Quinazolines and 1,4-Benzodiazepines. 77.[1] Reaction of 2-Amino-1,4-Benzodiazepines with Bifunctional Acylating Agents

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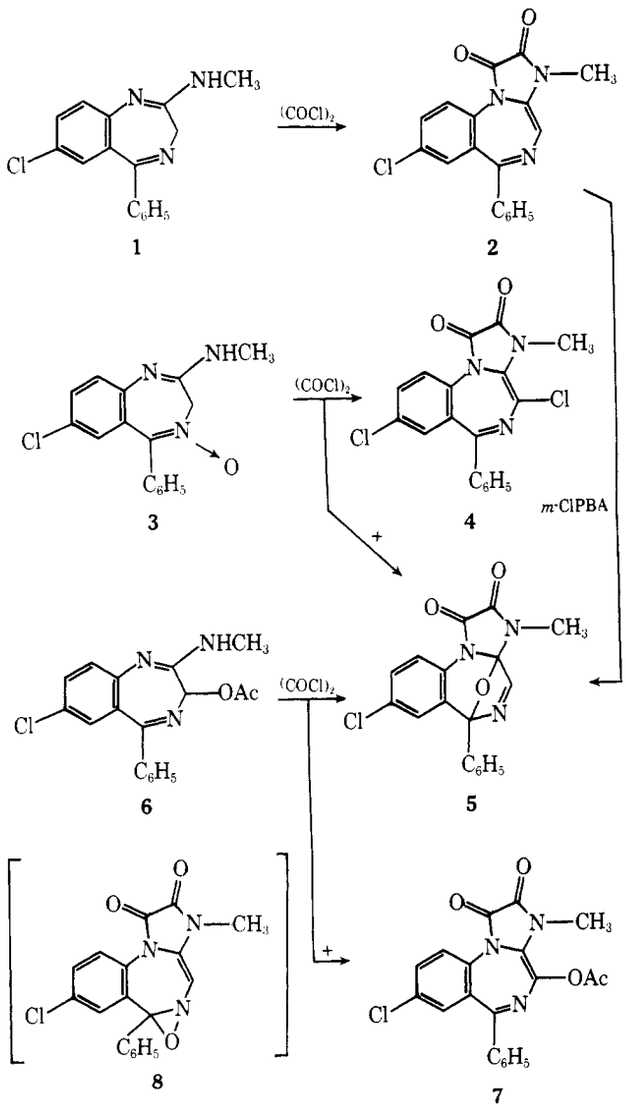
Treatment of 2-amino-1,4-benzodiazepines with acylating agents such as oxalyl chloride, ethyloxalyl chlorooxalate, and phosgene gave a variety of condensed ring products depending on the reagent used and the substituents present on the diazepine ring.

A major thrust in benzodiazepine chemistry in recent years has centered on compounds possessing an additional heterocyclic ring fused to the heterocyclic nucleus.[2] As part of this widespread research effort, we have investigated the reaction of 2-amino-1,4-benzodiazepines with bifunctional acylating reagents and found that a variety of condensed ring systems can be obtained.

The presence of reactive substituents at the 3 position of the diazepine ring can markedly influence the reaction course. Thus, while treatment of 1 (Scheme I) with oxalyl chloride gave the expected imidazolinedione **2**,[3] treatment of the *N*-oxide derivative **3** gave a mixture of two products, compounds **4** and **5**, both of which, while containing the anticipated new ring formed between the 1 and 2 positions of the benzodiazepine ring, were further modified as indicated by the structures shown. Treatment of the 3-acetoxy benzodiazepine **6** under the same conditions also gave a mixture of two products, compounds **5** and **7**.

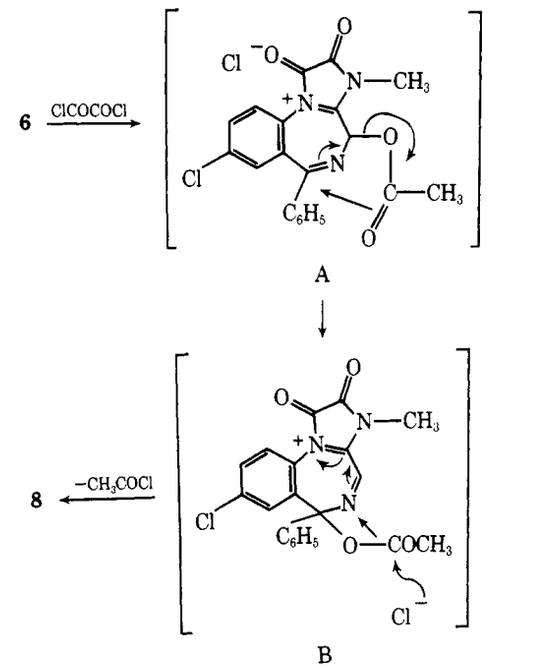
Scheme I



m-ClPBA = *m*-chloroperbenzoic acid

The formation of the imidazole ring in compounds **2**, **4**, **5**, and **7** is straightforward and it is readily apparent that the 4-chloro substituent in compounds **4** can be derived from a type of Polonovski rearrangement of the nitrone followed by a displacement of the resulting –OCOCOCl group by chloride ion.[4] The formation of compound **5** almost certainly proceeds via the tautomeric structure **8** since **5** can also be prepared from **2** by oxidation with *m*-chloroperbenzoic acid. In fact, on the basis of spectral data, we were unable to distinguish between structures **5** and **8** and therefore the compound was submitted for single crystal x-ray analysis. Figure 1 shows a stereodrawing for structure **5**.

A possible mechanism for the formation of **8** (i.e., **5**) is shown below.



Initial attack of the acid chloride on the amidine would lead to the imidazolinedione intermediate A. In a reverse of the allylic rearrangement observed in the Polonovski, the acetate could migrate to the 6 position as shown in B which could then undergo attack by chloride ion to give the oxaziridine **8**, tautomeric with compound **5**.

Treatment of **5** with ethanol leads to the hydroxy ether **9**, probably formed by the addition of ethanol to the Schiff base,

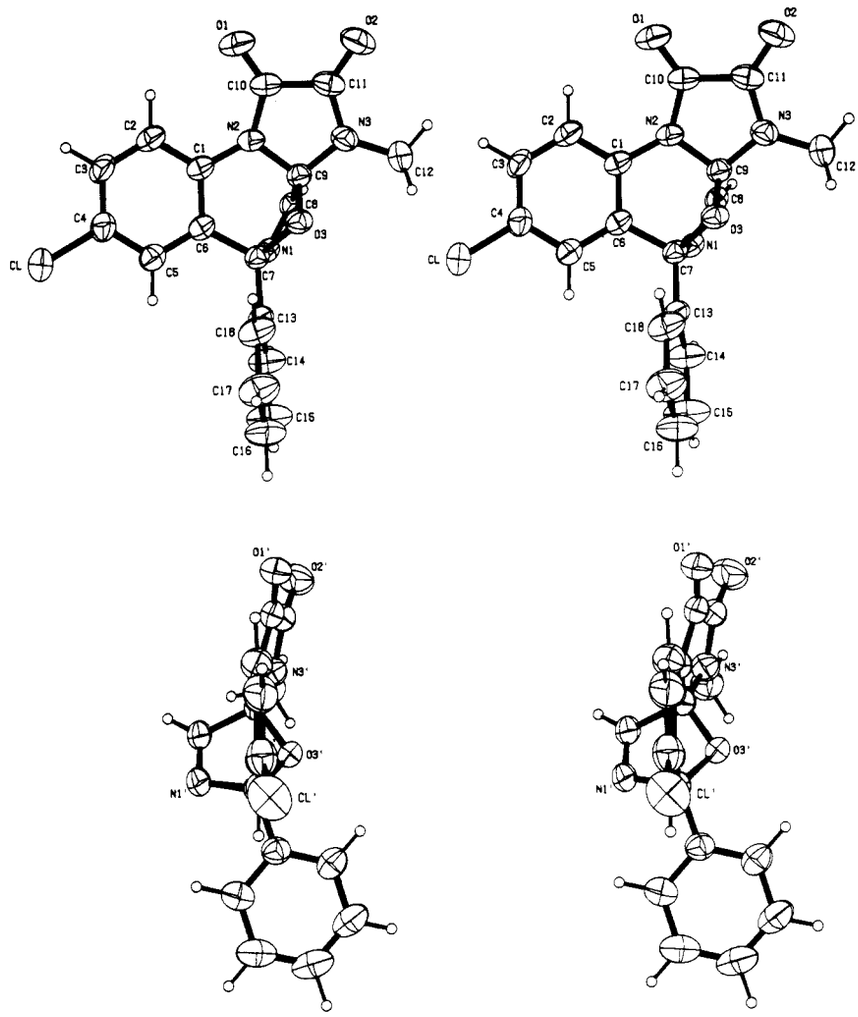


Figure 1. Stereodrawings of the two independent molecules of **5**. Two different views are shown because the conformations of the two independent molecules are essentially the same. The molecule in the lower view has been rotated 90° about the vertical axis from the orientation shown in the upper drawing.

followed by opening of the ether. The structure of **9** was established by ammonolysis of the imidazolindione ring to give the known 3-ethoxy compound **10**[4] (Scheme II). When compound **9** was treated first with thionyl chloride and then with ethanol, the diether, compound **11**, was obtained.

When **5** was treated with ammonia, the only product isolated was the diamide, compound **14**. The structure of **14** was assigned as shown, based on the NMR signal obtained for the $NHCH_3$ group (3 H doublet which collapses to a singlet in D_2O), and on the UV spectrum. Subsequently the structure of **14** was confirmed by single crystal x-ray analysis. Once again ammonolysis of the diamide would lead to an intermediate such as **12**, which could then give the tricyclic intermediate **13**. As in the case of compound **9** the hydrated amidine in **13** would cleave under the reaction conditions to afford the observed product, compound **14**.

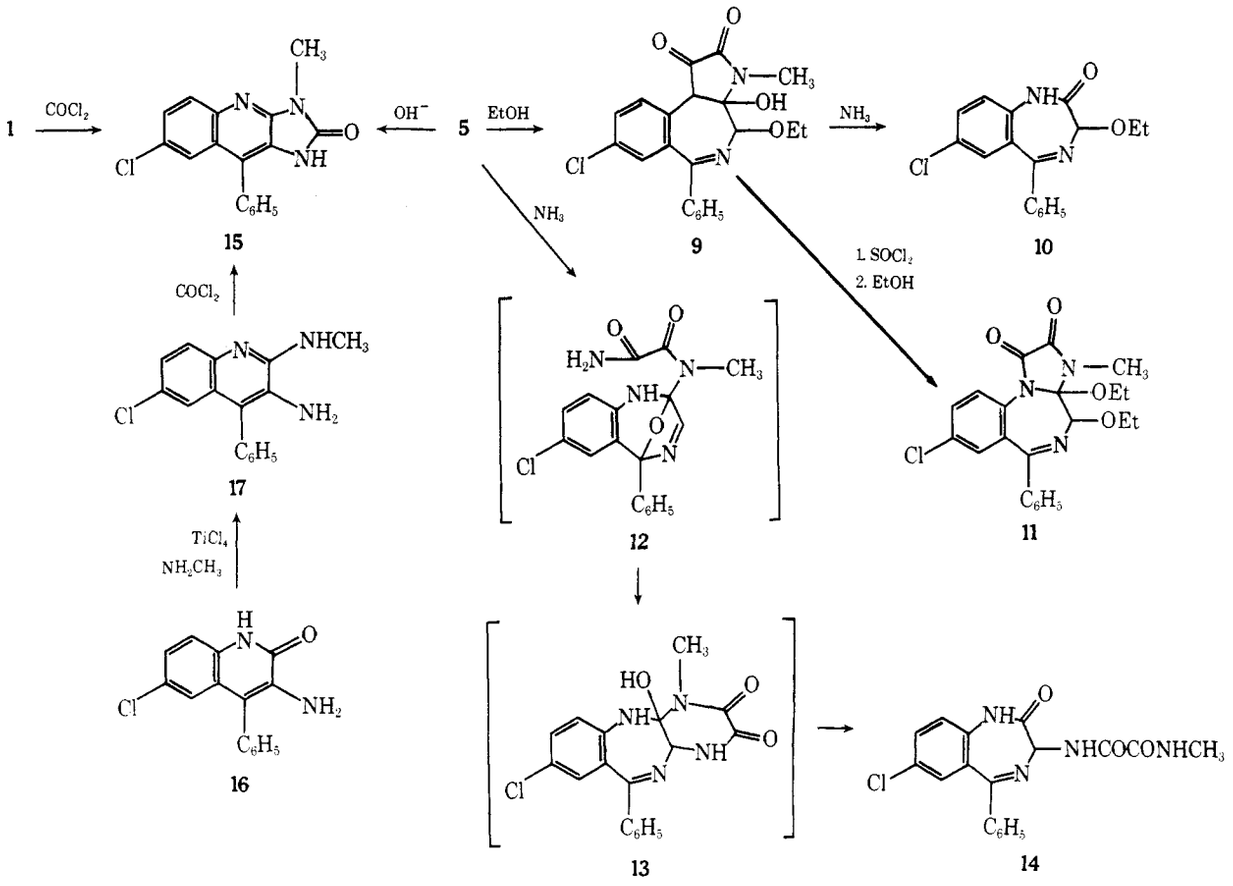
A rather unusual rearrangement was observed when the oxaziridine **5** was treated with base. In this instance the quinoline derivative **15** was isolated. The same product was also prepared by treatment of the amidine **1** with phosgene. The structure of **15** was confirmed by an alternative synthesis from the known carbostyril **16**.[6] Treatment of **16** with titanium tetrachloride and methylamine[7] afforded the 2-methylaminoquinoline **17** which was then cyclized to **15** using phosgene.

The formation of compound **15** from **1** is readily explained on the basis of the mechanism described in an earlier publication which reported the rearrangement of a benzodiazepin-2-one to a related oxazoloquinoline.[9] The mechanism for the formation of **15** from **5** is not so readily apparent, but might possibly be explained as indicated in Scheme III. Attack of hydroxide ion on the amide as shown, with concomitant formation of the amidine, cleavage of the oxide, and ring opening, would lead to an intermediate such as **18**. Cyclization could then occur to give the five-membered ring, structure **19**. Decarboxylation of **19** to the anion followed by an aldol type of cyclization would lead to **20**, dehydration of which would afford the observed product, compound **15**.

Treatment of compound **3** with ethyloxalyl chloride (Scheme IV) afforded a mixture of **4** and the interesting N-demethylated product, compound **21**. Compound **21** was also obtained either directly from **22** or again with N-demethylation from **23** by treatment with ethyloxalyl chloride. Deacylation of **21** with hydrazine gave compound **24**. Both **21** and and **24** gave compound **22** on treatment with aqueous sodium hydroxide. Treatment of compound **23** with phosgene afforded the expected oxazolone **25**.

A possible common intermediate in the cyclization of compounds **3**, **11**, and **23** to compound **21** could be the diester **26**. Whether or not a mono- or diamide is then formed is not significant since the next important intermediate would be a quaternary salt such as **27**. Where R = CH_3 and in the presence of chloride ion, **27** would readily demethylate to give compound **21**, after amide formation at the 1 nitrogen. Apart

Scheme II



from the demethylation step the reaction products shown in Scheme IV are similar to those obtained by the acetylation of compound **22** with acetic anhydride.[9]

Treatment of the 3-chloro benzodiazepine, compound **4**, with ammonia (Scheme V) afforded a mixture of the three compounds **28**, **29**, and **30**. The stereochemistry of the two spiro compounds is unknown and the structures are arbitrarily assigned. The mass spectra of **29** and **30** were identical and both exhibited a molecular ion indicative of loss of ammonia and a parent ion of *m/e* 241 which corresponds to 6-chloro-4-phenylquinazoline. It was not surprising, therefore, that both compound **29** and compound **30** underwent a thermal rearrangement with ring contraction to give the single quinazoline **31** whose mass spectrum was indistinguishable from those of compounds **29** and **30**. In order to exclude the possibility that compound **31** was a six-seven-six ring system, its structure was confirmed by single crystal x-ray analysis. Such a six-seven-six ring system, related to compound **34**, could be derived from spiro ring opening, loss of ammonia, and recyclization of the diamide onto the 3 position of the benzodiazepine.

With the definitive assignment of structure **31** as a quinazoline, doubts existed as to the authenticity of the unusual ortho-amide structures **29** and **30**. Spectral data were, at best, equivocal and therefore it was decided to prepare a related compound in which stereoisomers were eliminated and which would contain a methylene group at the 3 position of the benzodiazepine. Such a derivative would be amenable to ^{13}C NMR spectroscopic analysis and would distinguish the spiro benzodiazepine from the alternate dihydroquinazoline

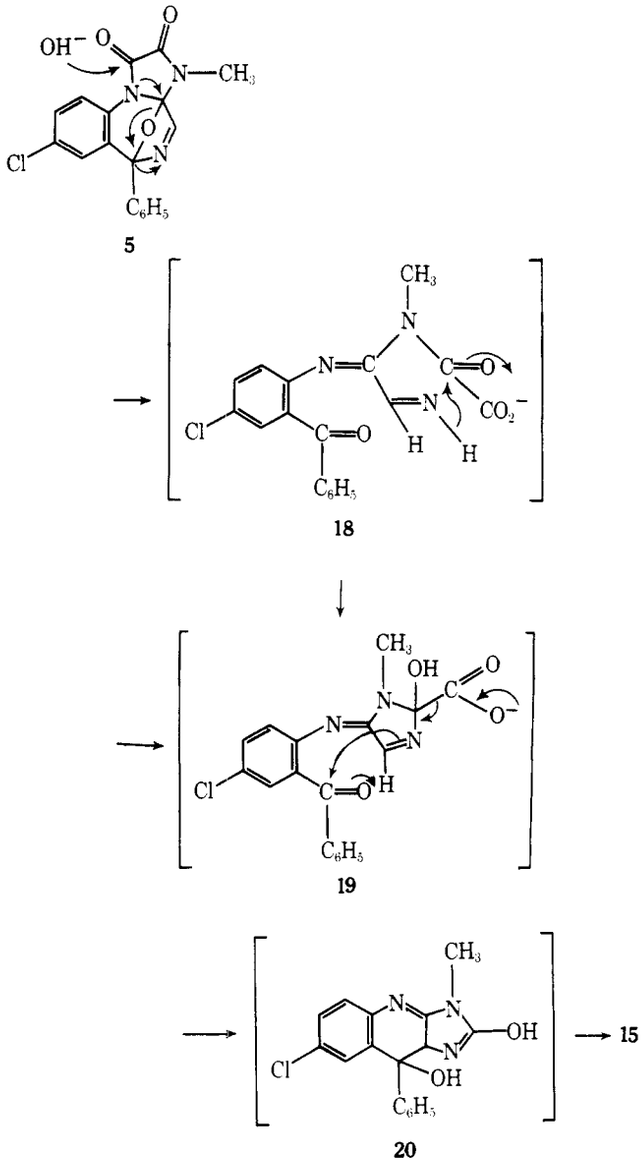
Table I. Crystal Data

Compd	5	14	31
Formula	$C_{18}H_{12}N_3O_3$	$C_{18}H_{15}ClN_4O_3$	$C_{18}H_{13}ClN_4O_2$
Formula weight	353.76	370.80	352.78
Space group	$P\bar{1}$	$Pbca$	$P2_1/n$
a, Å	8.865 (3)	9.570 (5)	9.598 (2)
b, Å	12.524 (3)	10.028 (7)	18.562 (4)
c, Å	15.352 (4)	37.449 (14)	9.264 (3)
α, deg	79.93 (2)		
β, deg	74.10 (2)		101.55 (2)
γ, deg	85.94 (2)		
Z	4	8	4
d_{calcd}, g cm^{-3}	1.455	1.370	1.448
μ(Cu Kα), cm^{-1}	23.1	21.2	22.8

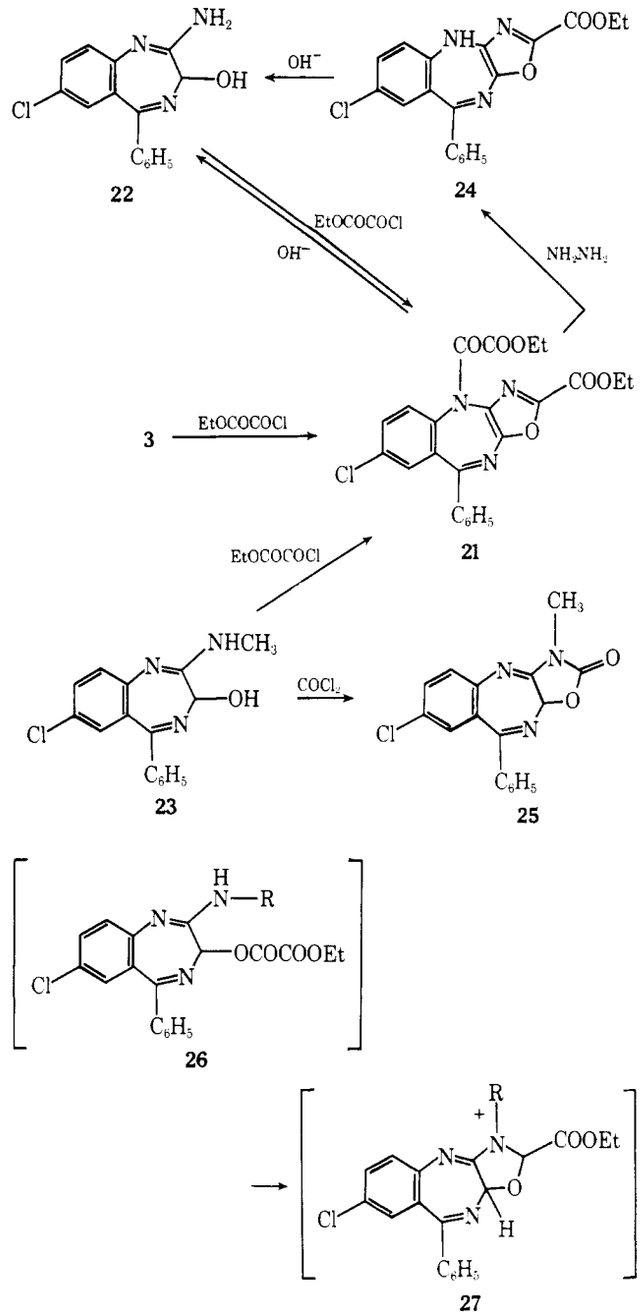
Table II. Experimental Details

Compd	5	14	31
Crystal size, mm	0.05 × 0.20 × 0.35	0.03 × 0.10 × 0.60	0.03 × 0.10 × 0.30
Maximum θ, deg	76	53.5	76
Number of reflections	6735	2128	3050
Absorption correction	Yes	Yes	Yes
Least-squares refinement	block diagonal (two blocks)	Full matrix	Full matrix
Heavier atoms	Anisotropic	Anisotropic	Anisotropic
Hydrogen atoms	Iso (fixed)	Iso (fixed)	Iso (fixed)
Final R	0.049	0.056	0.052
Rinal wR	0.075	0.051	0.045
Final difference map—largest peak (e A^{-3})	<±0.2	<±0.1	<±0.1

Scheme III



Scheme IV



structure A. For this reason then, compound **2** was treated with methylamine and afforded, after workup, a mixture of the hydrolysis product, compound **1**, together with the expected spiro derivative **32**. The ^{13}C NMR spectrum of **32** shows a singlet for the quaternary carbon and a triplet for the methylene carbon. This excludes structure A as a possibility and is compatable with the spiro structure as shown.

A related type of ammonolysis of compound **4** was observed when ethylenediamine was substituted for ammonia in the reaction. In this instance the two products isolated were the spiro derivative, compound **33**, and the piperazinobenzodiazepine, compound **34**. Compound **33** was converted to **34** in high yield by treatment with an organic base in methanol solution. Compound **34** exhibited the characteristic UV spectrum of a 3*H*-1,4-benzodiazepine and there was no fragmentation observed in the mass spectrum which could be attributable to a quinazoline structure.

Crystallography. Crystals of **5**, **14**, and **31** were obtained from acetone and dichloromethane/methanol, respectively. All intensity data were measured on Hilger-Watts four-circle diffractometers (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The crystal data are given in Table I. A multiple solution procedure[10] was used to solve the three structures. The experimental details are summarized in Table II.

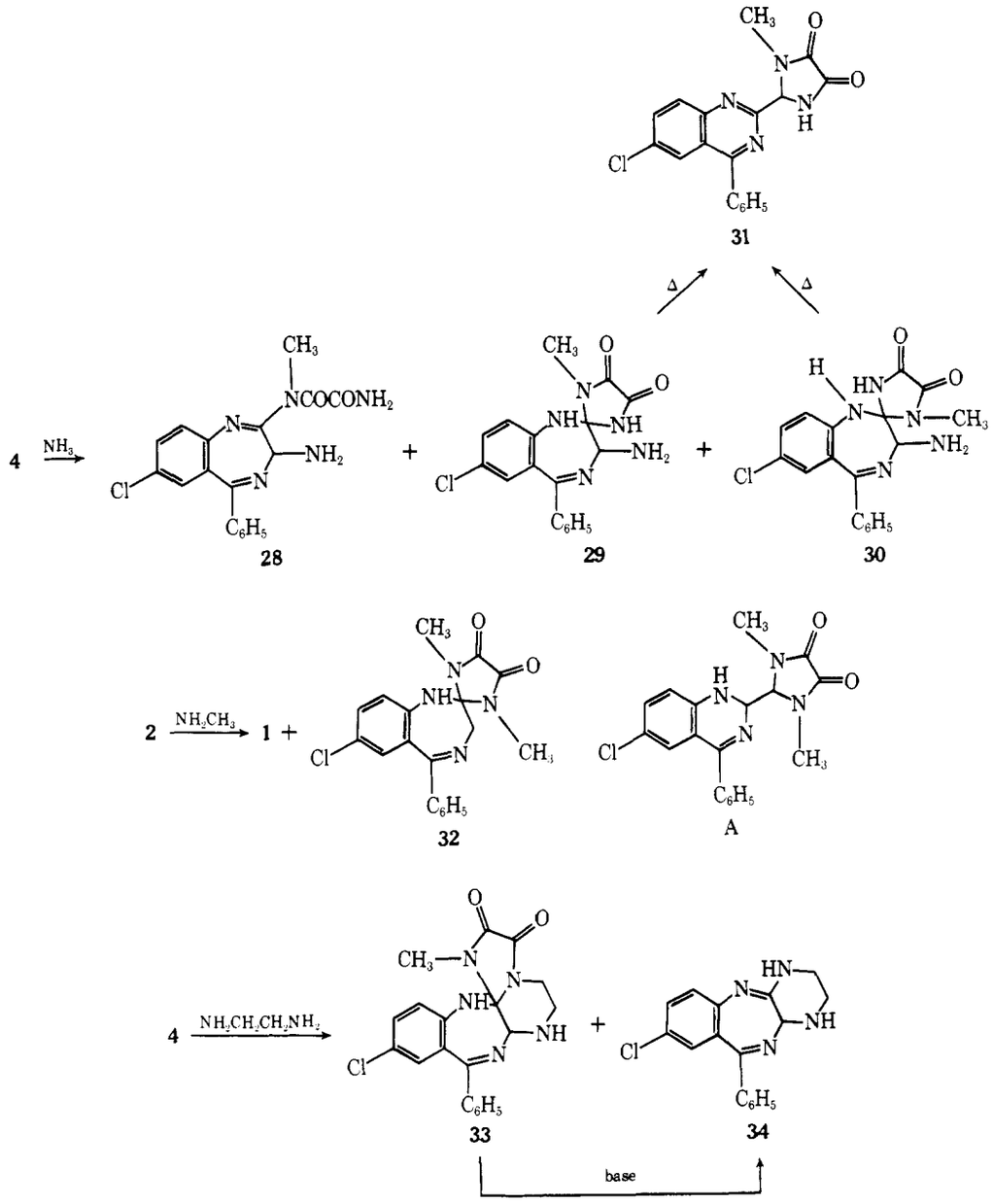
Experimental Section[11]

8-Chloro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*][1,4]benzodiazepine-1,2-dione (2). A solution of 40 g (0.141 mol) of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (**1**)[12] in 500 mL of dry benzene was treated with 21.5 g (0.17 mol) of oxalyl chloride. The reaction mixture was refluxed and stirred for 5 h, and then cooled and filtered. The filtrates were concentrated and crystallized from a mixture of dichloromethane and ether to give 11.4 g of product. The initial precipitate was extracted with a mixture of 100 mL of dichloromethane and dilute potassium carbonate solution and filtered. The organic layer was separated, dried, and added to the mother liquors from the first crop. The solution was concentrated, cooled, and filtered to yield 4 g of starting material. The filtrates were evaporated, dissolved in dichloromethane, and chromatographed through 200 g of Florisil. Elution with 1.5 L of dichloromethane gave, after evaporation and crystallization from a mixture of dichloromethane and ether, an additional 5 g (combined yield 16.4 g) of product. A sample was recrystallized from a mixture of dichloromethane and ether to give **2** as orange rods, mp 200–202 °C.

Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 64.01; H, 3.58; N, 12.44. Found: C, 63.98; H, 3.43; N, 12.47.

4,8-Dichloro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*][1,4]-

Scheme V



benzodiazepine-1,2-dione (4) and 8-Chloro-3a,6-epoxy-1,2,3a,6-tetrahydro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*]-[1,4]benzodiazepine-1,2-dione (5). A suspension of 40 g (0.133 mol) of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**3**)[12] in 500 mL of benzene was treated with 40 g (0.315 mol) of oxalyl chloride. The reaction mixture was refluxed for 3.5 h, and then evaporated to dryness. The residue was dissolved in 300 mL of dichloromethane, washed with 150 mL of 10% potassium carbonate solution, dried over sodium sulfate, and concentrated to 200 mL. This solution was filtered through 600 g of Florisil in a sintered glass funnel and eluted with 2 L of chloroform. The eluent was concentrated, cooled, and filtered to give 19.4 g of **4** as orange prisms, mp 252–260 °C. A second crop of 20 g was obtained from the mother liquors to give a combined yield of 39.4 g (79%). An analytical sample (mp 258–262 °C) was obtained by recrystallization from a mixture of dichloromethane and ether.

Anal. Calcd for $C_{18}H_{11}Cl_2N_3O_2$: C, 58.08; H, 2.98; N, 11.29; Cl, 19.05. Found: C, 57.82; H, 2.81; N, 11.27; Cl, 19.23.

In a reaction carried out as described for the preparation of compound **4**, using 5.0 g of **3** as starting material, the residue obtained after extraction, washing, and drying was carefully chromatographed over 150 g of Florisil. Using benzene as the eluent removed all of **4**. The eluent was then changed to a mixture of 10% ether in benzene. Removal of solvent from these fractions afforded 0.8 g of an oil. The oil was crystallized from ether and the product was recrystallized from a mixture of dichloromethane and ether to give 0.5 g (8%) of **5** as white needles, mp 165–175 °C, resetting to needles, mp 238–242 °C.

Anal. Calcd for $C_{18}H_{12}ClN_3O_3$: C, 61.10; H, 3.42; N, 11.88. Found: C, 61.00; H, 3.03; N, 11.97.

8-Chloro-3a,6-epoxy-1,2,3a,6-tetrahydro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*][1,4]benzodiazepine-1,2-dione (5) and 4-Acetoxy-8-chloro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*]-[1,4]benzodiazepine-1,2-dione (7). A solution of 10 g (0.0293 mol) of 3-acetoxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (**6**)[13] in 200 mL of benzene was treated with 8 g (0.064 mol) of oxalyl chloride, and the reaction mixture was refluxed for 5 h and then evaporated to dryness. The residue was dissolved in 75 mL of dichloromethane and filtered through 100 g of Florisil in a sintered glass funnel. Elution with dichloromethane followed by 10% ether in dichloromethane gave, after removal of solvents, 5 g of an oil. This was crystallized from a mixture of dichloromethane and ether to give 3.3 g (32%) of **5** as white needles, mp and mmp 238–243 °C.

The filtrates were concentrated and cooled. The precipitate was collected and recrystallized from a mixture of dichloromethane and ether to give 0.6 g (5%) of **7** as orange rods, mp 206–208 °C.

Anal. Calcd for $C_{20}H_{14}ClN_3O_4$: C, 60.69; H, 3.57; N, 10.62. Found: C, 60.41; H, 3.49; N, 10.55.

From Compound 2. A cold solution of 16 g (0.0473 mol) of **2** in 400 mL of dichloromethane was treated with 11.5 g (0.057 mol) of 85% *m*-chloroperbenzoic acid. After 18 h at room temperature the reaction

mixture was washed with dilute ammonium hydroxide (2 × 150 ml), dried over anhydrous sodium sulfate, and filtered through 100 g of Florisil in a sintered glass funnel. The product was eluted with 500 mL of dichloromethane and then 500 mL of a 10% solution of ether in dichloromethane. The eluents were combined and concentrated to give 14 g of crude oil. Crystallization from ether and recrystallization from a mixture of dichloromethane and ether gave 9.7 g (58%) of **5** as white prisms, mp and mmp 237–241 °C.

8-Chloro-4-ethoxy-3a-hydroxy-3-methyl-6-phenyl-2,3,3a,4-tetrahydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepine-1,2-dione (9). A solution of 0.3 g (0.848 mmol) of **5** in 25 mL of absolute ethanol was heated under reflux for 18 h and then evaporated to dryness. The residue was dissolved in 10 mL of dichloromethane and filtered through 25 g of Florisil. The column was eluted with 100 mL of dichloromethane and then with 300 mL of ethyl acetate. The ethyl acetate fraction was evaporated, and the product was crystallized from ether and recrystallized from a mixture of tetrahydrofuran and hexane to give 0.2 g (60%) of **9** as white prisms, mp 190–198 °C.

Anal. Calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 60.03; H, 4.35; N, 10.37.

7-Chloro-3-ethoxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (10). A solution of 0.1 g (0.25 mmol) of **9** in 20 mL of dioxane was added to 80 mL of liquid ammonia, and after 18 h the solution was evaporated under vacuum. The residue was dissolved in 20 mL of dichloromethane, washed with 10 mL of water, dried with sodium sulfate, and evaporated to dryness. The residue was crystallized from ether and recrystallized from a mixture of dichloromethane and ether to give 40 mg (44%) of **10** as off-white prisms, mp and mmp with an authentic sample prepared as described in the literature[4] 222–225 °C: UV λ_{max} (Me_2CHOH) 230 nm (ε 40 800), 318 (2830), infl 250 (16 000).

Anal. Calcd for $C_{17}H_{15}N_2O_2Cl$: C, 64.87; H, 4.80. Found: C, 64.76; H, 4.67.

8-Chloro-3a,4-diethoxy-3-methyl-6-phenyl-2,3,3a,4-tetrahydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepine-1,2-dione (11). A solution of 0.1 g (0.25 mmol) of **9** in 20 mL of dichloromethane was treated with 1 mL (0.0134 mol) of thionyl chloride, and heated under reflux for 10 min. The solution was evaporated under reduced pressure and the residue was immediately dissolved in 10 mL of absolute ethanol and heated under reflux for 3 h. The ethanol was removed under reduced pressure and the product was dissolved in 20 mL of dichloromethane. The solution was washed with 10 mL of dilute ammonium hydroxide and brine, dried over sodium sulfate, filtered, and evaporated. The residue was crystallized from ether and recrystallized from a mixture of dichloromethane and ether to give 50 mg (47%) of **11** as white prisms, mp 259–262 °C.

Anal. Calcd for $C_{22}H_{22}ClN_3O_4$: C, 61.75; H, 5.18; N, 9.82. Found: C, 61.95; H, 5.13; N, 9.83.

(7-Chloro-1,3-dihydro-2-oxo-5-phenyl-2*H*-1,4-benzodiazepin-3-yl)oxamic Acid *N*-Methylacetamide (14). A solution of 1.0 g (0.0028 mol) of **5** in 50 mL of dichloromethane was added to 50 mL of liquid ammonia. After standing for 4 h, 40 mL of water was added and the precipitate was recovered by filtration. Recrystallization from a mixture of dichloromethane and methanol gave 0.2 g (20%) of **14** as white prisms, mp 307–313 °C: NMR (Me_2SO-d_6) δ 11.19 (s, 1, NH), 8.91 (d, 1, J = 8 Hz, OH), 8.84 (b, 1, NH), 5.26 (d, 1, J = 8 Hz, CH), 2.76 (d, 3, J ≈ 5 Hz, NCH_3), 5.26 and 2.76 collapse to singlets on exchange with D_2O; UV λ_{max} (Me_2CHOH) 229 nm (ε 39 600), 316 (2330), infl 250 (15 800); mass spectrum m/e 370 (M^+).

Anal. Calcd for $C_{18}H_{15}ClN_4O_3$: C, 58.31; H, 4.08; N, 15.11. Found: C, 58.17; H, 3.89; N, 14.88.

7-Chloro-3-methyl-9-phenyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-one (15). A. From Compound 5. A solution of 0.8 g (2.26 mmol) of **5** in 20 mL of dioxane was treated with 5 mL (0.015 mol) of 3 N sodium hydroxide. After standing for 2 h at room temperature, the reaction mixture was poured into 100 mL of water. The solution was extracted with 150 mL of dichloromethane, which was washed with brine, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from a mixture of dichloromethane, methanol, and ether to give 0.5 g (71%) of **15** as white needles, mp 312–313 °C: NMR (Me_2SO-d_6) δ 11.2 (s, 1, NH), 3.49 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 205 nm (ε 23 300), 235 (50 600), 310 (9500), 325 (13 000), 340 (16 700); mass spectrum m/e 309 (M^+).

Anal. Calcd for $C_{17}H_{12}ClN_3O$: C, 65.90; H, 3.90; N, 13.57. Found: C, 66.11; H, 3.88; N, 13.82.

B. From Compound 17. A solution of 0.1 g (0.353 mmol) of **17** in 10 mL of dry benzene was treated with 0.32 mL (0.4 mmol) of a 12.5% solution of phosgene in benzene. The mixture was refluxed for 2 h and evaporated and the residue crystallized from methanol. Recrystallization from a mixture of dichloromethane and ether gave 40 mg (36%) of **15** as white plates which reset to needles at 290–300 °C and melted at 310–313 °C, mmp with a sample obtained from A 310–313 °C.

C. From Compound 1. A suspension of 6.0 g (0.0211 mol) of **1** in 100 mL of dry benzene was treated with 30 g (0.0375 mol) of a 12.5% solution of phosgene in benzene and the reaction mixture was refluxed for 7 h. The mixture was filtered and the filtrates were evaporated to dryness. The precipitate and the residue obtained from the filtrates were each dissolved in 100 mL of dichloromethane, washed with 40 mL of 10% potassium carbonate solution, dried over sodium sulfate, and evaporated to dryness. The fraction obtained from the precipitate was recrystallized from a mixture of dichloromethane and ether to give 1.5 g of starting material. The mother liquors were evaporated and the residue was combined with that obtained from the original filtrates. The oil was dissolved in 50 mL of dichloromethane and chromatographed through 200 g of Florisil. Elution with a 10% solution of ether in benzene, followed by ether and finally by ethyl acetate, gave, after removal of solvents, fractions of 0.5 and 1.0 g, respectively. The ethyl acetate fraction was crystallized from a mixture of dichloromethane and ether to give 0.8 g (12.3%) of **15** as white prisms, mp and mmp with the product obtained from A 310–313 °C.

3-Amino-6-chloro-2-methylamino-4-phenylquinoline (17). A solution of 3.0 g (11.1 mmol) of 3-amino-6-chloro-4-phenylcarbostyril (**16**)[6] in 250 mL of dry xylene was saturated with methylamine, and then 3.8 g (20 mmol) of titanium tetrachloride in 20 mL of xylene was added. After stirring and refluxing for 18 h, an additional 3.8 g of titanium tetrachloride was added, and the reaction mixture was again saturated with methylamine. The reaction mixture was then refluxed for 24 h, and the same amount of the two reagents was again added followed by 80 h of refluxing and stirring. After the reaction mixture was cooled to room temperature, concentrated ammonium hydroxide was added until the precipitate turned almost white. The precipitate was removed by filtration and washed with ethyl acetate, and the combined filtrates were dried with sodium sulfate and concentrated to dryness.

The residual oil was crystallized from ether to give 1.2 g of starting material. The filtrates were concentrated and dissolved in dichloromethane and the solution was chromatographed through a column of Florisil, eluting with 1 L of benzene, 1.5 L of dichloromethane, and 1 L of ether. From the combined dichloromethane and ether fractions, a total of 0.6 g of crude product was obtained. Recrystallization from a mixture of ether and petroleum ether gave 0.4 g (21%) of **17** as off-white prisms, mp 118–120 °C.

Anal. Calcd for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.85; H, 5.09; N, 14.95.

7-Chloro-2-ethoxycarbonyl-9-phenyl-4*H*-oxazolo[4,5-*b*]-[1,4]benzodiazepine-4-glyoxylic Acid Ethyl Ester (21). A. From Compound 3. A solution of 5.0 g (16.7 mmol) of **3** in 200 mL of benzene was treated with 5.0 g (36.5 mmol) of ethyloxalyl chloride and heated under reflux for 16 h. The reaction mixture was evaporated to dryness and the residue was dissolved in 100 mL of dichloromethane. The solution was washed with 50 mL of 10% potassium carbonate solution, dried over sodium sulfate, and evaporated to dryness. The residue was recrystallized from a mixture of dichloromethane and ether to give 4.2 g (54%) of **21** as yellow rods, mp 198–207 °C.

Anal. Calcd for $C_{23}H_{18}ClN_3O_6$: C, 59.05; H, 3.88; N, 8.98. Found: C, 58.69; H, 3.85; N, 8.91.

B. From Compound 22. A solution of 0.2 g (0.7 mmol) of 2-amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (**22**)[12] in 20 mL of benzene and 0.4 g (2.8 mmol) of ethyl oxalyl chloride was heated on the steam bath for 1 h and evaporated to dryness and the residue was crystallized from ether. Recrystallization of the product from a mixture of dichloromethane and ether gave 0.2 g (60%) of **21** as yellow rods, mp and mmp with the product obtained from A 195–205 °C.

C. From Compound 23. A mixture of 5.0 g (0.0167 mol) of 7-chloro-2-methylamino-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (**23**)[13] in 200 mL of benzene was treated with 5.0 g (0.0365 mol) of ethyloxalyl chloride and the reaction mixture was refluxed for 18 h and then evaporated to dryness. The residue was dissolved in 75 mL of dichloromethane, which was washed with a 10% solution of potassium carbonate, dried over sodium sulfate, and concentrated. The residue was crystallized from a mixture of dichloromethane and ether to give 4.1 g (53%) of **21** as yellow rods, mp and mmp 197–207 °C.

7-Chloro-9-phenyl-4*H*-oxazolo[4,5-*b*][1,4]benzodiazepine-2-carboxylic Acid Ethyl Ester (24). A solution of 1.0 g (2.13 mmol) of **21** in a mixture of 40 mL of tetrahydrofuran and 10 mL of methanol was treated with 2 g of an 85% solution of hydrazine hydrate in water, and after 1 h the solvent was removed under vacuum. The residue was warmed with 50 mL of methanol and filtered and the precipitate was

recrystallized from a mixture of *N,N*-dimethylformamide, methanol, and water to give 0.6 g (75%) of **24** as reddish-brown rods, mp 244–249 °C.

Anal. Calcd for $C_{19}H_{14}ClN_3O_3$: C, 62.05; H, 3.83; N, 11.43. Found: C, 61.78; H, 3.73; N, 11.56.

2-Amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (22). A. From Compound 21. A solution of 1.0 g (2.13 mmol) of **21** in 100 mL of methanol was treated with 10 mL of 10 N sodium hydroxide and the mixture was heated under reflux for 15 min. Solvents were removed by evaporation and the residue was dissolved in 100 mL of dichloromethane. The solution was washed with 50 mL of dilute acetic acid. The organic layer was separated, dried over sodium sulfate, and filtered through 100 g of Florisil. The Florisil was eluted first with 600 mL of a mixture of 10% ether in dichloromethane and then with 800 mL of ethyl acetate. Evaporation of the ethyl acetate fractions gave 0.5 g of an oil which was crystallized from a mixture of dichloromethane and ether and then recrystallized from a mixture of dichloromethane and methanol to give 0.4 g (67%) of **22** as white rods, mp and mmp with an authentic sample 177–185 °C dec.

B. From Compound 24. A solution of 0.1 g (0.27 mmol) of **24** in 10 mL of ethanol and 2 mL of 3 N sodium hydroxide was refluxed for 14 min and then evaporated to dryness. The residue was dissolved in 50 mL of dichloromethane, which was washed with 30 mL of water, dried over sodium sulfate, and evaporated to dryness. Recrystallization of the residue from a mixture of dichloromethane and ether gave 40 mg (50%) of **22** as white rods, mp and mmp with an authentic sample 178–182 °C dec.

7-Chloro-3-methyl-9-phenyl-10a*H*-oxazolo[4,5-*b*][1,4]benzodiazepin-2(3*H*)-one (25). A solution of 5.0 g (0.0167 mol) of **23** in 20 mL of pyridine and 40 mL of tetrahydrofuran was cooled in an ice bath and was treated with 26.1 g (0.033 mol) of a 12.5% solution of phosgene in benzene. After 20 h at room temperature, the solution was evaporated to dryness and the residue was dissolved in 100 mL of dichloromethane which was washed with 75 mL of a 5% solution of sodium bicarbonate, dried over sodium sulfate, and filtered through 100 g of Florisil. The Florisil was eluted with 500 mL of benzene and 750 mL of dichloromethane which were combined and concentrated. The residue was crystallized from a mixture of ether and petroleum ether and recrystallized from a mixture of dichloromethane and petroleum ether to give 3.9 g (72%) of **25** as white rods, mp 208–212 °C.

Anal. Calcd $C_{17}H_{12}ClN_3O_2$: C, 62.68; H, 3.71; N, 12.90. Found: C, 62.58; H, 3.54; N, 12.88.

3-Amino-7-chloro-2-(N^1-methyloxamido)-5-phenyl-3*H*-1,4-benzodiazepine (28), 3-Amino-7-chloro-5-phenyl-2,3-dihydro-3′-methylspiro[1*H*-1,4-benzodiazepine-2,2′-imidazolidine]-4′,5′-dione (29), and 3-Amino-7-chloro-5-phenyl-2,3-dihydro-1′-methylspiro[1*H*-1,4-benzodiazepine-2,2′-imidazolidine]-4′,5′-dione (30). A solution of 15 g (0.0402 mol) of **4** in 400 mL of dry dichloromethane was added to 300 mL of liquid ammonia. After standing for 2 h, 200 mL of water was added, and the reaction mixture was filtered. The filter cake was refluxed in a mixture of chloroform and ethanol (50/50) for 5 min, cooled, and filtered to give 9.1 g (61%) of **30** as pale yellow prisms. An analytical sample was recrystallized from a mixture of dichloromethane and methanol to give **30** as pale yellow prisms, mp 186–187 °C: IR (KBr) 3400, 3385, 3370 (NH, NH_2), 1740 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.73 (s, 1, NH), 6.65 (s, 1, NHC=O), 5.27 (s, 1, CH), 3.19 (s, 2, NH_2), 2.85 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 232 nm (ϵ 33 000), 395 (1300); mass spectrum *m/e* 352 ($M^+ - 17$), 240 (base peak).

Anal. Calcd for $C_{18}H_{16}ClN_5O_2$: C, 58.46; H, 4.36; N, 18.94. Found: C, 58.41; H, 4.30; N, 19.18.

The dichloromethane/water filtrates from above were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated to 100 mL. The solution was cooled and filtered. The solid residue was recrystallized from a mixture of dichloromethane and methanol to give 2.5 g (17%) of **29** as yellow rods, mp 183–187 °C: IR (KBr) 3420, 3315 (NH, NH_2), 1758, 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.75 (s, 1, NH), 6.57 (s, 1, NHC=O), 5.36 (d, 1, J = 2 Hz, CH), 2.98 (s, 2, NH_2), 2.87 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 230 nm (ϵ 34 200), 397 (1300); mass spectrum *m/e* 352 ($M^+ - 17$), 240 (base peak).

Anal. Calcd for $C_{18}H_{16}ClN_5O_2$: C, 58.46; H, 4.36; N, 18.94. Found: C, 58.47; H, 4.05; N, 19.00.

The filtrates from **29** were concentrated and the residue was crystallized from dichloromethane. The solid was recrystallized from a mixture of dichloromethane and finally from a mixture of dichloromethane and ether to give 0.3 g (2%) of **28** as white prisms, mp 280–284 °C: IR (KBr) 3380 (NH_2), 1720, 1675 cm^{-1} (C=O); NMR (CF_3COOD) δ 6.85 (s, 1, CH), 3.50 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 240 nm (ϵ 28 000), 265 (20 000), 350 (2500); mass spectrum *m/e* 369 (M^+).

Anal. Calcd for $C_{18}H_{16}ClN_5O_2$: C, 58.46; H, 4.36; N, 18.94. Found: C, 58.52; H, 4.46; N, 18.69.

1-Methyl-2-(6-chloro-4-phenyl-2-quinazolinyl)-4,5-imidazolidinedione (31). A. From Compound 29. A 1-g (0.0027 mol) sample of **29** was heated to 200 °C under nitrogen in an oil bath for 5 min. After cooling, the residue was dissolved in 25 mL of dichloromethane which was then washed with 20 mL of dilute ammonium hydroxide, dried over sodium sulfate, and chromatographed through 100 g of silica gel. The column was eluted with dichloromethane, dichloromethane and ether (10/1), and then with ether. The ether fraction was evaporated and the residue was crystallized from ethyl acetate and recrystallized from a mixture of dichloromethane and ether to give 0.35 g (37%) of **31** as white prisms, mp 205–235 °C: IR (KBr) 3395, 3330 (NH), 1750, 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 6.09 (s, 1, CH), 2.88 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 237 nm (ϵ 54 000), 273 (9300), 328 (6500); mass spectrum *m/e* 352 (M^+), 240 (base peak).

Anal. Calcd for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.12; H, 3.50; N, 15.76.

B. From Compound 30. Compound **31** was also prepared by heating 0.1 g (0.27 mmol) of **30** at 205 °C for 10 min under nitrogen in an oil bath. The residue was crystallized from a mixture of dichloromethane and ether and recrystallized from methanol to give 30 mg (32%) of **31** as white prisms, mp and mmp with a sample prepared as in A 205–238 °C.

7-Chloro-2,3-dihydro-1′,3′-dimethylspiro-5-phenyl[1*H*-1,4-benzodiazepine-2,2′-imidazolidine]-4,5′-dione (32). A solution of 1.2 g (0.00355 mol) of **2** in 20 mL of dry tetrahydrofuran was treated with a saturated solution of methylamine in dry tetrahydrofuran cooled in an ice bath. After 2.5 h at room temperature the mixture was concentrated to a small volume and hexane was added. The precipitate was filtered and recrystallized from the same solvents to give 0.5 g (38%) of **32** as white rods, mp 340–342 °C: IR (KBr) 3390 (NH), 1750, 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 6.96 (s, 1, NH), 4.02 (s, 2, CH_2), 2.80 (s, 6, 2 NCH_3); ^{13}C NMR (Me_2SO-d_6) δ 95.7 (s, 1, CN_3), 56.1 (t, 1, CH_2), 26.5 (q, 2, 2 NCH_3); UV λ_{max} (Me_2CHOH) 221 nm (ϵ 29 000), 234 (31 300), 332 (2610).

Anal. Calcd for $C_{19}H_{17}ClN_4O_2$: C, 61.87; H, 4.65; N, 15.19. Found: C, 62.03; H, 4.91; N, 15.02.

The mother liquors obtained from the above reaction were concentrated to dryness. The residue was crystallized from methanol, and recrystallized from a mixture of dichloromethane and petrol to give 0.2 g of **1** as white prisms, mp and mmp with an authentic sample 246–249 °C.

11-Chloro-1,5-6,7,7a,14-hexahydro-1-methyl-9-phenylimidazo[1,2-*b*][1,2]pyrazino[2,3-*b*][1,4]benzodiazepine-2,3-dione (33) and 8-Chloro-2,3,4,4a-tetrahydro-6-phenyl-1*H*-pyrazino[2,3-*b*][1,4]benzodiazepine (34). A suspension of 10 g (0.0269 mol) of **4** in 400 mL of dry benzene was treated with 4 g (0.0667 mol) of ethylenediamine and the reaction mixture was stirred at room temperature for 18 h. The solution was then warmed to 60 °C for 1 h and cooled in an ice bath and 100 mL of water was added. The solution was filtered, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was dissolved in benzene and chromatographed through 600 g of Florisil using benzene (1.5 L), ether (1.5 L), ethyl acetate (2 L), and methanol (1 L) as the eluents. The ethyl acetate fraction was evaporated to give 1.5 g of oil which was crystallized and recrystallized from a mixture of dichloromethane and ether to give 0.8 g (7.5%) of **33** as white prisms, mp 290–292 °C: IR (KBr) 3300 (NH), 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.86 (d, 1, CH), 2.93 (s, 3, CH_3), 2.00 (s, 1, NH); UV λ_{max} (Me_2CHOH) 241 nm (ϵ 32 000), 265 (14 800), 350 (2800); mass spectrum *m/e* 395 (M^+), 241.

Anal. Calcd for $C_{20}H_{18}ClN_5O_2$: C, 60.68; H, 4.58; N, 17.69. Found: C, 60.60; H, 4.60; N, 17.60.

The methanol fraction was evaporated to give 4 g of oil which was crystallized from a mixture of dichloromethane and ether and recrystallized from methanol to give 0.3 g (3.6%) of **34** as pale yellow rods, mp 194–198 °C dec: IR (KBr) 3250 (NH), 1620 cm^{-1} (C=N); NMR (Me_2SO-d_6) δ 4.04 (s, 1, CH), 2.80–3.65 (m, 6, CH_2CH_2 + 2 NH); UV λ_{max} (Me_2CHOH) 229 nm (ϵ 27 200), 273 (16 000) 347 (2500); mass spectrum *m/e* 310 (M^+).

Anal. Calcd for $C_{17}H_{15}ClN_4$: C, 65.70; H, 4.87; N, 18.03. Found: C, 65.32; H, 4.94; N, 17.81.

A solution of 0.1 g (0.271 mmol) of **33** in 40 mL of methanol and 2 mL of diethylamine was heated under reflux for 7 h. Solvents were evaporated, and the residue was dissolved in 25 mL of dichloromethane, which was washed with 15 mL of water, dried over sodium

sulfate, and evaporated to dryness. Crystallization from methanol gave 0.05 g (60%) of **34** as pale yellow rods, mp and mmp with a sample prepared as above 192–195 °C.

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Supplementary Material Available. Table of the positional and thermal parameters for **5**, **14**, and **31** (8 pages). Ordering information is given on any current masthead page.

References and Notes

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Synthesis and Acylation of Pyrrolinones

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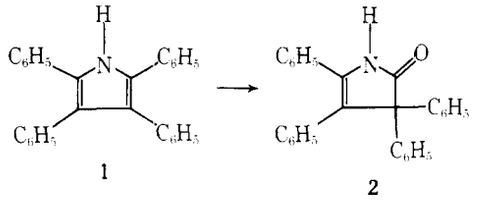
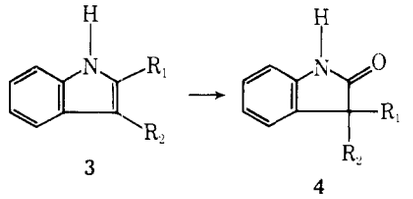
Ethyl 5-acetyl-2,4-dimethylpyrrole-3-carboxylate (**5a**) reacted with concentrated nitric acid to give pyrrolinone **6a** and nitropyrrole **7**. Several pyrroles related to **5a** were also oxidized to pyrrolinones. Diethyl 2-acetyl-3-methylsuccinate reacted with ammonia to give a mixture of ethyl 4,5-dihydro-2,4-dimethyl-5-oxo-1*H*-pyrrole-3-carboxylate (**13b**) and its Δ^3 isomer (**14b**). Acylation of **13b** and its *N*-methyl analogue **13a** with various reagents was studied. The reaction products were formulated as pyrrolinones or 5-acyloxypyrroles on the basis of spectral (^{1}H and ^{13}C NMR, UV, and IR) properties.

Wasserman and Liberles have described the oxidation of tetraphenylpyrrole (**1**) to pyrrolinone **2**;[1] related reactions



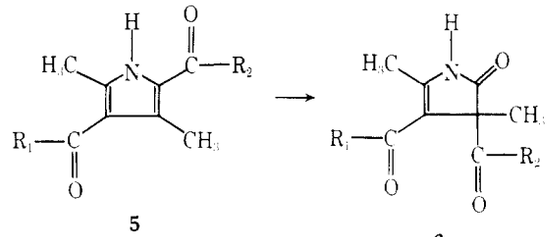
1 **2**



3 **4**

a, $R_1 = R_2 = C_6H_5$
b, $R_1 = COOC_2H_5$; $R_2 = CH_3$

leading to indolinones **4a** and **4b** have also been described.[2-4] In this paper we report additional examples of this oxidative rearrangement in which the migrating group is acetyl, carboalkoxy, or dialkylcarbamoyl. We have found that pyrroles **5a–i** react rapidly with concentrated nitric acid to give pyrrolinones **6a–i.** We have synthesized related 4,4-disubstituted pyrrolinones by acylation of **13a** and **13b** and also report iso-



5 **6**

a, $R_1 = OC_2H_5$; $R_2 = CH_3$
b, $R_1 = OCH_3$; $R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = OC_2H_5$
d, $R_1 = OCH_3$; $R_2 = OCH_3$
e, $R_1 = OCH_3$; $R_2 = OC_2H_5$
f, $R_1 = OC_2H_5$; $R_2 = OC_2H_5$
g, $R_1 = OCH_3$; $R_2 = N(CH_3)_2$
h, $R_1 = OCH_3$; $R_2 = N(CH_3)(C_2H_5)$
i, $R_1 = OCH_3$; $R_2 = N(C_2H_5)_2$