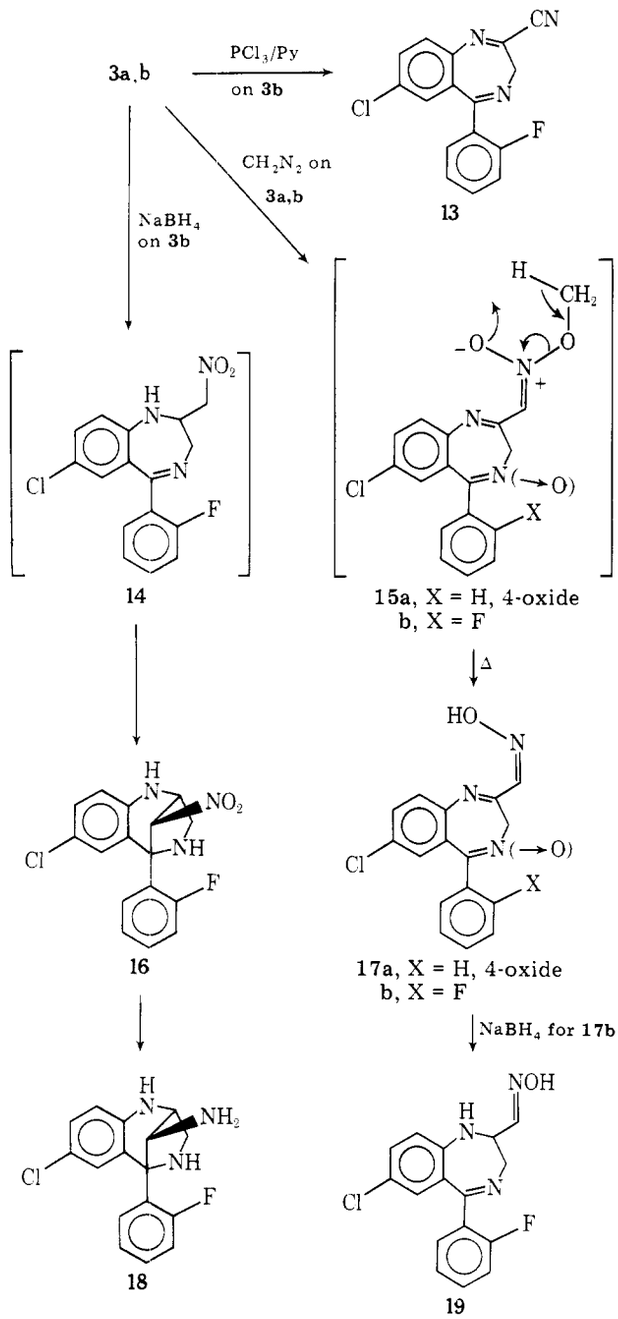
12

observed during the acetylation step, the switch of the endocyclic and exocyclic amino groups must have occurred during the treatment of A with polyphosphoric acid, most likely by formation of the bridged intermediate B. N → N migration of the acetyl groups would then lead to C which undergoes cyclization to the imidazoline D.

The 4-methylimidazobenzodiazepine **12** was better prepared by hydrogenation of the nitro compound **11**[6] followed by treatment with triethyl orthoacetate and oxidation with activated manganese dioxide. The two diastereoisomers formed by the reduction of **11** were not characterized but directly converted to a mixture of the corresponding imidazolines which again are not separated, since one asymmetric center was eliminated in the subsequent oxidation step. The racemate **12** was resolved into its optical antipodes using *O,O'*-dibenzoyl-*d*-tartaric acid. The levorotatory amorphous base gave a crystalline salt with *l*-tartaric acid with positive rotation, while the enantiomer formed a levorotatory salt with *d*-tartaric acid.

The borohydride in ethanol reduction of the exocyclic double bond in **3b** led to the bridged compound **16** (Scheme III), instead of the expected 2-nitromethyl derivative **14**. The structure of **16**, which was confirmed by single crystal x-ray analysis,[8] was originally derived from the analytical and

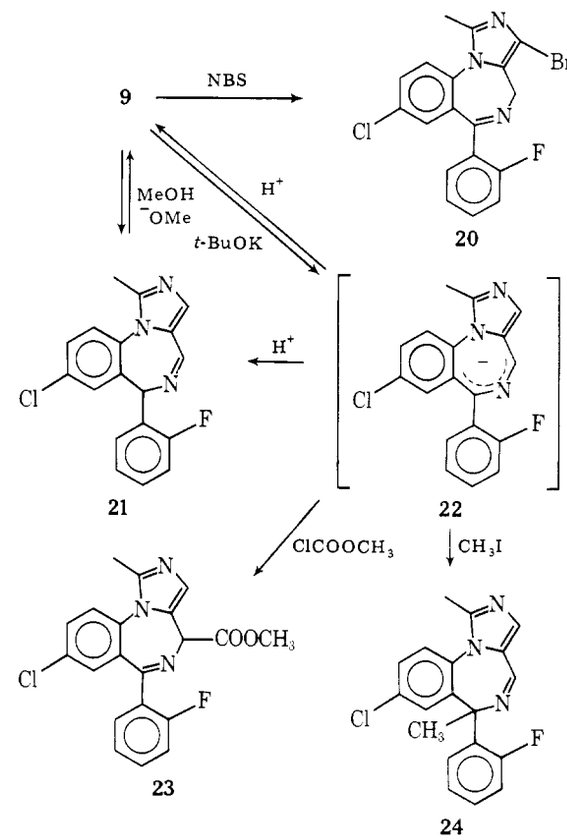
Scheme III




spectroscopic data. The coupling between the protons at positions 2 and 10 (the bridging carbon atom) was found to be zero, corresponding to a dihedral angle of ~90°. This observation would agree with the assigned stereochemistry. An unusual long-range coupling of 2 Hz between the fluorine and $C_{10}$ proton was observed and established by decoupling experiments. The transannular reaction of the nitromethyl intermediate **14** proceeded readily at room temperature and constitutes an exception to Baldwin's "Rules for Ring Closure",[9] since it involves a disfavored 5-endo trigonal cyclization. Catalytic reduction of the nitro group in **16** gave the corresponding amine **18**.

The nitrone function of **3a** was removed by treatment with phosphorus trichloride in methylene chloride without much affecting the nitromethylene moiety. However, a combination of phosphorus trichloride and pyridine converted the nitro compound **3b** in moderate yield to the 2-cyanobenzodiazepine **13**.[10] This reaction involved both a partial reduction of the nitro group and a dehydration.

Scheme IV




Another partial reduction of the nitro group was observed on treatment with diazomethane. This reagent methylated the nitromethylene derivatives **3a,b** on the oxygen of the nitro group to form the thermally labile compounds **15a,b** (of which **15a** was characterized by NMR). Heating the crude methylation products in boiling toluene for 30 min afforded the highly crystalline oximes **17**. The formaldehyde eliminated during this thermolysis by the indicated cyclic mechanism was detected and identified as its 2,4-dinitrophenylhydrazone.

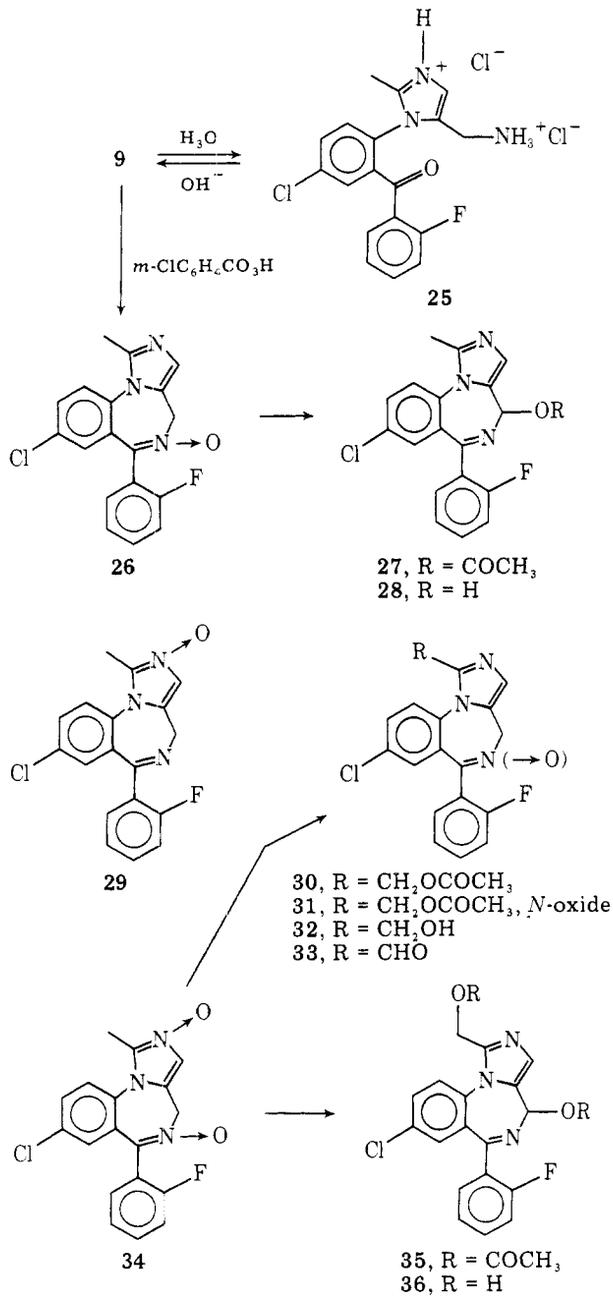
Sodium borohydride in ethanol selectively reduced the 1,2-imine moiety of **17b** and gave the 2-carboxaldoxime **19**.

The successful monoalkylation of the dianion of **3d** at low temperature to yield **11**[6] prompted us to investigate the alkylation of the imidazobenzodiazepine **9**. Methylation of this compound using potassium *tert*-butoxide and methyl iodide in dimethylformamide at −30 °C did not lead to **12** but only to the 6-methyl derivative **24** (Scheme IV). This shows that the ambident anion **22**, generated by abstraction of a proton from the 4 position, reacted with methyl iodide more readily at the 6 position. Protonation of the anion **22**, generated under the same conditions, was less selective and gave a mixture of the isomer **21** and starting material **9**. Equilibration of **21** in refluxing methanol containing methoxide resulted in almost complete conversion to **9**. According to an NMR spectroscopic estimate, the equilibrium mixture established under these conditions was composed of ~95% of **9** and 5% of **21**. Therefore it would appear that the isomer **21** is thermodynamically disfavored and that the formation of **24** and **21** by methylation or protonation of the anion **22** was due to kinetic control.

Reaction of the anion **22** with methyl chloroformate gave the 4-carboxylate **23**, although in low yield. Bromination of **9** with *N*-bromosuccinimide in acetic acid occurred predominantly on the imidazole ring and yielded the 3-bromo derivative **20**.

In acidic aqueous media, the imidazobenzodiazepine **9** exists in a pH-dependent equilibrium with the ring-opened structure **25** (Scheme V). The amount of ring-opened compound can be

Scheme V




determined spectroscopically or more accurately by reaction of the primary amino group of **25** with fluorescamine.[11] According to NMR, compound **9** was converted in over 90% to the open diprotonated species in a mixture of deuterium oxide–trifluoroacetic acid (1:1). The ring-opened compound **25** could be isolated as the crystalline dihydrochloride salt. The imidazole nitrogen in position 2 has a $pK_a$ of 6.15 ± 0.1 and is much more basic than the imine nitrogen in position 5 which shows a $pK_a$ of 1.7 ± 0.1. The open form **25** ring closes at neutral pH with a half-life of about 10 min.

The presence of two basic nitrogens complicated the oxidation of **9** with peracid. Thus, treatment of **9** with an excess of *m*-chloroperbenzoic acid led to a complex mixture containing the 5-oxide **26**, the 2-oxide **29**, and the 2,5-dioxide **34**. The 5-oxide **26** was the predominant product and was obtained by fractional crystallization. The much more polar and somewhat water-soluble 2-oxides, compounds **29** and **34**, were more difficult to isolate and had to be separated by chromatography.

The 5-oxide **26** underwent the usual Polonovsky reaction[12] and afforded the 4-acetoxy derivative **27** which was hydrolyzed to the corresponding alcohol **28**. We found that the 2-oxide function reacted preferentially under milder conditions with acetic anhydride, and thus we were able to convert the 2,5-dioxide **34** to the 1-acetoxymethyl 5-oxide **31**. Reduction of **31** with phosphorus trichloride gave compound **30**, which was also obtained by a Polonovsky rearrangement on compound **29**. For the preparation of **30**, it was therefore not necessary to separate the 2-oxide **29** from the 2,5-dioxide **34**. Hydrolysis of **30** gave the alcohol **32** which could be readily oxidized to the aldehyde **33** by the use of activated manganese dioxide. The di-*N*-oxide **34** was also subjected to a Polonovsky reaction and yielded the diacetate **35** and, after hydrolysis, the diol **36**.

## Experimental Section

Melting points were determined in a capillary melting point apparatus. The UV spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. NMR spectra were recorded with a Varian T-60 or Varian HA-100 instrument using $Me_4Si$ as an internal standard. IR spectra were determined on a Beckman IR-9 spectrometer. The mass spectra were determined on a CEC-21-100 B instrument at 70 eV. Silica gel from Merck (70–230 mesh) was used for chromatography and anhydrous sodium sulfate for drying purposes.

**7-Chloro-5-(2-fluorophenyl)-2-methylamino-3*H*-1,4-benzodiazepine (1b).** A solution of 200 g (0.695 mol) of 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one[13] in 2 L of tetrahydrofuran and 250 mL of benzene was saturated with methylamine with cooling in an ice bath. A solution of 190 g (1 mol) of titanium tetrachloride in 250 mL of benzene was added through a dropping funnel within 15 min. After addition, the mixture was stirred and refluxed for 3 h. Water, 600 mL, was added slowly to the cooled reaction mixture. The inorganic material was separated by filtration and washed well with tetrahydrofuran. The water layer was separated and the organic phase dried over sodium sulfate and evaporated. The crystalline residue was collected with ether to leave 205 g (98%) of product with mp 204–206 °C.

Anal. Calcd for $C_{16}H_{13}ClFN_3$: C, 63.69; H, 4.34; N, 13.93. Found: C, 63.57; H, 4.33; N, 14.00.

**7-Chloro-5-(2-fluorophenyl)-2-(*N*-nitrosomethylamino)-3*H*-1,4-benzodiazepine (2b).** Sodium nitrite, 34.5 g (0.5 mol), was added in three portions over a period of 30 min to a stirred solution of 120.6 g (0.4 mol) of **1b** in 500 mL of glacial acetic acid. The mixture was stirred for 3 h at room temperature and was then poured into water. The product was extracted with methylene chloride. The extracts were washed with water and saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated. Crystallization of the residue from ether yielded 79.4 g (60%) of product with mp 109–111 °C. For analysis, it was recrystallized from ether: mp 110–112 °C; UV $\lambda_{max}$ 231 ($\epsilon$ 30 700), 300 (9200), infl 340 nm (5600); NMR ($CDCl_3$) $\delta$ 3.38 (s, 3, $NCH_3$), 4.95 (br s, 2, $C_3$-H), 6.8–7.8 ppm (m, 7, aromatic H).

Anal. Calcd for $C_{16}H_{12}ClFN_4O$: C, 58.10; H, 3.65; N, 16.94. Found: C, 58.07; H, 3.73; N, 17.00.

**7-Chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-1,4-benzodiazepine 4-Oxide (3a).** A solution of 33 g (0.1 mol) of 7-chloro-2-(*N*-nitrosomethylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**2a**)[14] in 100 mL of dimethylformamide was added to a mixture of 50 mL of nitromethane, 12.5 g (0.11 mol) of potassium *tert*-butoxide, and 100 mL of dimethylformamide. The reaction mixture was stirred under a stream of nitrogen for 1 h. After the addition of 10 mL of glacial acetic acid, the product was crystallized by the gradual addition of 250 mL of water. The precipitated yellow material was collected and washed with water, methanol, and ether to leave 23.5 g (71%) with mp 253–255 °C (dec). The analytical sample was recrystallized from methylene chloride and showed the same melting point: UV $\lambda_{max}$ 235 ($\epsilon$ 26 600), 315 (18 200), 366 nm (19 400).

Anal. Calcd for $C_{16}H_{12}ClN_3O_3$: C, 58.28; H, 3.67; N, 12.74. Found: C, 58.41; H, 3.63; N, 12.74.

**7-Chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-1,4-benzodiazepine (3c).** A mixture of 3.3 g (0.01 mol) of **3a**, 3.3 mL of phosphorus trichloride, and 300 mL of methylene chloride was stirred at room temperature for 4 h. The solution was washed with 10% aqueous sodium carbonate solution, dried over sodium sulfate, and

evaporated. The crude product was purified by chromatography over 100 g of silica gel using 10% (v/v) ethyl acetate in methylene chloride. The combined clean fractions were crystallized from methylene chloride/hexane to yield 1.8 g (57.5%) of light yellow crystals with mp 184–186 °C; UV $\lambda_{max}$ 224 ($\epsilon$ 28 700), infl 260 (11 600), 364 nm (26 100); NMR ($CDCl_3$) $\delta$ 4.23 (s, 2, $C_3$-H), 6.68 (s, 1, =$CHNO_2$), 7.0–7.7 (m, 8, aromatic H), 11.3 ppm (br s, 1, NH).

Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.45; H, 3.80; N, 13.29.

**7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-2-nitromethylene-2*H*-1,4-benzodiazepine (3b).** A solution of 33 g (0.1 mol) of **2b** in 100 mL of dry dimethylformamide was added to a mixture of 200 mL of dimethylformamide, 50 mL of nitromethane, and 14 g (0.125 mol) of potassium *tert*-butoxide which had been stirred under nitrogen for 15 min.

After stirring for 1 h at room temperature, the reaction mixture was acidified by addition of glacial acetic acid, diluted with water, and extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate, and evaporated. Crystallization of the residue from ether yielded 17.5 g (53%) of yellow crystals with mp 170–172 °C. The analytical sample was recrystallized from methylene chloride/ethanol: mp 174–176 °C; UV $\lambda_{max}$ 223 ($\epsilon$ 28 000), 367 nm (25 100); NMR ($CDCl_3$) $\delta$ 4.33 (s, 2, $C_3$-H), 6.75 (s, 1, =$CHNO_2$), 6.8–7.8 (m, 7, aromatic H), 11.1 ppm (br s, 1, NH).

Anal. Calcd for $C_{16}H_{11}ClFN_3O_2$: C, 57.93; H, 3.34; N, 12.67. Found: C, 57.99; H, 3.53; N, 12.67.

**7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-2-(1-nitroethylene)-2*H*-1,4-benzodiazepine (4).** A mixture of 11.2 g (0.1 mol) of potassium *tert*-butoxide, 50 mL of nitroethane, and 200 mL of dimethylformamide was stirred at room temperature for 15 min. A solution of 29 g (0.088 mol) of crude, oily **2b** in 100 mL of dimethylformamide was then added and stirring under nitrogen was continued for 5 h. The reaction mixture was neutralized by addition of glacial acetic acid and diluted with water. The product was extracted with ether. The extracts were washed with saturated aqueous sodium bicarbonate solution, dried, and evaporated. Crystallization from ether yielded 8.1 g (26.5%) of yellow crystals with mp 136–142 °C.

The analytical sample was recrystallized twice from methylene chloride/ethanol, mp 153–155 °C; UV $\lambda_{max}$ 226 ($\epsilon$ 28 250), 390 nm (26 600); NMR ($CDCl_3$) $\delta$ 2.38 (s, 3, $CH_3$), 4.48 (br s, 2, $C_3$-H), 6.8–7.8 (m, 7, aromatic H), 12.4 (br s, 1, NH).

Anal. Calcd for $C_{17}H_{13}ClFN_3O_2$: C, 59.05; H, 3.79; N, 12.15. Found: C, 59.00; H, 3.79; N, 12.21.

**2-Aminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine Dimaleate (5).** A suspension of 17 g (0.05 mol) of **3d**[6] in 200 mL of tetrahydrofuran and 100 mL of methanol was hydrogenated in the presence of 17 g of Raney nickel at an initial pressure of 155 psi for 24 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was dissolved in 50 mL of 2-propanol and warmed on the steam bath. A warm solution of 17 g of maleic acid in 50 mL of ethanol was added and the salt was allowed to crystallize by cooling in the ice bath. The yellow crystals were collected to yield 21.9 g (83%) with mp 196–198 °C.

The analytical sample was recrystallized from methanol/water/2-propanol.

Anal. Calcd for $C_{16}H_{15}ClFN_3(C_4H_4O_4)_2$: C, 53.79; H, 4.45; N, 7.84. Found: C, 53.70; H, 4.65; N, 7.80.

**1-Acetyl-2-acetylaminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine (7).** Compound **5**, 8.0 g (0.015 mol), was partitioned between methylene chloride and aqueous ammonia. The methylene chloride solution was washed with water, dried over sodium sulfate, and evaporated. The residue was dissolved in 50 mL of pyridine. After the addition of 10 mL of acetic anhydride, the mixture was heated on the steam bath for 4 h. The reagents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and aqueous sodium bicarbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from methylene chloride/ether with seeding yielded 2.5 g (43%) of product with mp 213–215 °C. Seeds were obtained by chromatography over silica gel (40-fold amount) using 10% (v/v) ethanol in methylene chloride for elution. The analytical sample was recrystallized from ethyl acetate/hexane and had mp 215–217 °C; UV $\lambda_{max}$ infl 225 ($\epsilon$ 25 800), infl 270 (4400), infl 285 nm (2500); IR ($CHCl_3$) 3350 (NH), 1665, 1535 $cm^{-1}$ (–CON); NMR ($CDCl_3$) $\delta$ 1.88 (s, 3, $COCH_3$), 2.0 (s, 3, $COCH_3$), 2.7–3.8 (m, 3, –$CH_2$NHCO$CH_3$ and $C_3$-H), 4.1 (q, 1, $J_{AB}$ = 11 Hz, $J_{AX}$ = 4 Hz, $C_3$-H), 5.38 (m, 1, $C_2$-H), 6.66 (br s, 1, NH), 6.8–7.9 (m, 7, aromatic H).

Anal. Calcd for $C_{20}H_{19}ClFN_3O_2$: C, 61.94; H, 4.93; N, 10.83. Found: C, 62.25; H, 4.94; N, 10.71.

**8-Chloro-3a,4-dihydro-6-(2-fluorophenyl)-1-methyl-3*H*-imidazo[1,5-*a*][1,4]benzodiazepine (8).** (A) The dimaleate salt of **5**, 21.5 g (0.04 mol), was partitioned between 150 mL of methylene chloride and 100 mL of water containing 20 mL of concentrated aqueous ammonia. The organic phase was washed with water, separated, dried, and evaporated. The residue was dissolved in 100 mL of xylene and, following the addition of 22 mL (0.12 mol) of triethyl orthoacetate, the solution was heated to reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was crystallized from ether to yield 9 g (68%) of off-white crystals with mp 142–145 °C. The analytical sample was recrystallized from ethyl acetate: mp 144–146 °C; UV $\lambda_{max}$ 213 ($\epsilon$ 37 000), infl 250 (11 500), sh 280 nm (3700); NMR ($CDCl_3$) $\delta$ 1.70 (s with fine structure, 3, $CH_3$), 3.46 (q, 1, $J_{AB}$ = 12 Hz, $J_{AX}$ = 4 Hz, $C_4$-H), 3.7–4.2 (m, 3, $C_3$-H, $C_4$-H), 4.7 (m, 1, $C_{3a}$-H), 6.8–7.8 ppm (m, 7, aromatic H).

(B) Acetic anhydride, 7 mL, was added to a solution of 6.06 g (0.02 mol) of **5** in 200 mL of methylene chloride. The solution was layered with 200 mL of saturated aqueous sodium bicarbonate and the mixture was stirred for 20 min. The organic layer was separated, washed with bicarbonate solution, dried, and evaporated to leave 6.1 g of resinous 2-acetaminomethyl-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine (**6**). This material was heated with 40 g of polyphosphoric acid at 150 °C for 10 min. The initially orange color of the reaction mixture changed to a light yellow. The cooled reaction mixture was dissolved in water, made alkaline with ammonia and ice, and was extracted with methylene chloride. The extracts were dried and evaporated, and the residue was chromatographed over 120 g of silica gel using 20% (v/v) methanol in methylene chloride. Crystallization of the combined clean fractions from ether gave 3.5 g (53%) of crystalline **8** with mp 142–145 °C.

(C) A mixture of 0.5 g of (**7**) and 10 g of polyphosphoric acid was heated to 150–170 °C for 10 min. The cool reaction mixture was dissolved in ice water and the solution was made alkaline with ammonia. The precipitated base was extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed over 10 g of silica gel using 20% methanol in methylene chloride. The clean fractions were combined and evaporated. The residue was crystallized from ether to yield 0.1 g (23%) of product with mp 142–144 °C.

**8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (9).** A mixture of 13.1 g (0.04 mol) of **8**, 300 mL of toluene, and 65 g of activated manganese dioxide was heated to reflux with stirring for 40 min. The $MnO_2$ was filtered over Celite and was washed with tetrahydrofuran and methylene chloride. The filtrate was evaporated to leave 11.5 g of brown oil which was dissolved in 20 mL of hot ethanol and treated with a hot solution of 4.1 g (0.035 mol) of maleic acid in 15 mL of ethanol. After crystallization had started, 100 mL of ether was gradually added. The separated crystals were collected and washed with ether to yield 10.2 g (58%) of maleate with mp 114–117 °C (solvated).

This material was partitioned between methylene chloride and diluted aqueous ammonia. The organic phase was dried and evaporated. Crystallization from ether/methylene chloride/hexane yielded 6 g (46%) of colorless crystals with mp 158–160 °C; UV $\lambda_{max}$ 220 ($\epsilon$ 30 000), infl ca. 240 nm (20 000); NMR ($CDCl_3$) $\delta$ 2.56 (s, 3, $CH_3$), 4.03 (d, 1) and 5.13 (d, 1) (AB system, $J$ = 13 Hz, $C_4$-H), 6.8–7.8 ppm (m, 8, aromatic H and $C_3$-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3$: C, 66.36; H, 4.02; N, 12.90. Found: C, 66.35; H, 3.77; N, 12.78.

**8-Chloro-1,3-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (10) and 8-Chloro-1,4-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine Dihydrochloride (12).** Raney nickel, 5 teaspoonsful, was added to a solution of 17.3 g (0.05 mol) of **4** in 750 mL of tetrahydrofuran. The mixture was hydrogenated at atmospheric pressure for 4 h. The catalyst was removed by filtration over Celite and was washed well with methanol. The filtrate was evaporated to leave 14.1 g of crude 2-(1-aminoethyl)-7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine as a reddish oil. This material was dissolved in 300 mL of methylene chloride. Following the addition of 14 mL of acetic anhydride, 300 mL of saturated aqueous sodium bicarbonate solution was added and the two-phase mixture was stirred at room temperature for 1 h. The methylene chloride layer was separated, washed with bicarbonate, dried, and evaporated. The residue, 13.5 g, of crude A was heated with 40 g of polyphosphoric acid for 10 min at 160–170 °C. The cool reaction mixture was diluted with water, made alkaline with ammonia, and extracted with methylene chloride. The extracts were washed with water, dried, and evaporated to leave 11 g of a brown residue which was chromatographed on 250 g of silica gel using 20% (v/v) methanol in methylene chloride. The thin-layer chromatographically homogeneous fractions were combined to yield 5.1 g of

resinous imidazoline which was subjected to the following oxidation.

A mixture of the above material, 20 g of activated manganese dioxide, and 300 mL of toluene was heated to reflux for 3 h using a Dean–Stark trap to remove the water. The manganese dioxide was separated by filtration over celite and was washed well with methylene chloride. The filtrate was evaporated and the residue, 4.2 g, was chromatographed with pressure over 150 g of silica gel H using 3% ethanol in methylene chloride. The first eluted major component was 8-chloro-1,4-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine (**12**): NMR ($CDCl_3$) $\delta$ 1.85 (d, 3, $J$ = 6,5 Hz, $CHCH_3$), 3.04 (s, 3, $CH_3$), 4.18 (q, 1, $J$ = 6.5 Hz, $-CHCH_3$), 6.7–7.8 ppm (m, 8, aromatic H).

It was converted to a crystalline dihydrochloride by treatment with ethanolic hydrogen chloride in ether: mp 247–250 °C (dec); yield 1.5 g (7.5% overall from nitromethylene derivative); UV sh 215 ($\epsilon$ 34 400), infl 250 (14 000), infl 280 nm (3050).

Anal. Calcd for $C_{19}H_{15}ClFN_3 \cdot 2HCl$: C, 55.29; H, 4.11; N, 10.18. Found: C, 55.11; H, 4.39; N, 9.90.

The more polar component could be crystallized from methylene chloride/ether/hexane to yield 0.3 g (1.8% based on the nitromethylene derivative) of 8-chloro-1,3-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo [1,5-*a*][1,4]benzodiazepine (**10**) with mp 178–180 °C; UV $\lambda_{max}$ 218 ($\epsilon$ 32 000), infl 240 (19 200), infl 265 nm (8450); NMR ($CDCl_3$) $\delta$ 2.2 (s, 3, $CH_3$), 2.46 (s, 3, $CH_3$), 3.95 (d, 1) and 5.1 (d, 1) (AB system, $J$ = 13 Hz, $C_4$-H), 5.7–7.8 ppm (m, 7, aromatic H).

Anal. Calcd for $C_{19}H_{15}ClFN_3$: C, 67.16; H, 4.45; N, 12.37. Found: C, 67.10; H, 4.38; N, 12.36.

**8-Chloro-1,4-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine Dihydrochloride (12).** A mixture of 216 g (0.6 mol) of 7-chloro-5-(2-fluorophenyl-1,3-dihydro-3-methyl-2-(nitromethylene)-2*H*-1,4-benzodiazepine 4-oxide (**11**),[6] 300 g of Raney nickel and 3 L of ethanol was hydrogenated for 16 h at an initial pressure of 480 psi. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in 400 mL of hot 2-propanol and treated with a hot solution of 140 g of maleic acid in 200 mL of ethanol. The crystals which separated upon cooling were collected and washed with ether to give 185 g (56%) of the dimaleate salt of 2-(1-aminoethyl)-7-chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine.

A portion of this salt, 100 g, was partitioned between aqueous ammonia and methylene chloride. The organic phase was dried and evaporated. The residue was dissolved in 500 mL of xylene and the solution was heated to reflux for 2 h after the addition of 100 mL of triethyl orthoacetate. The solvent was removed under reduced pressure to give 55 g of crude imidazoline which was dissolved in 600 mL of toluene and treated with 250 g of activated manganese dioxide. The mixture was stirred and heated to reflux with separation of water for 2 h. The $MnO_2$ was filtered off and washed well with methylene chloride and tetrahydrofuran. The filtrate was evaporated and the residue was dissolved in 60 mL of 2-propanol. The dihydrochloride was precipitated by the addition of ethanolic hydrogen chloride. The crystals were collected and washed with ether to yield 25 g (33%) of product with mp 245–248 °C.

**Resolution of 12.** A mixture of 17 g (0.05 mol) of racemic 8-chloro-1,4-dimethyl-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine, which had been liberated from its dihydrochloride by partitioning between methylene chloride and aqueous ammonia, 18.8 g (0.05 mol) of *O,O'*-dibenzoyl-*d*-tartaric acid hydrate, and 170 mL of ethanol was boiled until the solution was complete. For crystallization, the solution was allowed to sit overnight. The separated crystals were collected and washed with ethanol and ether to yield 8.4 g (47%) with mp 140–142 °C. Recrystallization from ethanol/ether yielded 4.4 g with mp 141–142 °C and $[\alpha]^{25}_D$ −43.39° (*c* 1% in methanol).

A solution of 1.6 g (0.0106 mol) of *l*-tartaric acid in 11 mL of ethanol was added to a solution of 3.5 g of the levorotatory base liberated from the above *O,O'*-dibenzoyl-*d*-tartrate, in 11 mL of ethanol. The crystals obtained were collected and washed with ethanol and ether to yield 2.8 g (55%) of product with mp 178–180 °C. Recrystallization from ethanol gave 2.1 g with mp 183–185 °C and $[\alpha]^{25}_D$ + 25.69° (*c* 1.012% in methanol). The amorphous base liberated from this salt showed a rotation of $[\alpha]^{25}_D$ −36.74° (*c* 0.939% in methylene chloride).

The mother liquor left after separation of the crystalline salt with *O,O'*-dibenzoyl-*d*-tartaric acid described above was evaporated and reconverted to the base by partitioning between aqueous ammonia and methylene chloride. The methylene chloride solution was dried over sodium sulfate and evaporated to yield 12 g of partly resolved base.

A solution of 9.7 g (0.029 mol) of this material in 15 mL of ethanol was treated with a solution of 4.4 g of *d*-tartaric acid in 14 mL of ethanol. The crystals which separated after several hours were collected to yield 3.2 g (23%) with mp 176–178 °C. Recrystallization from ethanol gave 2.1 g of product with mp 182–184 °C and $[\alpha]^{25}_D$ −24.96° (*c* 0.616% in methanol). The amorphous base liberated from this salt showed a rotation of $[\alpha]^{25}_D$ + 37.6° (*c* 1.0% in methylene chloride).

**7-Chloro-2-cyano-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine (13).** Phosphorus trichloride, 0.5 mL, was added to a solution of 1 g (0.0003 mol) of **3b** in 20 mL of methylene chloride and 20 mL of pyridine. The solvents were evaporated under reduced pressure after 4 h and the residue was taken up in methylene chloride. Some insoluble material was removed by filtration and the filtrate was evaporated and chromatographed over 20 g of silica gel using methylene chloride. The clean fractions were combined and evaporated, and the residue was crystallized from ether/hexane to yield 0.285 g (31.5%) with mp 106–110 °C; UV $\lambda_{max}$ 215 ($\epsilon$ 28 500), sh 240 (20 200), sh 322 (3800), 338 nm (3820); NMR ($CDCl_3$) $\delta$ 4.18 (s, 2, $C_3$-H), 6.8–7.8 (m, 7, aromatic H).

Anal. Calcd for $C_{16}H_9ClFN_3$: C, 64.55; H, 3.05; N, 14.11. Found: C, 64.51; H, 2.96; N, 14.11.

**7-Chloro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-10-nitro-2,5-methano-1*H*-1,4-benzodiazepine (16).** A mixture of 20 g (0.06 mol) of **3b**, 200 mL of ethanol, 200 mL of methylene chloride, and 5 g (0.132 mol) of sodium borohydride was stirred at room temperature for 15 min. After dilution with water and methylene chloride, the organic layer was separated, dried, and evaporated. Crystallization of the residue from methylene chloride/ethyl acetate/hexane gave 17.7 g (88%) of light yellow crystals. The analytical sample was recrystallized from methylene chloride/ethyl acetate: mp 202–204 °C (dec); UV $\lambda_{max}$ 258 ($\epsilon$ 12 200), 318 nm (2900); IR ($CHCl_3$) 3400 (NH), 1550 $cm^{-1}$ ($NO_2$); NMR ($Me_2SO$-*d*) $\delta$ 3.24 (m, 1, $C_3$-H), 3.57 (m, 1, $C_3$-H), 3.98 (br t, $J$ = 5 Hz, NH), 4.33 (t, 1, $J$ = 4 Hz, $C_2$-H), 5.63 (d, 1, $J$ = 2 Hz, $C_{10}$-H), 6.07 (d, 1, $J$ = 2.5 Hz, $C_6$-H), 6.5–7.8 (m, 7, aromatic H and NH). Single crystal x-ray analysis[8] was performed on this compound.

Anal. Calcd for $C_{16}H_{13}ClFN_3O_2$: C, 57.58; H, 3.93; N, 12.59. Found: C, 57.59; H, 4.10; N, 12.55.

**10-Amino-7-chloro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-2,5-methano-1*H*-1,4-benzodiazepine (18).** A solution of 25 g (0.074 mol) of **16** in 500 mL of tetrahydrofuran and 250 mL of ethanol was hydrogenated at atmospheric pressure for 1 h in the presence of 2 teaspoonsful of Raney nickel. The catalyst was separated by filtration and the filtrate was evaporated under reduced pressure. Crystallization of the residue from ether yielded 16 g (70.5%) of colorless crystals with mp 138–140 °C. The analytical sample was recrystallized from ether/hexane: mp 142–145 °C; UV $\lambda_{max}$ 262 ($\epsilon$ 9350), 267 (9380), 317 nm (2560).

Anal. Calcd for $C_{16}H_{15}ClFN_3$: C, 63.27; H, 4.98; N, 13.83. Found: C, 63.18; H, 5.08; N, 13.61.

**7-Chloro-5-phenyl-3*H*-1,4-benzodiazepine-2-carboxaldoxime 4-Oxide (17a).** A solution of 6.8 g (0.02 mol) of **3a** in 1600 mL of methylene chloride and 400 mL of methanol was treated with an excess of a solution of diazomethane in ether. After sitting at room temperature for 30 min, the excess diazomethane was destroyed by the addition of 10 mL of glacial acetic acid. The reaction mixture was washed with water and sodium bicarbonate solution, dried, and evaporated. The orange oil obtained consisted, according to the thin-layer chromatogram [5% (v/v) of methanol in chloroform], mainly of a product less polar than starting material. A sample of this material was purified by thick-layer chromatography and characterized by NMR: NMR ($Me_2SO$-*d*) $\delta$ 3.84 (s, 3, $OCH_3$), 5.03 (br s, 2, $C_3$-H), 6.8–7.8 (m, 9, aromatic H and –CH=N).

The crude product **15a** was heated to reflux for 30 min with 25 mL of toluene. The crystals which separated from the cooled reaction mixture were collected and washed with a small amount of ethanol and ether to leave 3.5 g (56%) of product which was recrystallized from ethanol. The analytical sample was recrystallized from methylene chloride/ether to give off-white crystals with mp 226–231 °C; UV $\lambda_{max}$ 250 ($\epsilon$ 30 600), 291 (21 400), infl 350 nm (4200); NMR ($Me_2SO$-*d*) $\delta$ 4.86 (br s, 2, $C_3$-H), 6.96 (m, 1, $C_6$-H), 7.2–7.5 (m, 7, aromatic H), 8.02 (s, 1, –CH=N), 12.7 (br s, 1, OH).

Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.85; N, 13.39. Found: C, 61.24; H, 3.74; N, 13.35.

**7-Chloro-5-(2-fluorophenyl)-3*H*-1,4-benzodiazepine-2-carboxaldoxime (17b).** Similarly, reaction of 0.33 g (0.001 mol) of **3b** with diazomethane followed by a 10-min reflux in xylene yielded 0.085 g (27%) of **17b**. The analytical sample was recrystallized from methylene chloride/methanol/ethyl acetate to give yellow crystals with mp 250–251 °C (dec); UV $\lambda_{max}$ 232 ($\epsilon$ 31 500), infl 270 (16 000), 319 nm (5800); NMR ($Me_2SO$-*d*) $\delta$ 4.33 (br s, 2, $C_3$-H), 7–7.8 (m, 7, aromatic

H), 7.85 (s, 1, CH=N), 12.5 ppm (s, 1, OH).

Anal. Calcd for $C_{16}H_{11}ClFN_3O$: C, 60.87; H, 3.51; N, 13.31. Found: C, 60.70; H, 3.57; N, 13.12.

**7-Chloro-2,3-dihydro-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine-2-carboxaldoxime (19).** A mixture of 1.3 g (0.0038 mol) of **17b**, 50 mL of ethanol, 25 mL of methylene chloride, and 1 g (0.026 mol) of sodium borohydride was heated to reflux for 4 h. After standing overnight at room temperature, the reaction mixture was diluted with water. The organic layer was separated, dried, and evaporated. Crystallization from methylene chloride/ethyl acetate gave 0.4 g of yellowish crystals with mp 195–197 °C. An additional 0.3 g (total yield 58%) was obtained by chromatography of the mother liquor over 25 g of silica gel using 5% (v/v) ethanol in methylene chloride. For analysis, the product was recrystallized from methylene chloride/ethyl acetate, mp unchanged: UV $\lambda_{max}$ 237 ($\epsilon$ 24 800), infl 270 (7800), 368 nm (3200); NMR ($Me_2SO$-$d_6$) $\delta$ 3.94 (d, 2, $J$ = 4.5 Hz, $C_3$-H), 4.5 (m, 1, $C_2$-H), 6.5–7.6 (m, 9, aromatic H, NH, -CH=N), 10.85 ppm (s, 1, OH).

Anal. Calcd for $C_{16}H_{13}ClFN_3O$: C, 60.48; H, 4.12; N, 13.22. Found: C, 60.43; H, 4.27; N, 13.14.

**3-Bromo-8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (20).** A mixture of 10 g (0.03 mol) of **9**, 450 mL of chloroform, 30 mL of glacial acetic acid, and 13.7 g (0.077 mol) of *N*-bromosuccinimide was heated to reflux with stirring for 1.5 h. The cooled mixture was washed with saturated sodium bicarbonate solution and was dried and evaporated. The oily residue was chromatographed over 150 g of neutral aluminum oxide (Woelm). The impurities were eluted with methylene chloride and the product was eluted with ethyl acetate. Crystallization of the combined clean fractions from ether yielded 4.5 g (36.2%) of colorless crystals with mp 201–205 °C. For analysis, a sample was recrystallized from ether/hexane: mp 203–205 °C; UV sh 215 ($\epsilon$ 82 500), infl ~242 (44 500), infl 265 (20 700), infl 307 nm (2300); NMR ($CDCl_3$) $\delta$ 2.55 (s, 3, $CH_3$), 3.97 (d, 1) and 5.2 (d, 1) (AB system, $J$ = 13 Hz, $C_4$-H), 6.8–7.8 (m, 7, aromatic H).

Anal. Calcd for $C_{18}H_{12}BrClFN_3$: C, 53.42; H, 2.99; N, 10.38. Found: C, 53.65; H, 2.95; N, 10.19.

**8-Chloro-1,6-dimethyl-6-(2-fluorophenyl)-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine (24).** A solution of 1.6 g (5 mmol) of **9** in 30 mL of dimethylformamide was cooled to −30 °C when 0.85 g (7.5 mmol) of potassium *tert*-butoxide was added. After stirring under nitrogen for 15 min at −30 to −10 °C, 0.5 mL (8 mmol) of methyl iodide was added. The mixture was stirred for 15 min without cooling and was then partitioned between aqueous bicarbonate and methylene chloride/toluene (1:3). The organic phase was dried and evaporated. Crystallization of the residue from ether yielded 0.9 g (54%) of product which was recrystallized twice from ethyl acetate/hexane for analysis: mp 165–167°; UV $\lambda_{max}$ infl 228 ($\epsilon$ 16 600), 263 (8800), 270 (8500), infl 280 nm (7100); NMR ($CDCl_3$) $\delta$ 2.17 (s, 3, $CH_3$), 2.3 (s, 3, $CH_3$), 6.5–8.0 (m, 8, aromatic H, $C_3$-H), 8.47 (s, 1, $C_4$-H).

Anal. Calcd for $C_{19}H_{15}ClFN_3$: C, 67.16; H, 4.45; N, 12.37. Found: C, 67.41; H, 4.30; N, 12.42.

**8-Chloro-6-(2-fluorophenyl)-1-methyl-6*H*-imidazo[1,5-*a*][1,4]benzodiazepine (21).** (A) Potassium *tert*-butoxide, 0.625 g (5.5 mmol), was added to a solution of 1.625 g (5 mmol) of **9** in 20 mL of dimethylformamide cooled to −30 °C. After stirring under nitrogen for 10 min at −30 °C, the dark mixture was acidified with 1 mL of glacial acetic acid and was then partitioned between aqueous bicarbonate and toluene/methylene chloride (3:1, v/v). The organic layer was separated, dried, and evaporated. the residue was chromatographed over 50 g of silica gel using 25% (v/v) methylene chloride in ethyl acetate. The less polar product was eluted first and was crystallized from ethyl acetate/hexane to yield 340 mg (21%) of product with mp 180–181 °C: UV $\lambda_{max}$ infl 218 nm ($\epsilon$ 20 600), sh 265 (11 150), 255 (11 500), 267 (10 980), infl 288 (5600); NMR ($CDCl_3$) $\delta$ 2.7 (s, 3, $CH_3$), 5.61 (d, 1, $J$ = 2 Hz, $C_6$-H), 6.77 (s, with fine structure, 1, $C_3$-H), 8.4 (d, 1, $J$ = 2 Hz, $C_4$-H), 6.8–8.3 ppm (m, 7, aromatic H).

Anal. Calcd for $C_{18}H_{13}N_3ClF$: C, 66.37; H, 4.02; N, 12.90. Found: C, 66.56; H, 4.01; N, 12.85.

**(B) Equilibration of 9 with Methoxide in Methanol.** A mixture of 0.65 g (2 mmol) of **9**, 20 mL of methanol, and 0.1 g (0.9 mmol) of potassium *tert*-butoxide was heated to reflux for 16 h. After dilution with water, the mixture was extracted with methylene chloride. The extracts were dried and evaporated. A portion was azeotroped with carbon tetrachloride to determine the NMR spectrum which indicated 5 ± 1% of the isomer **21** having formed.

**Equilibration of 21 to 9. (A) With *tert*-Butoxide in DMF.** Potassium *tert*-butoxide, 0.125 g (1.1 mmol), was added to a solution of 0.325 g (1 mmol) of **21** in 20 mL of dimethylformamide cooled to −30 °C. After stirring at −30 to −20 °C for 15 min, the reaction mixture was acidified by the addition of 0.2 mL of glacial acetic acid and was partioned between aqueous sodium bicarbonate and methylene chloride/toluene (1:3). The organic phase was washed with water, dried, and evaporated. The residue was chromatographed over 20 g of silica gel using ethyl acetate for elution. After elution of 125 mg of starting material, 130 mg of **9** was collected and crystallized from ether/hexane, mp 156–158 °C.

**(B) With Methoxide in Methanol.** A solution of 0.325 g (1 mmol) of **21** in 10 mL of methanol was heated to reflux for 4 h after the addition of 50 mg (0.44 mmol) of potassium *tert*-butoxide. The reaction mixture was diluted with water and was extracted with methylene chloride. The extracts were dried and evaporated.

The residue was dissolved in a small amount of hot 2-propanol and combined with a hot solution of maleic acid in 2-propanol. The maleate salt of **9** was crystallized by the addition of ether to yield 380 mg (86%) of colorless crystals which, after drying at 90 °C under high vacuum, had mp 148–150 °C. Conversion to the base gave 220 mg (67.5%) of crystals with mp 156–158 °C.

Thin-layer chromatography showed the presence of a small amount of starting material.

**Methyl 8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-4-carboxylate (23).** Potassium *tert*-butoxide, 0.25 g (2.2 mmol), was added to a solution of 0.65 g (2 mmol) of **9** in 10 mL of dimethylformamide cooled to −30 °C. After stirring under nitrogen for 10 min, 0.2 mL of methyl chloroformate was added in one portion at −30 °C. When the reaction mixture had warmed to 0 °C it was partitioned between methylene chloride and saturated sodium bicarbonate solution. The methylene chloride layer was diluted with benzene, washed with bicarbonate solution and water, dried, and evaporated. The residue was chromatographed over 20 g of silica gel using ethyl acetate. Crystallization of the combined clean fractions of products from ether yielded 0.13 g (17%) of colorless crystals with mp 203–205 °C. The analytical sample was recrystallized from ethyl acetate/hexane: UV $\lambda_{max}$ 220 ($\epsilon$ 32 000), infl 240 (21 200), infl 300 nm (1600); IR (KBr) 1750 $cm^{-1}$ (COOMe); NMR ($CDCl_3$) $\delta$ 2.56 (s, 3, $CH_3$), 4.0 (s, 3, $COOCH_3$), 4.9 (s, 1, $C_4$-H), 6.8–8.0 (m, 8, aromatic H, $C_3$-H).

Anal. Calcd for $C_{20}H_{15}ClFN_3O_2$: C, 62.59; H, 3.94; N, 10.95. Found: C, 62.63; H, 3.92; N, 10.78.

**5-Aminomethyl-1-[4-chloro-2-(2-fluorobenzoyl)phenyl]-2-methylimidazole Dihydrochloride (25).** A solution of 25 g of **9** in 50 mL of water and 50 mL of concentrated hydrochloric acid was allowed to stand at room temperature for 3 h. Following the addition of 250 mL of 2-propanol, the mixture was evaporated partially under reduced pressure without heating. An additional 200 mL of 2-propanol was added and partial evaporation was resumed. The precipitated crystals were collected and washed well with 2-propanol and ether to yield 31.7 g (98%) of product with mp 302–307 °C (dec).

The analytical sample was recrystallized from methanol/2-propanol without heating: UV (0.1 N HCl) $\lambda_{max}$ sh 215 ($\epsilon$ 26 700), 258 (12 000), infl 290 (4700); IR (KBr) 1650 $cm^{-1}$ (CO).

Anal. Calcd for $C_{18}H_{15}ClFN_3O{\cdot}2HCl$: C, 51.88; H, 4.11; N, 10.08. Found: C, 52.06; H, 4.13; N, 10.21.

**8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 5-Oxide (26).** A mixture of 9.75 g (0.03 mol) of **9**, 200 mL of methylene chloride, and 12 g (0.07 mol) of *m*-chloroperbenzoic acid was stirred for 1.5 h. The solution was then extracted with 3 × 150 mL of 1 N hydrochloric acid. The extracts were washed with ether, made alkaline with ammonia, and extracted with methylene chloride. The methylene chloride extracts were dried and evaporated, and the residue was crystallized from ethyl acetate to leave 4 g of product which was further purified by chromatography over 100 g of silica gel using 5% (v/v) ethanol in methylene chloride. The clean fractions were combined and evaporated. Crystallization of the residue from ethyl acetate/ether yielded 3.4 g (33%) of colorless crystals with mp 245–246 °C (dec): NMR ($Me_2SO$-$d$) $\delta$ 2.53 (s, 3, $CH_3$), 4.95 (d, 1) and 5.28 (d, 1) (AB system, $J$ = 14 Hz, $C_4$-H), 6.8–8.0 (m, 8, aromatic H and $C_3$-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3O$: C, 63.26; H, 3.83; N, 12.30. Found: C, 63.35; H, 4.11; N, 12.22.

**4-Acetoxy-8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (27).** A solution of 4 g of **26** in 100 mL of acetic anhydride was heated on the steam bath for 24 h. The reagent was evaporated under reduced pressure, at the end azeotropically with xylene. The residue was chromatographed over 80 g of silica gel using 20% (v/v) methylene chloride in ethyl acetate. Crystallization of the clean fractions from methylene chloride/ether yielded 1.4 g of colorless crystals, mp 201–202 °C. A second crop (1.5 g) of contaminated product was recovered from other fractions to yield a total of 2.9 g (64.5%).

Anal. Calcd for $C_{20}H_{15}ClFN_3O_2$: C, 62.42; H, 4.19; N, 10.92. Found: C, 62.69; H, 3.96; N, 10.87.

**8-Chloro-6-(2-fluorophenyl)-4-hydroxy-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (28).** Compound **27**, 0.5 g (1.3 mmol), was added to 40 mL of methanol containing 4 mmol of sodium methoxide. After stirring under nitrogen for 0.5 h at room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in water and the solution was acidified with acetic acid. The precipitated crystals were collected and dissolved in methylene chloride. The solution was dried and evaporated, and the residue was crystallized from methylene chloride/ether to yield 0.4 g (90%) of colorless crystals with mp 185–186 °C: UV $\lambda_{max}$ sh 220 ($\epsilon$ 34 800), infl 241 (21 200), infl 260 (10 600), infl 305 nm (1500); NMR ($Me_2SO$-*d*) $\delta$ 2.47 (s, 3, $CH_3$), 5.6 (br s, 1, $C_4$-H), 6.8–8.0 ppm (m, 9, aromatic H, $C_3$-H, OH).

Anal. Calcd for $C_{18}H_{13}ClFN_3O$: C, 63.26; H, 3.83; N, 12.29. Found: C, 63.04; H, 3.73; N, 12.01.

**8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 2-Oxide (29) and 8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 2,5-Dioxide (34).** A mixture of 9.75 g (0.03 mol) of **9**, 18 g (0.105 mol) of *m*-chloroperbenzoic acid, and 200 mL of methylene chloride was stirred at room temperature overnight. After dilution with 500 mL of ether, the reaction mixture was extracted two times with 100 mL of 2 N hydrochloric acid and two times with 100 mL of 1 N hydrochloric acid. The extracts were washed with ether, made alkaline with ammonia, and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from ethanol gave 2.2 g of the 5-oxide **26**. The mother liquor was saved for chromatography. The aqueous phase was evaporated under reduced pressure to dryness. The residue was washed out well with methylene chloride containing 20% (v/v) ethanol. The combined washings were evaporated to leave 1.5 g of oxide mixture which was chromatographed together with the material from the evaporated mother liquor above over 65 g of silica gel using first 20% (v/v) ethanol in methylene chloride to elute an additional 1.0 g of the 5-oxide **26** for a total of 3.2 g (31%). The solvent mixture methanol–methylene chloride (3:7) then eluted the 2-oxide **29** which was crystallized from ethyl acetate to give 0.26 g (2.5%) of crystals with mp 179–181 °C (dec), after recrystallization from ethyl acetate/methanol; UV $\lambda_{max}$ 227 ($\epsilon$ 34 400), infl 245 (30 100), infl 270 (12 900), infl 315 nm (2750); NMR ($CDCl_3$) $\delta$ 2.67 (s, 3, $CH_3$), 4.05 (d, 1) and 5.1 (d, 1) (AB system, $J$ = 13 Hz, $C_4$-H), 6.8–7.8 ppm (m, 8, aromatic H, $C_3$-H).

The 2,5-dioxide **34** was obtained from the later fractions and was crystallized from ethyl acetate to give 1.2 g (11%) of off-white crystals with mp 225–230 °C (dec). The analytical sample was recrystallized from methanol/ethyl acetate: UV $\lambda_{max}$ 219 ($\epsilon$ 26 700), infl 241 (17 700), 267 (24 900), sh 308 nm (10 700); NMR ($Me_2SO$-*d*) $\delta$ 2.67 (s, 3, $CH_3$), 5.0 (s, 2, $C_4$-H), 6.8–7.8 ppm (m, 8, aromatic H and $C_3$-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3O_2$: C, 60.43; H, 3.55; N, 11.75. Found: C, 60.37; H, 3.61; N, 11.87.

**1-Acetoxymethyl-8-chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine 5-Oxide (31).** A solution of 1 g (2.5 mmol) of **34** in 10 mL of acetic anhydride was heated on the steam bath for 15 min. The reagent was evaporated under reduced pressure and the residue was crystallized from ethyl acetate/ether to yield 0.9 g (80%) of crystals with mp 203–205 °C. For analysis it was recrystallized from ethyl acetate: UV $\lambda_{max}$ 216 ($\epsilon$ 26 500), infl 230 (24 600), infl 257 (17 000), 297 nm (10 700); IR ($CHCl_3$) 1745 $cm^{-1}$ (OCO); NMR ($CDCl_3$) $\delta$ 2.1 (s, 3, $COCH_3$), 5.08 (d, 1) and 5.61 (d, 1) (AB system, $J$ = 13.5 Hz, $-CH_2O$), 5.13 (s, 2, $C_4$-H), 6.8–7.8 ppm (m, 8, aromatic H and $C_3$-H).

Anal. Calcd for $C_{20}H_{15}ClFN_3O_3$: C, 60.09; H, 3.78; N, 10.51. Found: C, 59.97; H, 3.71; N, 10.59.

**1-Acetoxymethyl-8-chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (30).** A mixture of 1 g (2.5 mmol) of **31**, 30 mL of methylene chloride, and 3 mL of phosphorus trichloride was allowed to sit at room temperature for 24 h. After evaporation under reduced pressure, the residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from ethyl acetate/hexane gave 0.75 g (78%) of colorless product with mp 151–152 °C. For analysis it was recrystallized from ethyl acetate/ether: UV $\lambda_{max}$ 215 ($\epsilon$ 40 600), infl 241 (22 750), infl 305 nm (1300); IR ($CHCl_3$) 1745 $cm^{-1}$ (OCO); NMR ($CDCl_3$) $\delta$ 2.08 (s, 3, $COCH_3$), 4.1 (d, 1) and 5.23 (d, 1) (AB system, $J$ = 13 Hz, $C_4$-H), 5.03 (d, 1) and 5.65 (d, 1) (AB system, $J$ = 13.5 Hz, $-CH_2O$), 6.8–7.8 ppm (m, 8, aromatic H, and $C_3$-H).

Anal. Calcd for $C_{20}H_{15}ClFN_3O_2$: C, 62.59; H, 3.94; N, 10.95. Found: C, 62.70; H, 3.83; N, 11.17.

**8-Chloro-6-(2-fluorophenyl)-1-hydroxymethyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (32).** Sodium methoxide, 0.3 g, was added to a solution of 1 g (2.6 mmol) of **30** in 20 mL of methanol. After standing for 10 min at room temperature, the separated crystals were collected, washed with aqueous methanol, methanol, and ether to yield 0.8 g (89%) of colorless product. The analytical sample was recrystallized from methylene chloride/ethanol: mp 258–260 °C; UV $\lambda_{max}$ sh 215 ($\epsilon$ 33 100), infl 240 (25 000), infl 305 nm (1600); NMR ($Me_2SO$-*d*) $\delta$ 4.05 (d, 1) and 5.1 (d, 1) (AB system, $J$ = 13 Hz, $C_4$-H), 4.33 (q, 1, $J_{AB}$ = 13 Hz, $J_{AX}$ = 6 Hz, $-CH_2O$), 4.76 (q, 1, $J_{AB}$ = 13 Hz, $J_{AX}$ = 5 Hz, $-CH_2O$), 5.66 (t, 1, $J$ = 5.5 Hz, OH), 6.95 (s, 1, $C_3$-H), 7.0–7.8 (m, 6, aromatic H), 8.1 ppm (d, 1, $J$ = 8 Hz, $C_{10}$-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3O$: C, 63.26; H, 3.83; N, 12.30. Found: C, 63.10; H, 3.70; N, 12.47.

**8-Chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-1-carboxaldehyde (33).** A mixture of 0.2 g (0.58 mmol) of **32**, 20 mL of methylene chloride, and 1 g of activated manganese dioxide was stirred at room temperature for 2 h. The manganese dioxide was removed by filtration over celite and the filtrate was evaporated. Crystallization of the residue from methylene chloride/ethyl acetate/hexane gave 90 mg (45%) of colorless crystals with mp 182–183 °C: UV $\lambda_{max}$ infl 215 ($\epsilon$ 36 200), infl 250 (15 200), 294 nm (11 300); IR (KBr) 1690 $cm^{-1}$ (CHO); NMR ($CDCl_3$) $\delta$ 4.0 (d, 1) and 5.21 (d, 1) (AB system, $J$ = 13 Hz, $C_4$-H), 6.8–7.8 (m, 8, aromatic H, $C_3$-H), 9.9 ppm (s, 1, CHO).

Anal. Calcd for $C_{18}H_{11}ClFN_3O$: C, 63.63; H, 3.26; N, 12.37. Found: C, 63.69; H, 3.36; N, 12.57.

**4-Acetoxy-1-acetoxymethyl-8-chloro-6-(2-fluorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (35).** A solution of 1.5 g (4.18 mmol) of **34** in 50 mL of acetic anhydride was heated to reflux for 1.5 h. The reagent was evaporated under reduced pressure, at the end azeotropically with toluene. The residue was filtered over a pad of silica gel using methylene chloride/ether. The filtrate was evaporated and crystallized from ethyl acetate/ether with seeding. Seeds were obtained by chromatography over a 40-fold amount of silica gel using benzene/ether, 1:1. The separated colorless crystals (0.65 g or 31.7%) were collected and recrystallized from ethyl acetate/hexane: mp 175–177 and 184–187 °C; NMR ($CDCl_3$) $\delta$ 2.05 (s, 3, $COCH_3$), 2.32 (s, 3, $COCH_3$), 4.96 (d, 1) and 5.56 (d, 1) (AB system, $J$ = 13.5 Hz, $-CH_2O$), 6.66 (s, 1, $C_4$-H), 6.8–7.9 ppm (m, 8, aromatic H, and $C_3$-H).

Anal. Calcd for $C_{22}H_{17}ClFN_3O_4$: C, 59.80; H, 3.88; N, 9.51. Found: C, 59.82; H, 4.05; N, 9.40.

**8-Chloro-6-(2-fluorophenyl)-4-hydroxy-1-hydroxymethyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (36).** Sodium hydroxide, 10 mL, 1 N, was added to a solution of 0.65 g (1.47 mmol) of **35** in 30 mL of methanol. The mixture was heated on the steam bath for 15 min and was then partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from methylene chloride/ethanol yielded 0.39 g (74%) of colorless crystals. The analytical sample was recrystallized from tetrahydrofuran/ethanol: mp 238–240 °C; UV $\lambda_{max}$ 216 ($\epsilon$ 36 600), sh 240 (23 500), sh 305 nm (1300); NMR ($Me_2SO$-*d*) $\delta$ 4.29 (q, 1, $J_{AB}$ = 13 Hz, $J_{AX}$ = 6 Hz, $-CH_2O$), 4.70 (q, 1, $J_{AB}$ = 13 Hz, $J_{AX}$ = 5.5 Hz, $-CH_2O$), 5.55 (d, 1, $J$ = 6.5 Hz, $C_4$-H), 5.66 (t, 1, $J$ = 5.5 Hz, $-CH_2OH$), 6.84 (d, 1, $J$ = 6.5 Hz, –OH), 6.92 (s, 1, $C_3$-H), 7.0–7.8 (m, 6, aromatic H), 8.10 ppm (d, 1, $J$ = 8 Hz, $C_{10}$-H).

Anal. Calcd for $C_{18}H_{13}ClFN_3O_2$: C, 60.43; H, 3.66; N, 11.75. Found: C, 60.37; H, 3.85; N, 11.66.

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**Registry No.**—**1b**, 59467-61-7; **2a**, 51715-17-4; **2b**, 59467-62-8; **3a**, 59467-81-1; **3b**, 59467-63-9; **3c**, 59470-03-0; **3d**, 60656-76-0; **4**, 59467-87-7; **5**, 59467-64-0; **5** maleate, 59469-29-3; **6**, 59467-68-4; **7**, 59469-30-6; **8**, 59467-69-5; **9**, 59467-70-8; **9** maleate, 64740-70-1; **10**, 59467-90-2; **11**, 64740-71-2; (±)-**12**, 64740-72-3; (−)-**12**, 59468-15-4; (+)-**12**, 59468-18-7; (±)-12·2HCl, 64740-73-4; (−)-**12** *l*-tartrate, 63151-05-3; (−)-**12**, *O,O'*-dibenzoyl-*d*-tartrate, 64740-74-5; (+)-**12** *d*-tartrate, 63151-04-2; (+)-**12** *O,O'*-dibenzoyl-*d*-tartarate, 64740-75-6; **13**, 64740-58-5; **15a**, 64740-59-6; **16**, 64740-60-9; **17a**, 64740-61-0; **17b**, 64740-62-1; **18**, 64740-63-2; **19**, 64740-64-3; **20**, 59468-92-7; **21**,

59469-74-8; **23**, 64740-65-4; **24**, 64740-66-5; **25**, 59468-73-4; **26**, 59468-83-6; **27**, 59468-84-7; **28**, 5968-85-8; **29**, 59468-86-9; **30**, 59468-89-2; **31**, 59468-88-1; **32**, 59468-90-5; **33**, 59468-91-6; **34**, 59468-87-0; **35**, 64740-67-6; **36**, 64740-68-7; 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one, 2886-65-9; methylamine, 74-89-5; sodium nitrite, 7632-00-0; nitromethane, 75-52-5; nitroethane, 79-24-3; acetic anhydride, 108-24-7; triethylorthoacetate, 78-39-7; 2-(1-aminoethyl)-7-chloro-2,3-dihydra-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepine, 59467-88-8; 2-(1-aminoethyl)-7-chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine dimalate, 64740-69-8; *O,O'*-dibenzoyl-*d*-tartaric acid, 2743-38-6; *l*-tartaric acid, 87-69-4; *d*-tartaric acid, 147-71-7; diazomethane, 334-88-3; *N*-bromosuccinimide, 128-08-5; methyl iodide, 74-88-4; methyl chloroformate, 79-22-1.

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# Photochemistry of 2-Picolines in Alkaline Media. Intermediacy of Dewar Pyridines and Their Methides


Yoshiro Ogata* and Katsuhiko Takagi

*Contribution No. 237, Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan 464*


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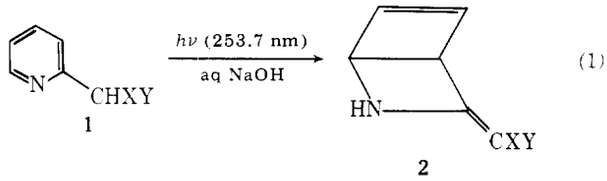
Photolysis of substituted 2-picoline (1) at 253.7 nm in aqueous alkali gives quantitatively 3-substituted methylene-2-azabicyclo[2.2.0]hex-5-ene (**2**). Hydration of **2** in the dark with neutral $H_2O$ affords a product having absorption maxima (380 nm from **2a** and 383 nm from **2b**) which are the same as those of the product from direct photohydration of **1** in neutral aqueous solution. Independent irradiation of **2** with a high pressure Hg lamp in diethyl ether affords its isomer, ortho-substituted aniline (**3**). Thermolysis of **2** in refluxing *t*-BuOH gives **1** inefficiently, but not **3**. The results show that photoisomerization of **1** to **3** proceeds by means of a two-photon process via a Dewar pyridine analogue as its methide (**2**).


As reported in a preliminary communication,[1] the 2-picolines **1** can be photoisomerized to ortho-substituted anilines. A Dewar pyridine intermediate was postulated, but no decisive evidence for this was available. We have now isolated an intermediate ($\lambda_{max}$ 284 nm from **1a** and 274 nm from **1b**) which collapses to the aniline on further irradiation at about 280 nm.

**Irradiation of Substituted 2-Picolines (1) in Alkaline Media.** Irradiation of alkyl 2-pyridylacetate (**1a**) (R = Me or Et) in aqueous NaOH[2] (pH 10–12) with 253.7-nm light afforded a single photoproduct (**2a**) with $\lambda_{max}$ of 284 nm in a




(1)

1 2

a, X = H; Y = $CO_2R$ (R = Me or Et)
b, X = H; Y = CN
c, X = Me; Y = $CO_2Et$

yield of 40% for R = Et. The 2-aza-3-alkoxycarbonylmethylenebicyclo[2.2.0]hex-5-ene structure (**2a**) is based on spectral evidence.

The molecular ion, 165, indicates that it is an isomer of **1a** (R = Et). The NMR spectrum shows five multiplets of equal area at $\delta$ 3.70, 3.92, 4.80, 6.37, and 6.43 which correspond to the protons at positions 7, 4, 1, 6, and 5, respectively.[4] It exhibits conjugated carbonyl at 1680 $cm^{-1}$ in its infrared absorption region. Similarly, in the case of **2b**, the NMR spectra indicated the structure of **2b** (see Experimental Section). Moreover, a cyano group at 2180 $cm^{-1}$ similarly indicates its conjugation with an enamine moiety.[5] 2-Alkoxycarbonyl- and 2-cyanoenamines are known to absorb at 270–290 nm with extinction coefficients in the magnitude of ~10 000[6,7] the order similar to 284 nm ($\epsilon$ 14 000) and 274 nm ($\epsilon$ 10 400) for **1a** (R = Me) and **1b**, respectively.

The NMR assignment for **2a** and **2b** was confirmed using **2c**, which was formed from **1c** and has a methyl at position 7. The NMR of **2c** indicates methyl protons at $\delta$ 1.64 with no signal of the lowest field at position 7. As reported with parent *cis*-$\beta$-aminoacrylonitriles, signals of the $\alpha$ proton and $\alpha$ methyl appear at $\delta$ 3.88 and 1.66, respectively,[7c] which are comparable with those of **2**.

On standing under air at room temperature, **2a** and **2b** were gradually converted into tarry materials which cannot be redissolved in diethyl ether, but **2a** and **2b** are stable in diethyl ether in the dark.

**Dark Reaction of 3-Substituted Methylene-2-azabicyclo[2.2.0]hex-5-enes (2).** On dissolution of **2a** (R = Me) in neutral water its UV peak migrates from 284 to 380 nm with an isosbestic point at 307 nm (Figure 1). Likewise, the peak of **2b** shifts to 383 nm with an isosbestic point at 295 nm on dissolution in water (Figure 1). A similar trend was also observed with hydration of **2c** (292 nm → 384 nm with an isobestic point at 315 nm). Their first-order rate constants of decomposition at 15 °C are $1.7 \times 10^{-2}$ $min^{-1}$ for **2a** (R = Me), $0.98 \times 10^{-2}$ $min^{-1}$ for **2b**, and $0.73 \times 10^{-2}$ $min^{-1}$ for **2c**. Their

0022-3263/78/1943-0944$01.00/0 