# Pyrrolo[3,2,1-*jk*][1,4]benzodiazepines and Pyrrolo[1,2,3-*ef*][1,5]benzodiazepines Which Have Central Nervous System Activity

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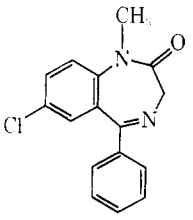
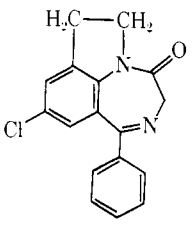
A series of pyrrolo[3,2,1-*jk*][1,4]benzodiazepines and pyrrolo[1,2,3-*ef*][1,5]benzodiazepines which is related to the clinically effective benzodiazepine, diazepam, has been prepared. Pharmacological data are presented which demonstrate that some of the compounds have CNS activity in mice.

The remarkable clinical success of the 1,4-benzodiazepine antianxiety drugs[1-3] (*viz.* diazepam, **1**) prompted our interest in the chemistry of the related pyrrolo[3,2,1-*jk*][1,4]benzodiazepines (*viz.* **2**) as a possible route to compounds with useful CNS activity.



1

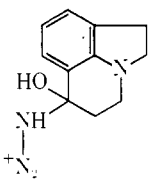


2

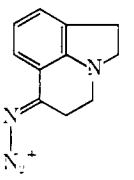
Casual inspection of structure **2** will reveal that it differs from **1** only by the insertion of a $CH_2$ between the N-Me function and C-9 of the benzodiazepine nucleus to form a new five-membered ring. At the outset we were also intrigued by the possibility of aromatizing the pyrroline ring to give a system, formally a 1,7-disubstituted indole, which might have both interesting biological activity and chemical reactivity.

For one approach to this system, we envisioned a Beckmann-type ring expansion of 1-ketolilodidine (**4**). The preparation and chemistry of **4** had been studied previously by Astill and Boekelheide[4] and by Rapoport and Tretter[5] who were interested in intermediates suitable for the preparation of apo-β-erythroidine. The former investigators[4] explored both the Beckmann and the Schmidt reactions on this ketone. They reported that although various attempts to accomplish the Beckmann rearrangement were unsuccessful the reaction of **4** in $CHCl_3$ with $NaN_3$ and $H_2SO_4$ gave a low yield of a substance which had a composition and physical properties that could accommodate either structure **14** or **12** (Scheme I). Because of our previous experience[6] and the absence of experimental detail in the paper cited, we reinvestiaged the Beckmann rearrangement of **4**-oxime. In agreement with the previous work,[4] reaction of the oxime with either polyphosphoric acid[7] or refluxing $HCO_2H$[8] or reaction of the tosyloxy oxime with neutral alumina which had been deactivated with 1% $H_2O$[6,9] gave none of the expected rearrangement products. On the other hand the reaction of **4** with $NaN_3$ in polyphosphoric acid[10] gave a 73.5% yield of a 5:1 mixture of the isomeric lactams **14** and **12** which could be separated by silica gel chromatography. The structure assignments were based on spectral data[11] and the LAH reduction product **29** of **14** which had a singlet for the C-7 protons at δ 3.89 in the nmr spectrum.

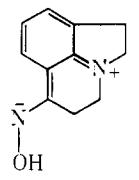
From a mechanistic standpoint the formation of **14** and **12** by the Schmidt and not by the Beckmann reaction is important since *in this case* the tetrahedral intermediate I[12] must be the immediate precursor of the rearrangement products. The alternative trigonal intermediate II[13] is analogous to the oxime intermediates necessary for the Beckmann rearrangement; it should have electronic characteristics similar



I



II



III

to those of the oxime intermediates and thus in this case would not be expected to undergo rearrangement. Failure of the Beckmann rearrangement in this case must be due, at least in part, to a large contribution of resonance structure III to the electronic nature of the molecule.[14,15]

Chloro derivatives **15** and **13** were similarly prepared from 5-chloroindoline (**61**)[16] *via* acid **3** and ketone **5**. In this case the Schmidt reaction gave a 67.6% yield of **15** and **13** with an isomer ratio of 11:1. The low yield of **13** prompted an alternate method for its preparation (Scheme II). Nitration of 1-acetyl-5-chloroindoline with fuming $HNO_3$ in AcOH–$Ac_2O$ gave

(1) G. Zbinden and L. O. Randall, *Advan. Pharmacol.*, **5**, 213 (1967).

(2) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr, in "Drugs Affecting the Central Nervous System," Vol. I, A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, Chapter 6.

(3) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964).

(4) B. D. Astill and V. Boekelheide, *J. Org. Chem.*, **23**, 316 (1958).

(5) H. Rapoport and J. R. Tretter, *ibid.*, **23**, 248 (1958).

(6) J. B. Hester, Jr., *ibid.*, **32**, 3804 (1967).

(7) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Amer. Chem. Soc.*, **74**, 5153 (1952).

(8) T. van Es, *J. Chem. Soc.*, 3881 (1965).

(9) J. C. Craig and A. R. Naik, *J. Amer. Chem. Soc.*, **84**, 3410 (1962).

(10) N. J. Doorenbos and R. E. Havranek, *J. Org. Chem.*, **30**, 2474 (1965).

(11) Spectral data supporting the structure may be found at the end of the Experimental Section.

(12) M. S. Newman and H. L. Gildenhorn, *J. Amer. Chem. Soc.*, **70**, 317 (1948).

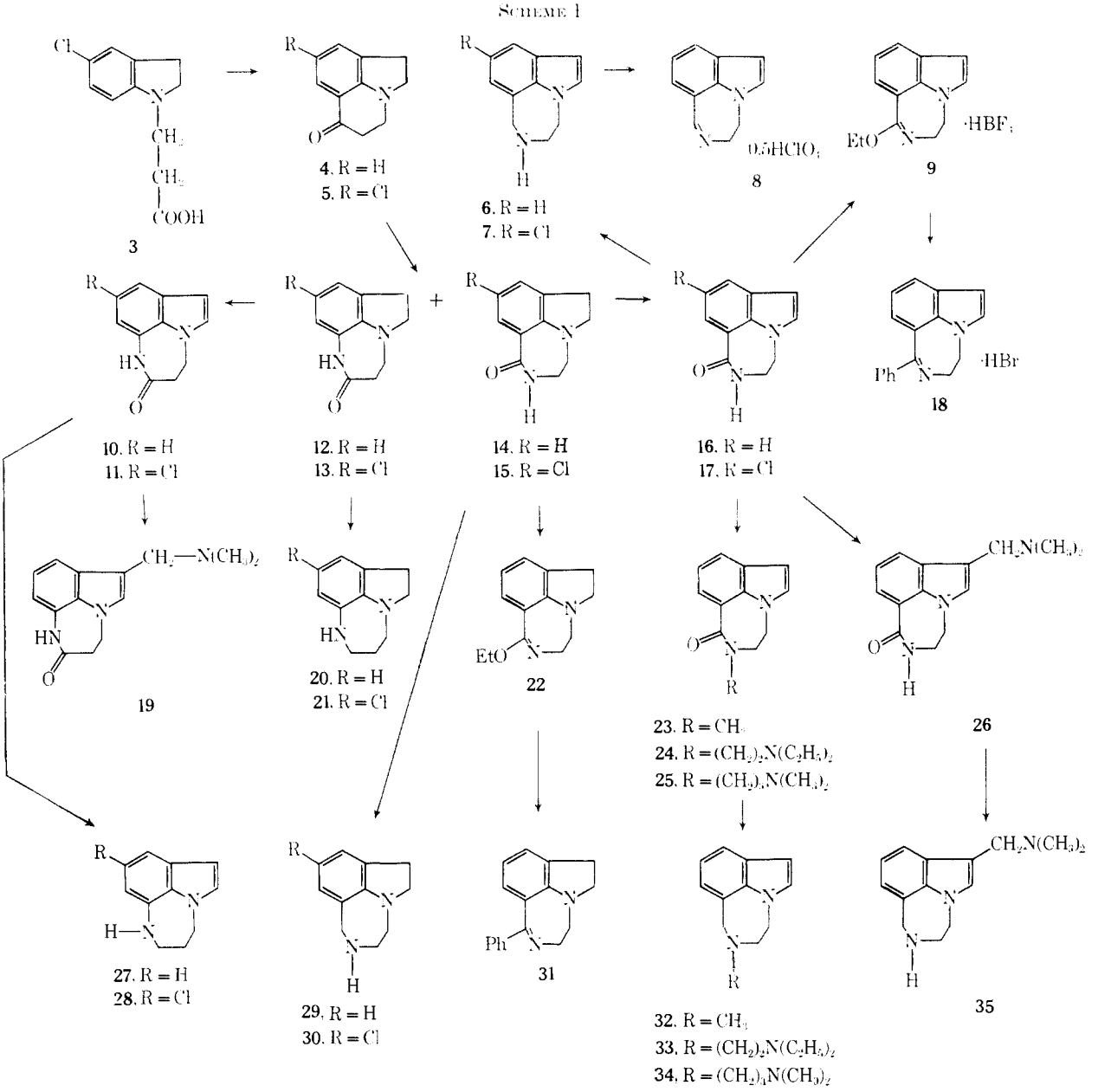
(13) P. A. S. Smith, *ibid.*, **70**, 320 (1948).

(14) R. Hoisgen, J. Witte, and I. Ugi, *Chem. Ber.*, **90**, 1844 (1957).

(15) For an excellent recent discussion of the Beckmann and Schmidt rearrangements see P. A. S. Smith in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience, New York, London, 1963, Chapter 8.

(16) Preparation of **61** by direct chlorination of 1-acetylindoline followed by acid hydrolysis of the amide is an improvement over the literature method [R. Ikan, E. Hoffman, E. D. Bergmann, and A. Galun, *Israel J. Chem.*, **2**, 37 (1964)]. This method is similar to that used by W. G. Gall, B. D. Astill, and V. Boekelheide [*J. Org. Chem.*, **20**, 1538 (1955)] to prepare 5-bromoindoline.

SCHEME I



**36** which was hydrolyzed with HCl in EtOH to give 5-chloro-7-nitroindoline (**62**). Reduction of **62** with Zn and NaOH[17] gave diamine **37** which was isolated as its HCl salt. Condensation of **37** with acrylic acid in HCl[18] produced **13** in 63% yield.

Dehydrogenation of **14** and **12** with a Pd–C catalyst in refluxing decalin gave the expected products (**16** and **10**) without difficulty. The analogous reaction with **15**, however, failed due to hydrogenolysis of the Cl group. Dehydrogenation of **15** and **13** to give **17** and **11** was accomplished with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene.[19] Compounds **16** and **10** reacted with $CH_2O$ and $Me_2NH$ in AcOH give the Mannich bases **26** and **19**, respectively. Several derivatives of the lactams were prepared by alkylating the amide N with NaH and an appropriate alkyl halide and/or by reducing the amide with LAH. These reactions are summarized in Scheme I.

Oxidation of **6** with activated $MnO_2$[20] gave imine **8** which was isolated as its hemiperchlorate salt in 73% yield. In addition to the usual spectral evidence catalytic (Pt) and chemical ($NaBH_4$) reduction of **8** to **6** firmly established the structure of this unusual salt. It is of passing interest that oxidation of the 1,2-dihydro compounds **29**, **39**, and **58** with activated $MnO_2$ was unsuccessful.

From its conception this investigation was designed to produce pyrrolo[3,2,1-*jk*][1,4]benzodiazepines with aromatic substituents at C-7. This result was initially achieved by alkylating lactams **14** and **16** with triethyloxoniumfluoroborate[21] to give imino ethers **22** and **9**. The reaction of these compounds with PhMgBr in refluxing $n$-$Bu_2O$[22] gave the desired 7-phenyl derivatives **31** and **18**. Successive reaction of **16** with

(17) E. L. Martin, "Organic Syntheses," Collected Vol. II, Wiley, New York, N. Y., 1943, p 501.

(18) G. B. Bachman and L. V. Heisey, *J. Amer. Chem. Soc.*, **71**, 1985 (1949).

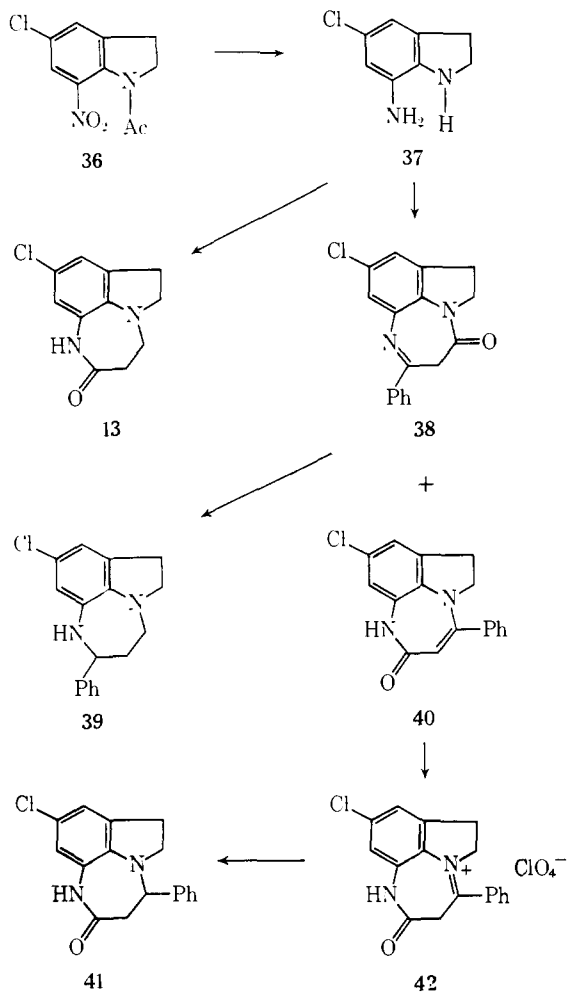
(19) H.-D. Becker, *J. Org. Chem.*, **30**, 982 (1965).

(20) E. F. Pratt and T. P. McGovern, *ibid.*, **29**, 1540 (1964).

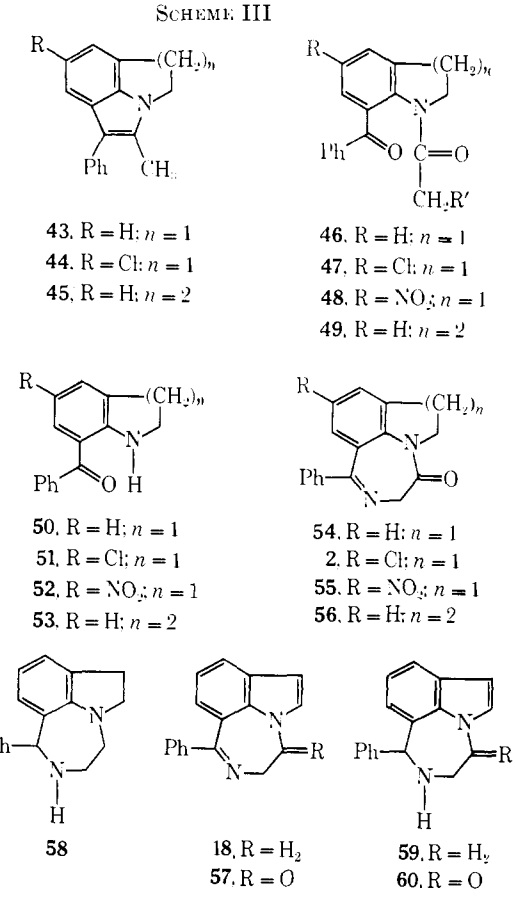
(21) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(22) O. Cervinka, *Collect. Czech. Chem. Commun.*, **24**, 1146 (1959).

SCHEME II



SCHEME III



$PCl_5$ and PhLi[23] resulted in the 1-chloro derivative **64** of **18**. Nuclear chlorination by $PCl_5$ has been observed previously.[24] An attempt to apply the former series of reactions to the preparation of 1,2,4,5-tetrahydro-6-phenylpyrrolo[1,2,3-*ef*][1,5]benzodiazepine failed due to the unsuccessful reaction of lactam **12** with triethyloxoniumfluoroborate. Apparently in this case alkylation occurs at N-3 rather than at the lactam carbonyl. The 6-phenylpyrrolo[1,2,3-*ef*][1,5]benzodiazepines were prepared (Scheme II) *via* the reaction of **37** with ethylbenzoylacetate.[25] In addition to **38** the isomeric compound **40** was also obtained from this reaction. Reduction of **38** with LAH was not successful. The reduction product **39** could, however, be obtained in 72% yield by the reaction of **38** with $BH_3$.[26] Acidification of enamine **40** with $HClO_4$ gave iminium perchlorate **42** which could then be reduced with $NaBH_4$ to **41**.[27]

An alternate method for the preparation of 7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepines is shown in Scheme III. Nitrosation of 5-chloroindoline (**61**) with $NaNO_2$ and $H_2SO_4$ gave 5-chloro-1-nitrosoindoline which was reduced to 1-amino-5-chloroindoline (**63**) with LAH.[28] Condensation of **63** with 1-phenyl-2-propanone gave a hydrazone which without isolation was cyclized to indole **44** with $H_2SO_4$ in EtOH.[29] Oxidation of **44** with $NaIO_4$[30] in warm dioxane–$H_2O$ gave a mixture of ketoamide **47** (R′ = H) and its hydrolysis product **51**. A facile conversion of **47** (R′ = H) into **51** was accomplished with 6 *N* HCl in EtOH. Condensation of **51** with bromoacetyl bromide followed by cyclization of the resulting bromoacetyl derivative (**47**, R′ = Br) with methanolic $NH_3$[31] gave 9-chloro-1,2-dihydro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4-(5*H*)-one (**2**). Application of this sequence to indoles **43**[29] and **45**[32] gave the corresponding benzodiazepines **54** and **56**[33] without difficulty. In the latter series the reaction of amino ketone **53** with ethyl glycinate·HCl in refluxing pyridine[31] (method N) gave a better yield of **56** than did the bromoacetyl bromide–MeOH–$NH_3$ (method M) sequence. Nitration of 1-acetyl-7-benzoylindoline (**46**, R′ = H) with fuming $HNO_3$ in AcOH–$Ac_2O$ gave an 84.2% yield of the pure 5-nitro derivative (**48**, R′ = H). Conversion of **48** (R′ = H) to 1,2-dihydro-9-nitro-7-phenylpyrrolo[3,2,1-*jk*][1,4]-benzodiazepin-4(5*H*)-one (**55**) was accomplished *via* amino ketone **52** by either method M or, preferably; method N.

Reduction of **54** with LAH gave the hexahydro derivative **58**. Dehydrogenation of **58** with a Pd–C cat-

(23) E. E. Smissman and J. L. Diebold, *J. Org. Chem.*, **30**, 4002 (1965).
(24) W. Autenrieth and P. Mühlinghaus, *Chem. Ber.*, **39**, 4098 (1906).
(25) W. Ried and P. S. Stahlhofen, *ibid.*, **90**, 828 (1957).
(26) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).
(27) N. A. Nelson, J. E. Ladbury and R. S. P. Hsi, *ibid.*, **80**, 6633 (1958).
(28) D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.*, 1509 (1962).
(29) A. N. Kost, L. G. Yudin, Yu. A. Berlin, and A. P. Terent'ev, *J. Gen. Chem. USSR*, **29**, 3782 (1959).
(30) L. J. Dolby and D. L. Booth, *J. Amer. Chem. Soc.*, **88**, 1049 (1966).
(31) L. H. Sternbach, R. I. Fryer, M. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
(32) A. N. Kost, L. G. Yudin, and A. N. Terent'ev, *J. Gen. Chem., USSR*, **29**, 1920 (1959).
(33) A synthesis of the 10-chloro derivative of **56** has been reported [H. P. Härter and S. Lüsberg, *Acta Chim. Scand.*, **22**, 3332 (1968)].

TABLE I

PHYSICAL, ANALYTICAL, AND PHARMACOLOGICAL DATA FOR THE PYRROLO[3,2,1-*jk*][1,4]BENZODIAZEPINES, PYRIDO[3,2,1-*jk*]BENZODIAZEPINE, AND PYRROLO[1,2,3-*ef*][1,5]BENZODIAZEPINES

| No. | Yield % | Method | Mp, °C | Recrystn solvent | Formula | Analyses | $LD_{50}$[a,w] | $LRR_{50}$ | $TR_{50}$ | $Cb_{50}$ | $D_{50}$ | $P_{50}$ | $FM_{50}$ | TE | D |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[z] | | | | | | | 650 | >25 | 5 | 1 | 1 | 2.5 | 3.8 | 0.28 | 0.28 |
| 2 | 81.7 | M | 116–117.5 | EtOAc–Sk B | $C_{17}H_{13}ClN_2O$ | C, H, Cl, N | 56 | >12.5 | >12.5 | 8.8 | 8.8 | >12.5 | *u* | >12.5 | 12.5 |
| 6 | 51 | A | 62.5–63.5 | EtOAc–Sk B | $C_{11}H_{12}N_2$ | C, H, N | 178 | >20[y] | 142 | 45 | 11[y] | 23[y] | 11.2 | 14[y] | 19[y] |
| 7 | 63.8 | A | 70–71.5 | $Et_2O$–Sk B | $C_{11}H_{11}ClN_2$ | C, H, Cl, N | >1000 | 178 | 126 | 27[y] | 32[y] | 50[y] | >20 | 16[y] | 15[y] |
| 8 | 73.7 | b | 171–174 | MeOH | $C_{11}H_{10}N \cdot 0.5\text{-}HClO_4$ | C, H, Cl, N | >200 | >100 | >100 | 79 | 29 | 50 | | 45 | 45 |
| 9 | 82.7 | H | 142–143.5 | $CH_2Cl_2$–EtOAc | $C_{13}H_{15}N_2OBF_4$[b] | C, H, F, N | | | | | | | | | |
| 10 | 81.5 | D | 213–214.5 | EtOAc | $C_{11}H_{10}N_2O$ | C, H, N | >1000 | >200 | >200 | 45 | 35 | 89 | >20 | 200 | 159 |
| 11 | 53.2 | E | 234–235 | $CH_2Cl_2$–MeOH | $C_{11}H_9ClN_2O$ | C, H, Cl, N | | | | | | | | | |
| 12 | 12.7 | B[c] | 163–164 | $CH_2Cl_2$–EtOAc | $C_{11}H_{12}N_2O$ | C, H, N | 233 | 89 | 63 | 32 | 18 | >50 | >20 | 25 | 25 |
| 13 | 63 | C | | | | | | | | | | | | | |
| | 5.6 | B | 169.5–170 | EtOAc–Sk B | $C_{11}H_{11}ClN_2O$ | C, H, Cl, N | 1000 | >200 | >100 | 71 | 71 | 79 | | 36 | 36 |
| 14 | 60.8 | B[c] | 151–152.5 | EtOAc | $C_{11}H_{12}N_2O$ | C, H, N | 562 | >100 | 71 | 23 | 32 | >50 | >20 | 32 | 32 |
| 15 | 62 | B | 201.5–202 | $CH_2Cl_2$–EtOAc | $C_{11}H_{11}ClN_2O$ | C, H, Cl; N[x] | >1000 | >200 | >200 | 126 | 25 | 89 | | 159 | 142 |
| 16 | 68.3 | D | 173–174 | MeOH–EtOAc | $C_{10}H_{10}N_2O$ | C, H, N | 422 | >50 | >50 | >50 | 50 | >50 | >20 | >50 | >50 |
| 17 | 60.8 | E | 231.5–232.5 | $CH_2Cl_2$–MeOH | $C_{11}H_9ClN_2O$ | C, H, Cl; N[x] | | | | | | | | | |
| 18 | 43.1 | I | 275 dec | MeOH–EtOAc | $C_{17}H_{15}BrN_2$[y] | C, H, N; Br[x] | >200 | >200 | 159 | 16 | 56 | 63 | | 56 | 56 |
| 19 | 79.4 | F | 193–193.5 | MeOH–EtOAc | $C_{14}H_{17}N_3O$ | C, H, N | 233 | >200 | 159 | 63 | 20 | 29 | *m* | 63 | 63 |
| 20 | 91 | A | 227–231 | MeOH–HCl | $C_{9}H_{16}Cl_2N_2$[c] | C, H, N; Cl[c] | 233 | >50 | >50 | 25 | 36 | >50 | >20 | >50 | >50 |
| 21 | 72.5 | A | 77.5–78.5 | EtOAc–Sk B | $C_{10}H_{13}ClN_2$ | C, H, Cl, N | 316 | 89 | >50 | 23 | 36 | 45 | | 36 | 36 |
| 22 | 62.2 | H | 47.5–49 | Petr ether | $C_{13}H_{16}N_2O$ | C, H, N | >1000 | | | | | | *m* | | |
| 23 | 59.5 | G | 105.5–106.5 | EtOAc–Sk B | $C_{12}H_{12}N_2O$ | C, H, N | 79 | >25 | >25 | 20 | 20 | 25 | | >25 | >25 |
| 24 | 75.8 | G | 168–170 | EtOH–EtOAc | $C_{19}H_{25}N_3O_2$[c] | C, H, N | 100 | >100 | 89 | >50 | 25 | >50 | *n* | 40 | 40 |
| 25 | 60.7 | G | 101.5–102.5 | EtOAc | $C_{16}H_{25}N_3O$ | C, H; N[x] | 200 | >100 | 79 | 36 | 36 | 40 | | 45 | 45 |
| 26 | 58.8 | F | 171–172.5 | EtOAc | $C_{14}H_{17}N_3O$ | C, H, N | 178 | >50 | >50 | 16 | 32 | 32 | | 15 | 16 |
| 27 | 75.6 | A | 79.5–80.5 | EtOAc–Sk B | $C_9H_{12}N_2$ | C, H, N | 316 | >200 | 92[y] | 24[y] | 10[y] | 22[y] | 20 | 19[y] | 16[y] |
| 28 | 84.2 | A | 128.5–129.5 | EtOAc–Sk B | $C_9H_9ClN_2$ | C, H, Cl, N | >1000 | >200 | 200 | >100 | >89 | 100 | | 20 | 20 |
| 29 | 79.3 | A | 67–68 | EtOAc–Sk B | $C_9H_{10}N_2$ | C, H, N | 133 | >50 | >50 | 20 | 25 | 36 | 12.6 | 25 | 20 |
| 30 | 74 | A | 281 dec | MeOH–EtOAc | $C_{10}H_{11}Cl_2N_3$[c] | C, H, Cl, N | 178 | >100 | 71 | 15 | 11 | 18 | | 13 | 13 |
| 31 | 37.1 | I | 245.5–246.5 | EtOH–EtOAc | $C_{9}H_{9}BrN_2$[c] | C, H, Br, N | 71 | >50 | >50 | 10 | 36 | 50 | | 40 | 40 |
| 32 | 77.4 | A | 42.5–44 | Petr ether | $C_{9}H_{11}N_2$ | C, H, N | 142 | >100 | >100 | >100 | 45 | >100 | | 45 | 45 |
| 33 | 80.2 | A | 244.5–246.5 | EtOH–EtOAc | $C_{9}H_{27}Cl_3N_3$[c] | C, H, Cl, N | 178 | >100 | 89 | >50 | >50 | >50 | *m* | 12 | 12 |
| 34 | 91 | A | 244–246 | MeOH–EtOAc | $C_{16}H_{25}Cl_2N_3$[c] | C, H, Cl, N | 237 | >200 | 200 | >100 | >100 | 63 | *m* | 18 | 18 |
| 35 | 82.3 | A | 67.5–68.5 | EtOAc–Sk B | $C_{14}H_{19}N_3$ | C, H, N | 562 | >50 | >50 | 36 | >50 | 32 | *m* | 36 | 36 |
| 38 | 44.3 | *b* | 124.5–125.5 | $Et_2O$ | $C_{17}H_{19}ClN_2O$ | C, H, Cl, N | >1000 | >200 | >200 | >200 | 112 | >200 | *m* | 126 | 126 |
| 39 | 71.8 | *b* | 208.5–209.5 dec | EtOH | $C_{17}H_{18}Cl_2N_2$[c] | C, H, Cl, N | >200 | >200 | >200 | >200 | >200 | >200 | | 100 | 100 |
| 40 | 11.5 | *b* | 280–281 | $CH_2Cl_2$ | $C_{17}H_{19}ClN_2O$ | C, Cl; H, N[x] | >1000 | >200 | >200 | 142 | 89 | 28 | *m* | 142 | 142 |
| 41 | 65.6 | *b* | 183–187 | EtOAc | $C_{17}H_{17}ClN_2O$ | C, H, Cl, N | >200 | >200 | >200 | 159 | 126 | >200 | | >200 | >200 |
| 42 | | *b* | 270 | MeOH–EtOAc | $C_{17}H_{19}Cl_2N_3O_3$ | C, H, Cl, N | | | | | | | | | |
| 54 | 80.7 | M | 140–141.5 | EtOAc–Sk B | $C_{14}H_{17}N_3O$ | C, H, N | >200 | >200 | 126 | 20 | >100 | >100 | >20 | 18 | 20 |
| 55 | 8.7 | M | | | | | | | | | | | | | |
| | 51.5 | N | 157–158.5 | EtOAc–Sk B | $C_{15}H_{12}N_4O_3$ | C, H, N | >1000 | >200 | 159 | 56 | 63 | 79 | | >100 | >100 |
| 56 | 18.9 | $L_0$, M | 170.5–171.5 | | | | | | | | | | | | |
| | 38.3 | N | | EtOAc | $C_{18}H_{16}N_2O$ | C, H, N | >1000 | >200 | >200 | >200 | 48[y] | 134[y] | | 20[y] | 20[y] |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 57 | 13.7 | *b* | 151.5–152 | EtOAc–Sk B | $C_{17}H_{12}N_2O$ | C, H, N | >200 | >200 | >200 | 159 | 178 | 178 | 178 |
| 58 | 84.7 | A | 102–103.5 | EtOAc | $C_{17}H_{18}N_2$ | C, H, N | | >50 | >50 | >50 | 40 | 45 | 36 |
| 59 | | *b* | 276 dec | MeOH-EtOAc | $C_{17}H_{17}ClN_2$[e] | C, H, Cl; N[t] | | | | | | | |
| 60 | 23.8 | *b* | 115–117 | EtOAc–Sk B | $C_{17}H_{14}N_2O$ | C, H, N | >200 | >200 | >200 | 159 | 25 | 32 | >200 |
| 64 | 8.2 | *b* | 301.5–304 dec | MeOH–EtOAc | $C_{17}H_{14}BrClN$[q] | C, H, Br, Cl, N | >200 | >200 | 159 | 79 | >100 | >100 | 45 |

[a] Isolated by silica gel chromatography with 15% MeOH–85% EtOAc. [b] See Experimental Section. [c] Hydrochloride salt. [d] Oxalate salt. [e] Dihydrochloride salt. [f] Dihydrochloride, hydrate. [g] Hydrobromide salt. [h] $HBF_4$ salt. [i] Crystallized at 0°. [j] Average of two determinations. [k] Average of three determinations. [l] Average of four determinations. [m] Tested orally, inactive at 40 mg/kg. [n] N: calcd, 12.58; found, 12.09. [o] N: calcd, 12.70; found, 12.27. [p] Cl: calcd, 28.69; found, 28.26. [q] N: calcd, 15.49; found, 15.91. [r] Br: calcd, 24.42; found 24.01. [s] H: calcd, 4.41; found, 4.89, N: calcd, 9.44; found, 8.95. [t] N: calcd, 9.84; found, 9.35. [u] Not tested. [v] See text for an explanation of the symbols. [w] Values are $ED_{50}$'s in mg/kg. [x] L. H. Sternbach and E. Reeder, *J. Org. Chem.*, *26*, 4936 (1961). A sample of diazepam was obtained from Hoffmann-LaRoche, Inc.

alyst in refluxing decalin gave a mixture of dihydro and tetrahydro derivatives **18** and **59**, respectively. A similar reaction converted **54** into the analogous products **57** and **60**. Borane reduction of **60** gave **59** which was also prepared by catalytic (Pt) reduction of **18**.

**Pharmacology. Methods.**—Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for the studies reported here. The test compounds were dissolved or suspended in 0.25% aq methyl cellulose solution and administered ip to groups of 6 mice per dose. Procedures for measuring acute toxicity ($LD_{50}$) and the effect of the test compounds on overt behavior: loss of righting reflex ($LRR_{50}$), traction ($Tr_{50}$), chimney ($Ch_{50}$), dish ($D_{50}$), and pedestal ($P_{50}$); fighting behavior ($FM_{50}$); and antagonism of nicotine-induced tonic-extensor convulsions (TE) and death (D) have been described previously.[34]

## Results and Discussion

The pharmacologic results obtained for the benzodiazepines are presented in Table I and are compared with the results obtained for diazepam (**1**) in the same test systems. The 1,2-dihydro-7-phenylpyrrolo-[3,2,1-*jk*][1,4]benzodiazepin-4(5*H*)-ones (**2** and **54**) had CNS activity as measured by their ability to antagonize nicotine-induced TE and D. The 9-chloro derivative **2** was more active than **54** in this test and was also active in the Ch and D tests. Both **2** and **54** were less active and **2** more toxic than diazepam. The 9-nitro derivative **55** had only slight activity in the Ch and D tests. Incorporation of a 3-C bridge between N-1 and C-9 of the benzodiazepine moiety **56** did not improve the activity of this series. Other compounds which had significant CNS activity, as measured by these test systems, were the 4,5,6,7-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepines (**6**, **7**, **33**, and **34**). the 1,2,4,5,6,7-hexahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepine (**30**), the 4,5-dihydropyrrolo[3,2,1-*jk*][1,4]-benzodiazepin-7(6*H*)-one (**26**), and the 4,5,6,7-tetrahydro[1,2,3-*ef*][1,5]benzodiazepine (**27**).

## Experimental Section[35]

A procedure for LAH reductions (method A) has been described previously.[6]

**1-Acetyl-5-chloroindoline.**—Liquid $Cl_2$ (165 ml) was evapd into a stirred solution of 1-acetylindoline (584.3 g, 3.63 moles), NaOAc (300 g), and HOAc (3650 ml) which was maintained at 17–22°. After the addition the mixture was stirred for 1 hr and poured into ice–water. The solid was collected by filtration, washed with $H_2O$, dried, and recrystd from EtOAc–Skellysolve B to give 419.4 g (59.4%) of product, mp 114–115° (lit.[16] mp 115–116°).

**5-Chloroindoline-1-propionic Acid (3).**—A stirred mixture of 5-chloroindoline (15.4 g, 0.100 mole), acrylonitrile (9.5 g), glacial HOAc (3.57 ml), and powdered reagent grade $Cu_2Cl_2$ (0.95 g)

(34) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DaVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964).

(35) Physical and analytical data for the benzodiazepines are listed in Table I; for other new compounds the data are listed in Table II. Melting points, taken in a capillary tube, are corrected. Analyses, indicated by the symbols of the elements, are within ±0.4% of the theoretical values. Skellysolve B (Sk B) is commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Celite is a filter aid manufactured by Johns-Manville, New York, N. Y. The silica gel used for chromatography was obtained from E. Merck A.G., Darmstadt, Germany. Darco G 60 is an activated carbon prepared by Atlas Chemical Industries, Inc., Wilmington, Del.

TABLE II

PHYSICAL AND ANALYTICAL DATA FOR NEW COMPOUNDS NOT LISTED IN TABLE I

| No. | Yield, % | Procedure | Mp, °C | Recrystn solvent | Formula | Analyses |
|---|---|---|---|---|---|---|
| 3 | 92.6 | *a* | 86–87 | EtOAc–Sk B | $C_{10}H_{12}ClNO_2$ | C, H, Cl, N[c] |
| 5 | 62.2 | *a* | 113.5–114.5 | EtOAc–Sk B | $C_9H_{10}ClNO$ | C, H, Cl, N |
| 36 | 91.4 | *a* | 174–175 | EtOAc | $C_{10}H_9ClN_2O_3$ | C, H, Cl, N |
| 62 | 89.7 | *a* | 125–126 | EtOAc | $C_{11}H_7ClN_2O_2$ | C, H, Cl, N |
| 37 | 55.6 | *a* | 218.5–220 dec | EtOH | $C_{11}H_{10}Cl_2N_2O$ | C, H, Cl, N |
| 44 | 47.8 | *a* | 205.5–206.5 | $CH_3COCH_2CH_3$ | $C_{12}H_{14}ClN$ | C, H, Cl, N[d] |
| 47 (R′ = H) | 26.2[e] | *d* | 163–164.5 | $CH_3COOC_2H_5$ | $C_{12}H_{14}ClNO_2$ | C, H, Cl, N |
| 47 (R′ = Br) | 78.3 | *b* | 165.5–166.5 | EtOAc–Sk B | $C_{12}H_{13}BrClNO_2$ | C, H, Br, Cl, N |
| 51 | 98.6 | K | 123–123.5 | EtOAc–Sk B | $C_{13}H_{12}ClNO$ | C, H, Cl, N |
| 43 | 62.2 | *b* | 139–140 | EtOH | $C_{12}H_{13}N$ | C, H, N |
| 45 | 75.5 | *c* | 129–130 | EtOAc | $C_{13}H_{15}N$ | C, H, N |
| 53 | 88.9 | K | 68–69.5 | Petr ether | $C_{13}H_{17}NO$ | C, H, N |
| 46 (R′ = H) | 24.8 | *d* | 142.5 | EtOAc | $C_{11}H_{11}NO_2$ | C, H, N |
| 46 (R′ = Br) | 78.8 | *b*, | 132.5–133 | EtOAc | $C_{11}H_{10}BrNO_2$ | C, H, Br, N |
| 48 (R′ = H) | 84.2 | *a* | 200–201 | $CH_2Cl_2$–EtOH | $C_{11}H_{10}N_2O_3$ | C, H, N |
| 48 (R′ = Br) | 90.4 | L | 169–171 | EtOAc | $C_{11}H_9BrN_2O_3$ | C, H, Br, N[g] |
| 52 | 87.3 | K | 223–224 | EtOAc | $C_{13}H_{12}N_2O$ | C, H, N[h] |
| 49 (R′ = H) | 46 | *J* | 132–133.5 | EtOAc | $C_{13}H_{17}NO_2$ | C, H, N |
| 50 | 84.5 | K | 124–125 | EtOAc–Sk B | $C_{13}H_{15}NO$ | C, H, N |

[a] See Experimental Section. [b] Lit.[29] mp 145–146°. [c] Lit.[32] mp 128°. [d] Hydrochloride salt. [e] C: Calcd, 58.54; found, 85.11. [f] C: Calcd, 76.25; found, 75.79. [g] N: Calcd, 7.20; found, 6.78. [h] C: Calcd, 67.15; found, 66.65.

was warmed in an oil bath under $N_2$ to 75° (bath temperature). At this temp, a vigorous exothermic reaction took place. The oil bath was kept at 75–95° for 1 hr, additional acrylonitrile (10 ml) was added to the reaction which was then refluxed for 18 hr (bath temp 125°). The cooled reaction mixture was poured into ice–water, made alk with concd $NH_4OH$, and extracted with $CH_2Cl_2$. The extract was washed with water, dried ($K_2CO_3$), and concd. The residual oil was distd under reduced pressure (0.03 mm) to give: 2.76 g, bp 131–139°; 8.53 g, bp 132–141°; 7.36 g, bp 141–143° (90.2% yield) of 5-chloroindoline-1-propionitrile.

A stirred mixture of 5-chloroindoline-1-propionitrile (8.22 g, 0.0398 mole) and 3 *N* aq KOH (100 ml) was refluxed under $N_2$ for 3 hr, cooled, and extracted with $CH_2Cl_2$. The aq layer was cooled in an ice bath and acidified to pH 3.5 with concd HCl. The crystalline product was collected by filtration, washed with water, dried, and recrystd from EtOAc–Skellysolve B to give **3**.

**8-Chloro-1,2,4,5-tetrahydro-6*H*-pyrrolo[3,2,1-*ij*]quinolin-6-one (5).**—A stirred mixture of **3** (11.5 g, 0.0512 mole) and polyphosphoric acid (350 g) was heated under $N_2$ at 100–110° for 22 hr, cooled, and poured into ice–water. The resulting mixture was neutralized to pH 4.5 with 50% aq NaOH and extracted several times with $Et_2O$. The $Et_2O$ extract was washed successively with water, dil NaOH, and brine, dried ($K_2CO_3$), and concd under reduced pressure. Crystallization of the residue from EtOAc–Skellysolve B (Darco G 60) gave **5**.

**9-Chloro-1,2,4,5-tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-7(6*H*)-one (15). 9-Chloro-1,2,4,5-tetrahydropyrrolo[1,2,3-*ef*]-[1,5]benzodiazepin-6(7*H*)-one (13). Method B.**—A stirred mixture of **5** (4.15 g, 0.0200 mole) and polyphosphoric acid (120 g) was heated under $N_2$ to 50–60° and treated portionwise, during 1 hr with $NaN_3$ (1.69 g, 0.0260 mole). The mixture was kept at 50–60° for an additional 4 hr and poured into ice–water. The resulting solution was rendered alkaline with 50% NaOH and extracted several times with $CHCl_3$. The extract was washed with brine, dried ($K_2CO_3$), and concd under reduced pressure. Crystallization of the residue from MeOH–EtOAc (Darco G 60) gave pure **15**.

The mother liquor was concd and chromatographed on silica gel (150 g) with 5% MeOH–95% EtOAc. The second band eluted from the column was crystallized from EtOAc to give **13**.

Further elution of the column with 10% MeOH–90% EtOAc yielded additional **15**.

**1-Acetyl-5-chloro-7-nitroindoline (36).**—A stirred mixture of 1-acetyl-5-chloroindoline (66.9 g, 0.342 mole), $Ac_2O$ (342 ml), and HOAc (136 ml) was cooled to 10–15° and treated during 15 min with a solution of fuming $HNO_3$ (35.9 g) in HOAc (34.2 ml). The mixture was kept at 10–15° during the addition and for an additional 2 hr. It was then poured into cold $H_2O$. The solid was collected by filtration, washed with water, dried, and recrystd from EtOAc to give **36**.

**5-Chloro-7-nitroindoline (62).**—A stirred mixture of **36** (3.62 g, 0.0150 mole), 6 *N* HCl (50 ml), and EtOH (100 ml) was refluxed under $N_2$ for 2 hr, and allowed to stand at ambient temp for 18 hr. The reaction mixture which contained crystalline product was poured into $H_2O$. The solid was collected by filtration, washed with $H_2O$, dried, and recrystd from EtOAc to give **62**.

**7-Amino-5-chloroindoline (37) Hydrochloride.**—A stirred mixture of **36** (19.9 g, 0.100 mole), 95% EtOH (52 ml), and 20% aq NaOH (48 ml) was warmed under $N_2$ to the reflux temp and treated portionwise with Zn dust (26 g) at such a rate that the mixture refluxed without external heating. At the end of the addition, the mixture had changed from red to light yellow. Additional EtOH (13 ml) was added and the mixture was refluxed for 1 hr, cooled, and filtered. The solid was washed with $Et_2O$. The combined filtrate was treated with a little $Na_2S_2O_4$ and concentrated *in vacuo*. A suspension of the residue in $H_2O$ was extracted with $Et_2O$. The extract was washed with brine, dried ($K_2CO_3$), and concentrated *in vacuo*. A solution of this residue in a little EtOH was cooled in an ice bath and acidified with dry methanolic HCl. The resulting crystalline solid was collected by filtration and washed with EtOH. A small amount of additional product was obtained by concentrating the filtrate. The combined product was recrystd from EtOH (Darco G 60) to give pure **37**·HCl.

**9-Chloro-1,2,4,5-tetrahydropyrrolo[1,2,3-*ef*][1,5]benzodiazepin-6(7*H*)-one (13). Method C.**—A mixture of **37**·HCl (26.6 g, 0.100 mole), acrylic acid (10.8 g, 0.150 mole), and 5.7 *N* HCl (15 ml) was heated on the steam bath for 1.5 hr. The mixture went into solution and then solidified. The solid was suspended in $H_2O$ and made ammoniacal with concd $NH_4OH$. The resulting mixture was stirred for 1 hr and filtered. The solid was washed with $H_2O$, dried, and recrystd from EtOAc to give **13**.

**4,5-Dihydropyrrolo[1,2,3-*ef*][1,5]benzodiazepin-6(7*H*)-one (10). Method D.**—A mixture of **12** (17.5 g, 0.0930 mole), decalin (280 ml), and 10% Pd–C was refluxed under $N_2$ for 1.5 hr, cooled, and diluted with Skellysolve B (1000 ml). This mixture was kept in an ice bath for 2 hr and then filtered. The solid was washed with Skellysolve B and extracted with hot MeOH. The MeOH extract was concd and the residue was crystallized from MeOH–EtOAc to give **10**.

**9-Chloro-4,5-dihydropyrrolo[3,2,1-*jk*][1,4]benzodiazepin-7-(6*H*)-one (17). Method E.**—A stirred mixture of **15** (10.0 g, 0.0450 mole), DDQ (12.3 g, 0.0542 mole), and dry $C_6H_6$ (200 ml) was refluxed under $N_2$ for 7 hr, cooled, and filtered. The solid was suspended in a mixture of cold, dil NaOH and $CH_2Cl_2$, stirred for 30 min, and filtered. The $CH_2Cl_2$ solution was washed with brine, dried ($K_2CO_3$), and concentrated. Crystallization of the residue from THF (Darco G 60) gave 2.20 g of **17**. The sticky solid obtained from the above filtration was mixed with Celite, washed several times with cold, dil NaOH and $H_2O$, and then

extracted with hot MeOH–$CH_2Cl_2$. The extract was concd and the residue was crystallized from THF to give 3.81 g of additional **17**.

**1-[(Dimethylamino)methyl]-4,5-dihydropyrrolo[3,2,1-*jk*][1,4]-benzodiazepin-7(6*H*)-one (26). Method F.**—Aqueous (25%) $Me_2NH$ (2.43 ml) was cooled with stirring in an ice bath and treated successively with HOAc (5.0 ml) and aq (37%) $H_2CO$ (0.893 ml). This solution was allowed to warm to ambient temp and was treated with **16** (1.86 g, 0.0100 mole). This mixture was stirred, under $N_2$, for 2 hr and poured into ice–water. The resulting solution was made alkaline with dil NaOH and was extracted with $CH_2Cl_2$. The extract was dried ($K_2CO_3$) and concentrated *in vacuo*. The residue was treated with EtOAc and a small amount of insol material was removed by filtration. The filtrate was concd and crystallized to give **26**.

**4,5-Dihydro-6-methylpyrrolo[3,2,1-*jk*][1,4]benzodiazepin-7-(6*H*)-one (23). Method G.**—A stirred solution of **16** (10.0 g, 0.0538 mole) in dry DMF (500 ml) was cooled in an ice bath under $N_2$ and treated with a 57.1% mineral oil suspension of NaH (2.43 g). The resulting mixture was warmed on the steam bath for 1 hr, cooled in an ice bath, and treated with a solution of MeI (8.38 g) in $Et_2O$ (90 ml). This mixture was kept at ambient temp for 18 hr and concentrated *in vacuo*. The residue was suspended in $H_2O$ and extracted with $CH_2Cl_2$. The extract was dried ($K_2CO_3$) and concd *in vacuo*. The residue was chromatographed on silica gel (800 g) with 50% $Me_2CO$–Skellysolve B. The product was the first material eluted from the column. It was crystallized from EtOAc–Skellysolve B to give **23**.

**4,5-Dihydropyrrolo[3,2,1-*jk*][1,4]benzodiazepine Hemiperchlorate (8).**—A stirred mixture of activated $MnO_2$ (26.6 g) and $C_6H_6$ (740 ml) was refluxed, under $N_2$, for 4 hr with azeotropic distillation of $H_2O$. It was then cooled and treated with **29** (13.2 g, 0.0765 mole). This mixture was refluxed for 18 hr, cooled, and filtered. The solid was washed with $CH_2Cl_2$ and the combined filtrate was concd *in vacuo*. A solution of the residual oil in $Et_2O$ was acidified with 70% $HClO_4$. The yellow solid was collected by filtration, washed with $Et_2O$, and recrystd from MeOH to give **8**.

**4,5,6,7-Tetrahydropyrrolo[3,2,1-*jk*][1,4]benzodiazepine (6) Hydrochloride from 8.**—A mixture of **8** (0.500 g), abs EtOH (50 ml), and $NaBH_4$ (0.50 g) was stirred under $N_2$ at ambient temp for 18 hr and concd *in vacuo*. The residue was mixed with $H_2O$ and extracted with $CH_2Cl_2$. The extract was washed with $H_2O$, dried ($K_2CO_3$), and concd. A solution of the residue in EtOAc was acidified with dry ethereal HCl and the salt was recrystd from MeOH–EtOAc to give 0.186 g of **6**·HCl, mp 246.5–248°. The analytical sample had mp 247–249°. It was identical with the hydrochloride prepared from authentic **6** by ir and uv spectral comparison. The mixture melting point was undepressed. *Anal.* ($C_{11}H_{13}ClN_2$) C, H, Cl, N.

**7-Ethoxy-4,5-dihydropyrrolo[3,2,1-*jk*][1,4]benzodiazepine Fluoroborate (9). Method H.**—A stirred solution of **16** (3.72 g, 0.0200 mol) in dry $CH_2Cl_2$ (100 ml) was cooled in an ice bath, under $N_2$, and treated with 25 ml (0.05 mole) of a $CH_2Cl_2$ solution of triethyloxonium fluoroborate.[21] The resulting solution was kept at ambient temp for 19 hr, refluxed for 4 hr, cooled in an ice bath, and treated with 7.92 g of 50% $K_2CO_3$. The mixture was stirred for a few min and filtered through $K_2CO_3$. The filtrate was concd *in vacuo*, and the residue was crystallized from $CH_2Cl_2$–EtOAc to give **9**. A small second crop was obtained by crystallizing the mother liquors using a small amount of silica gel to remove the contaminants.

**4,5-Dihydro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepine Hydrobromide (18) from 9. Method I.**—A stirred suspension of **9** (3.02 g, 0.01 mole) in $Et_2O$ was cooled in an ice bath and treated with a dil $K_2CO_3$ solution. The mixture was stirred until the yellow salt had dissolved. The aq layer was extracted with $Et_2O$ and the combined $Et_2O$ solution was washed with brine, dried ($K_2CO_3$), and concd *in vacuo*. A solution of the residual oil (**9**, free base) in $C_6H_6$ was concd *in vacuo* to remove the last traces of $H_2O$.

$Et_2O$ was distilled, under $N_2$, from a solution of 3 *M* ethereal PhMgBr (5.0 ml) in *n*-$Bu_2O$ (20 ml). To the resulting refluxing solution was added during 15 min a solution of **9** (free base) in *n*-$Bu_2O$ (15 ml). The resulting yellow suspension was refluxed for 8 hr, cooled, and poured into ice water. This mixture was acidified with HCl and filtered through Celite. The solid was washed with dil HCl and the filtrate was washed with $Et_2O$. The combined aq layer was cooled in an ice bath, made alkaline with NaOH, and extracted with $Et_2O$. The $Et_2O$ extract was washed with brine, dried ($K_2CO_3$), and concd *in vacuo*. A solution of the residue in EtOAc was acidified with dry methanolic HBr and the resulting salt was recrystd from MeOH–EtOAc (Darco G-60) to give **18**.

**1-Chloro-4,5-dihydro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepine Hydrobromide (64).**—A stirred mixture of **16** (4.65 g, 0.0250 mole), $PCl_5$ (11.45 g, 0.0550 mole), and dry $C_6H_6$ (150 ml), under $N_2$, was kept at ambient temp for 1.5 hr and was refluxed for 3 hr. The mixture was cooled and concd *in vacuo*. The residue was twice suspended in $C_6H_6$ with concentration after each addition. A stirred suspension of the resulting yellow–green solid in $Et_2O$ (150 ml) was cooled in an ice bath, under $N_2$, and treated during about 30 min with 1.99 *M* PhLi (25 ml). This mixture was allowed to remain in the ice bath for an additional 35 min and was poured into $H_2O$. The resulting mixture was filtered through Celite; the solid was washed well with $Et_2O$. The filtrate was extracted with $Et_2O$, and the combined $Et_2O$ extract was back extracted with cold, dil HCl. This acid solution was cooled in an ice bath, made alkaline with NaOH, and extracted with $Et_2O$. The $Et_2O$ extract was washed with brine, dried ($K_2CO_3$), and concd *in vacuo*. An EtOAc solution of the residue was acidified with dry methanolic HBr, and the salt was crystallized from MeOH–EtOAc to give **64**.

**9-Chloro-1,2-dihydro-6-phenylpyrrolo[1,2,3-*ef*][1,5]benzodiazepin-4(5*H*)-one (38). 9-Chloro-1,2-dihydro-4-phenylpyrrolo-[1,2,3-*ef*][1,5]benzodiazepin-6(7*H*)-one (40).**—A solution of **37**·HCl (2.05 g, 0.0100 mole) in cold water was made alkaline with NaOH and extracted with $Et_2O$. The extract was washed with brine, dried ($K_2CO_3$), and concd *in vacuo*. A solution of the residue in xylene (20 ml) was heated to the reflux temp, under $N_2$, and treated during 26 min with a solution of ethyl benzoylacetate (1.92 g, 0.0100 mole) in xylene (10 ml). During the addition and for an additional 36 min the EtOH–water azeotrope was distd from the mixture; the volume was kept constant by the addition of fresh xylene (9.5 ml). The mixture was cooled and diluted with Skellysolve B. The solid product was collected by filtration, washed with Skellysolve B, and extracted with $Et_2O$. The solid remaining after the $Et_2O$ extraction was dissolved in $CH_2Cl_2$–MeOH, decolorized with Darco G 60, and crystallized to give **40**. The $Et_2O$ extract was decolorized with Darco G 60 and crystallized to give **38**.

**9-Chloro-1,2,4,5,6,7-hexahydro-6-phenylpyrrolo[1,2,3-*ef*][1,5]-benzodiazepine Hydrochloride (39).**—A stirred solution of **38** (14.8 g, 0.0500 mole) in dry THF (300 ml) was cooled in an ice bath, under $N_2$, and treated with a 1 *M* solution of $BH_3$ in THF (150 ml). This solution was allowed to remain in the ice bath for 1.5 hr and was refluxed for 2.5 hr. It was then cooled in an ice bath, treated with 6 *N* HCl (22.5 ml), and concd *in vacuo*. The residue was suspended in $Et_2O$ and water and made alkaline with NaOH. The aq layer was extracted with $Et_2O$ and the combined $Et_2O$ layers were washed with brine, dried ($K_2CO_3$), and concd *in vacuo*. A solution of the residue in EtOAc was acidified with dry methanolic HCl and the resulting salt was recrystd from MeOH–EtOAc to give **39**.

**9-Chloro-1,2-dihydro-4-phenylpyrrolo[1,2,3-*ef*][1,5]benzodiazepin-6(7*H*)-one Perchlorate (42).**—A suspension of **40** (2.0 g) in $Et_2O$ and 70% $HClO_4$ was stirred for 2 hr. The solid was collected by filtration, washed with $Et_2O$, and dried to give **42**.

**9-Chloro-1,2,4,5-tetrahydro-4-phenylpyrrolo[1,2,3-*ef*][1,5]benzodiazepin-6(7*H*)-one (41).**—A stirred mixture of $NaBH_4$ (2.5 g) in abs EtOH was cooled in an ice bath and treated, portionwise, with **42** (2.51 g). The mixture was allowed to warm slowly to ambient temp and stand for 22 hr under $N_2$. It was then concd *in vacuo*. The residue was mixed with $H_2O$, stirred in an ice bath for a few min, and filtered. The solid was washed with $H_2O$, dried, and recrystd from EtOAc to give **41**.

**7-Chloro-1,2-dihydro-4-methyl-5-phenylpyrrolo[3,2,1-*hi*]indole (44).**—5-Chloroindoline (61.4 g, 0.400 mole) was added to a solution of $H_2SO_4$ (64.6 ml) in $H_2O$ (258 ml). The resulting stirred solution was cooled in a salt–ice bath to −8° and treated with a solution of $NaNO_2$ (28.9 g) in $H_2O$ (120 ml) at such a rate that the temp remained at −5° to −1°. The thick ppt which formed was collected by filtration, washed with $H_2O$ until free of $NO_2^-$, and dried under reduced pressure at 40° to give 71.0 g (97.2%) of 5-chloro-1-nitrosoindoline.

A solution of the crude 5-chloro-1-nitrosoindoline (71.0 g, 0.389 mole) in dry $C_6H_6$ (1650 ml) was added under $N_2$, during 30 min to a stirred, refluxing suspension of LAH (15.5 g, 0.408 mole) in $Et_2O$ (1300 ml). The resulting mixture was refluxed for an additional 1.5 hr, cooled in an ice bath, and treated successively with

$H_2O$ (15.5 ml), 15% aq NaOH (15.5 ml), and $H_2O$ (46.5 ml). The solid was collected by filtration and the filtrate was concd under reduced pressure. Distillation of the resulting oil gave 1.97 g, bp 153–156° (14 mm); 28.31 g, bp 156–160° (14 mm), and 13.13 g, bp 160–161° (14 mm) (72.3% yield) of **63**. A stirred mixture of **63** (45.8 g, 0.297 mole), 1-phenyl-2-propanone (39.8 g, 0.297 mole), glacial HOAc (5.91 ml), and $C_6H_6$ (760 ml) was refluxed under $N_2$ for 2.5 hr with azeotropic distillation of $H_2O$. The resulting solution was cooled and concd under reduced pressure. A solution of concd $H_2SO_4$ (114.2 g) in abs EtOH (592 ml) was added to the residue, and the resulting mixture was heated on the steam bath for 10 min, cooled, and poured into ice water. The product pptd during the reaction. It was collected by filtration, washed with $H_2O$, dried, and crystallized from $Me_2CO$ to give **44**.

**1-Acetyl-7-benzoyl-5-chloroindoline (47, R′ = H). Method J.**—A stirred solution of **44** (38.0 g, 0.142 mole) in 1800 ml of hot dioxane (70–75°) was treated, under $N_2$, during 1.5 hr with a solution of $NaIO_4$ (79.0 g) in warm $H_2O$ (375 ml). The resulting mixture was kept at about 70° for 20 hr, cooled, poured into ice–$H_2O$, and extracted several times with $CHCl_3$. The extracts were washed with $H_2O$, dried ($MgSO_4$), and concd under reduced pressure. Crystallization of the residue from $Me_2CO$ gave 8.69 g, mp 205–206.5°, and 0.71 g, mp 202–203.5°, of recovered **44**. The mother liquor was concd and chromatographed on silica gel (2 kg) with EtOAc. The first band contained 7-benzoyl-5-chlorindoline which was isolated as **47** (R′ = Br), 3.85 g (7.17%), mp 162.5–166.5°. The second band eluted from the column was crystallized from EtOAc to give **47** (R′ = H).

**7-Benzoyl-5-chloroindoline (51). Method K.**—A stirred mixture of **47** (R′ = H) (1.95 g, 0.00652 mole), abs EtOH (33.3 ml), and 6 *N* HCl (16.7 ml) was refluxed under $N_2$ for 4 hr, cooled, and poured into ice–water. The resulting mixture was made alkaline with 50% aq NaOH. The yellow, crystalline product was collected by filtration, washed ($H_2O$), and dried to give **51**.

**7-Benzoyl-1-(bromoacetyl)-5-chloroindoline (47, R′ = Br). Method L.**—A stirred mixture of **51** (1.50 g, 5.83 mole), $C_6H_6$ (50 ml), and $BrCH_2COBr$ (2.35 g, 11.7 mole) was refluxed for 45 min with a slow stream of $N_2$ flowing through the system to flush out the HBr formed. The mixture was cooled in an ice bath and diluted with Skellysolve B (50 ml). The crystalline product was collected by filtration, washed with Skellysolve B, and recrystd from EtOAc–Skellysolve B to give **47** (R′ = Br). Additional product was obtained by concentrating the $C_6H_6$–Skellysolve B filtrate.

**1-(Bromoacetyl)-7-benzoylindoline (46, R′ = Br). Method L.**—A stirred solution of **50** (2.23 g, 0.01 mole) and $C_5H_5N$ (0.806 ml, 0.01 mole) in $Et_2O$ was treated, under $N_2$ with a solution of $BrCH_2COBr$ (2.24 g, 0.012 mole) in a little $Et_2O$. The resulting mixture was stirred at room temp for 2.5 hr and poured into $H_2O$. The solid product was collected by filtration, washed with $H_2O$, dried *in vacuo*, and crystallized from EtOAc to give **46** (R′ = Br). A small amount of additional product was obtained from the $Et_2O$ filtrate.

**9-Chloro-1,2-dihydro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(5*H*)-one (2). Method M.**—A solution of **47** (R′ = Br) (13.5 g, 0.0357 mole) in THF (525 ml) was treated with 450 ml of MeOH that had been satd at room temp with $NH_3$. This solution was stirred, under $N_2$, at room temp for 18 hr and concd under reduced pressure at 20–25°. The residue was suspended in $H_2O$ and extracted several times with $CH_2Cl_2$. The extract was dried ($K_2CO_3$) and concd under reduced pressure. Crystallization of the residue from EtOAc–Skellysolve B gave **2**.

**1-Acetyl-7-benzoyl-5-nitroindoline (48, R′ = H).**—A stirred mixture of **46** (21.8 g, 0.0823 mole), $Ac_2O$ (82.3 ml), and HOAc (41 ml) was cooled to 10° and treated during 15 min with fuming (90%) $HNO_3$ (8.64 g, 0.123 mole); the temp was kept below 13° during the addition. The reaction mixture was allowed to warm slowly to ambient temp during 4.5 hr and was then poured into ice–water. This mixture was stirred for 30 min, and the solid was collected by filtration, washed ($H_2O$), and dried *in vacuo*. Crystallization of this solid from EtOH–$CH_2Cl_2$ gave pure **48** (R′ = H).

**1,2-Dihydro-9-nitro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(5*H*)-one (55). Method N.**—A stirred mixture of **52** (5.18 g, 0.0194 mole), ethyl glycinate·HCl (5.40 g, 0.0387 mole), and $C_5H_5N$ (40 ml) was refluxed under $N_2$ for 24 hr. During the first 6 hr of the reaction $C_5H_5N$–$H_2O$–EtOH azeotrope (50 ml) was slowly distd from the reaction and replaced with fresh dry $C_5H_5N$. The cooled reaction mixture was concd under reduced pressure. The residue was suspended in cold $H_2O$, made ammoniacal, and extracted with $CH_2Cl_2$. The extract was washed with $H_2O$, dried ($K_2CO_3$), concd under reduced pressure, and chromatographed on silica gel (250 g) with 60% EtOAc–40% cyclohexane. The first material eluted was recovered starting material (**52**), 1.27 g, mp 221.5–223°. Further elution of the column gave **55** which was crystallized from EtOAc–Skellysolve B.

**4,5,6,7-Tetrahydro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepine Hydrochloride (59). 4,5-Dihydro-7-phenylpyrrolo[3,2,1-*jk*]-[1,4]benzodiazepine Hydrobromide (18) from 58.** A stirred mixture of **58** (5.00 g, 0.0200 mole), 10% Pd–C (2.5 g), and decalin (100 ml) was refluxed under $N_2$ for 1.5 hr, cooled, and filtered through Celite. The solid was washed with $Et_2O$ and the combined filtrate was acidified with cold, dil HCl. The organic layer was separated from the aq layer and an insol gum and was washed with dil HCl. The combined aq solution (and gum) was washed with $Et_2O$, treated with $CH_2Cl_2$, and made alkaline with NaOH. The aq layer was extracted with $CH_2Cl_2$ and the combined solution was washed with water, dried ($K_2CO_3$), and concd. The residue was chromatographed on silica gel (250 g) with 2% $Et_3N$–48% EtOAc–50% cyclohexane; but the product thus obtained (1.48 g of a crystalline HBr salt, mp 238–245° dec) was a mixture of two compounds. The base was, therefore, rechromatographed on silica gel (100 g) with 40% EtOAc–60% cyclohexane. The first compound eluted was acidified with dry methanolic HCl and crystallized from MeOH–EtOAc to give **59**. The second compound eluted was acidified with dry methanolic HBr and crystallized from MeOH–EtOAc to give **18**.

**7-Phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(5*H*)-one (57). 6,7-Dihydro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepin-4(5*H*)-one (60).** $H_2O$ was removed from a mixture of 10% Pd–C (2.6 g) and decalin (100 ml) by distn. The resulting mixture was cooled, treated with **54** (5.24 g, 0.02 mole), refluxed under $N_2$ for 1.5 hr, cooled, and filtered. The solid was washed with a little EtOAc and the EtOAc solution was concd to dryness. The residue was combined with the decalin filtrate and poured onto a silica gel (400 g) column which had been prepared with cyclohexane. The material was washed onto the column with cyclohexane and the column was eluted successively with 15% EtOAc–85% cyclohexane and EtOAc. The first compound eluted from the column was crystallized from Skellysolve B to give **57**. The second compound eluted from the column was crystallized from EtOAc–Skellysolve B to give **60**. Recovered starting material [(**54**), 1.59 g, mp 110–114°] was obtained by further elution of the column.

**4,5,6,7-Tetrahydro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepine Hydrochloride (59) from 60.**—A solution of **60** (262 mg, 1 mmole) in dry THF (20 ml), under $N_2$, was cooled in an ice bath and treated with a 1 *M* solution of $BH_3$ in THF (3 ml). This mixture was warmed to ambient temp during 2 hr and was refluxed for 2 hr. It was then cooled, treated with 6 *N* HCl (0.5 ml), and concd *in vacuo*. The residue was mixed with dil NaOH and extracted with $CH_2Cl_2$. The extract was washed with $H_2O$, dried ($K_2CO_3$), and concd. A solution of the residue in EtOAc was acidified with dry ethereal HCl and the salt was crystallized from MeOH–EtOAc to give 60 mg of **59**, mp 273–275° dec.

**4,5,6,7-Tetrahydro-7-phenylpyrrolo[3,2,1-*jk*][1,4]benzodiazepine Hydrochloride (59) from 18.**—A mixture of **18** (0.723 g), $PtO_2$ (100 mg), and 95% EtOH (50 ml) was hydrogenated at an initial pressure of 2.8 kg/cm² for 4 hr 50 min. The catalyst was removed by filtration and the filtrate was concd *in vacuo*. The residue was mixed with dil NaOH and extracted with $CH_2Cl_2$. The extract was washed with $H_2O$, dried ($K_2CO_3$), and concd. An EtOAc solution of the residue was acidified with dry ethereal HCl. The solid was collected by filtration and recrystd from MeOH–EtOAc (Darco G-60) to give 0.155 g of **59**, mp 275.5–277.5°.

## Spectral Data[36]

**6**: Uv max 223 (ε 32,550), 272 (ε 6050), 295 (ε 4300), inflection 283 mμ (ε 5550).

(36) Uv spectra were determined in 95% EtOH using a Cary Model 11 spectrophotometer. Ir spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. The nmr spectra were recorded on a Varian Model A-60A; chemical shifts are recorded in parts per million downfield from $Me_4Si$. Mass spectra were obtained on an Atlas CH-1 spectrometer. In general, ir, uv, and nmr spectra were routinely run on all compounds. Only the data considered important for characterizing or establishing the assigned structure are included. All other data were as expected.

**8**: Uv max 229.5 (ε 14,600), 246 (ε 12,200); 251 (ε 11,050), 335 (ε 6160), 340 (ε 6270), 388 mμ (ε 2520); ir 1660, 1630 $cm^{-1}$ (C=N); mass spectrum *m/e* 170 ($M^+$); nmr [$(CD_3)_2SO$] δ 8.91 (s, 1, H-7).

**9**: Uv max 228 (ε 16,800), 321 (ε 6350), inflection 356 mμ (ε 2450); ir 1635 $cm^{-1}$ (C=N).

**10**: Uv max 215 (ε 30,050), 298 (ε 11,200), 308 (ε 11,150), inflections 222 (ε 27,900); 236 (ε 2400), 253 (ε 6400), 285 mμ (ε 8500); ir 1680 $cm^{-1}$ (C=O).

**12**: Uv max 233 (ε 27,900), 314 (ε 3900), inflection 263 mμ (ε 4700); ir 1675, 1650 $cm^{-1}$ (C=O).

**14**: Uv max 228 (ε 21,200), 356 (ε 4850), inflection 260 mμ (ε 5700); ir 1635 $cm^{-1}$ (C=O).

**16**: Uv max 232 (ε 21,950), 316 mμ (ε 7400); ir 1640 $cm^{-1}$ (C=O).

**18**: Uv max 252 (ε 12,300), 267 (ε 11,100), 355 (ε 4200), 401 (ε 8050), inflection 224 mμ (ε 18,900); mass spectrum *m/e* 246 ($M^+$).

**20**: Uv max 226 (ε 22,800), 250 (ε 7700), 299 mμ (ε 2350).

**22**: Uv max 227 (ε 35,500), 352 (ε 6200), inflection 263 mμ (ε 7100); ir 1650 $cm^{-1}$ (C=N).

**29**: Uv max 211 (ε 24,000), 250 (ε 6950), 293 mμ (ε 2300).

**31**: Uv max 262 (ε 16,150), 464 (ε 6800), inflections 224 (ε 12,000), 244 (ε 11,400), 295 mμ (ε 10,000).

**36**: Uv max 244 (ε 17,350), 342 mμ (ε 2650).

**37**: Uv max 222 (ε 32,350), 246 (ε 8070), 299 mμ (ε 2220).

**38**: Uv max 219 (ε 28,300), 256 (ε 33,200), 336 (ε 7200), inflection 285 mμ (ε 10,150); ir 1675 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 4.23 (t, 2, *J* = 8 Hz, H-2), δ 3.57 (s, 2, H-5), δ 3.14 (t, 2, *J* = 8 Hz, H-1); mass spectrum *m/e* 296, 298 ($M^+$).

**40**: Uv max 208 (ε 33,800), 215 (ε 33,200), 272 (ε 32,500), 282 (ε 32,400), 313 (ε 1310), 426 (ε 1150), inflections 235 (ε 26,500), 262 (ε 24,600), 322 (ε 1195), 340 mμ (ε 514); ir 3300 (NH), 1650 $cm^{-1}$ (C=O); nmr [$(CD_3)_2SO$] δ 4.09 (d, 1, *J* = 2 Hz, H-5), δ 8.75 (s, 1, H-7); mass spectrum *m/e* 296, 298 ($M^+$).

**41**: Uv max 234.5 (ε 31,050), 272 (ε 8600), 281 (ε 7800), 333 mμ (ε 3900); ir 3300 (NH), 1655 $cm^{-1}$ (C=O).

**42**: Uv max 220 (ε 28,600), 236 (ε 20,850), 262 (ε 20,350), 272 (ε 27,150), 282 (ε 27,150), 314 (ε 1800), 425 (ε 1050), inflection 324 mμ (ε 1650); ir 1690 (C=O), 1620 $cm^{-1}$ (C=N).

**46**: Uv max 243 (ε 24,800), 313 mμ (ε 2350); ir 1670 $cm^{-1}$ (C=O).

**48**:[37] Uv max 343 (ε 11,500), inflections 225 (ε 18,300), 232 mμ (ε 17,950);

**54**: Uv max 236 (ε 29,950), 325 mμ (ε 3150); ir 1670 $cm^{-1}$ (C=O).

**57**: Uv max 258 (ε 16,650); 308 (ε 7250), inflection 318 mμ (ε 6400); ir 1710 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 4.68 (s, 2, H-5); mass spectrum *m/e* 260 ($M^+$).

**60**: Uv max 246 (ε 20,410), 296 (ε 5330), 304 (ε 6030), inflection 284 mμ (ε 3290); ir 3340 (NH), 1690 $cm^{-1}$ (C=O); nmr [$(CD_3)_2SO$] δ 5.49 (s, 1, H-7), 3.83 (s, 2, H-5).

**62**: Uv max 244 (ε 18,950), 437 (ε 6250), inflection 275 mμ (ε 5700).

**64**:[38] Uv max 225 (ε 19,800), 252 (12,850), 276 (9800), 356 (4420), 401 mμ (ε 5850); ir 1615 $cm^{-1}$ (C=N); mass spectrum *m/e* 280, 282 ($M^+$).

**Acknowledgment.**—The authors are indebted to Dr. E. C. Olson and his associates for physical and analytical data and to Mr. J. Robert Greene for laboratory assistance.

(37) The nmr spectrum [$(CD_3)_2SO$] of **52** had peaks at δ 8.17 (d, *J* = 2 Hz) and 7.99 (broad singlet) for H-6 and H-4 which thus estblished the location of the $NO_2$.

(38) The nmr spectrum [$(CD_3)_2SO$] of **64** was essentially the same as that of **18** except that in **64** H-1 (δ 6.89, d, *J* = 3 Hz) was absent and H-2 was represented by a singlet at 8.01.

# 4-Substituted Piperidines. V.[1] Local Anesthetic 4-Aminoalkoxy-4-arylpiperidines

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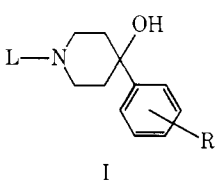
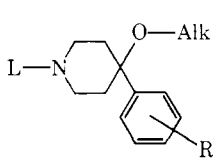
The synthesis of a new series of 4,4-disubstituted piperidines is described. These 4-aminoalkoxy-4-arylpiperidines are obtained by performing successively a Grignard reaction on *N*-carbethoxy-4-piperidone, transformation of the tertiary alcohol in an ether, decarbethoxylation, and finally reaction of the secondary amine with a halide. The compounds are good local conduction anesthetics in laboratory animals.

In previous publications[1] of this series the synthesis and pharmacological activity of several 4,4-disubstituted and 4-monosubstituted piperidines were described. One of the most important series was that of the well-known 4-aryl-4-hydroxypiperidine compounds[2] (I), of which haloperidol, moperone, and trifluperidol are the most important drugs.

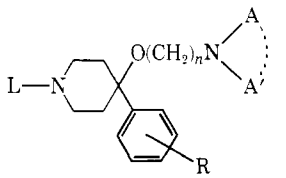


I

In a first trial to change the chemical structure of these compounds, a series of 4-lower alkoxy-4-arylpiperidines (II) with anticonvulsant properties[3] was synthesized and a further variant was the introduction of an amine function in this 4-alkoxy group, giving a new series of 4-aminoalkoxy-4-arylpiperidines (III) in which *n* = 2 or 3, $-\overset{\frown}{NAA'}$ stands for lower dialkylamino, piperidino, or hexamethyleneimino, R represents H, Cl, $CH_3$, or $CF_3$, and, as in all our series, L can be any substituent retaining the basic character of the piperidine nucleus.



II



III

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