Central Nervous System Depressants. 15. 1,4-Benzodiazepines

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A number of 5-phenyl-1,4-benzodiazepines and a few 2-phenyl-1,4-benzodiazepines were prepared and screened for central nervous system activity in mice. Some were highly active. An unusual substitution of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one by trichloroacetylisocyante is reported.

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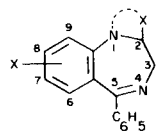
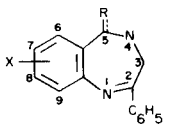
In our continuing search for superior central nervous system drugs (1a), a variety of 1,4-benzodiazepines were prepared. Some of these are close analogs of benzodiazepines known to have high anxiolytic activity and others are more remote analogs made in order to explore new avenues of activity. Most of these are derivatives of the well known 5-phenyl-1,4-benzodiazepine, with or without a ring fused at 1,2-positions (I) but a few are derivatives of the isomeric 2-phenyl-1,4-benzodiazepine (II). Compounds of type I are listed in Table I and their preparations, along with compounds of type II, are described in Experimental.

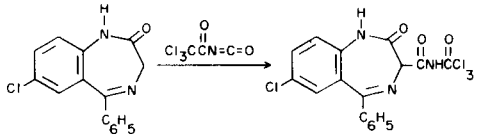


I

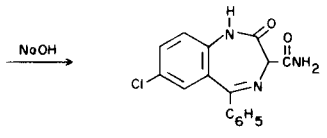


II

One reaction is worth special mention. It is well known that most isocyanates give 1-carbamoyl derivatives with 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (2). However, treatment of **1** with trichloroacetylisocyanate gave a different product, which was shown to be **2** by ir, nmr, ms and elemental analysis. This assignment was confirmed by hydrolysis to the known **3**.



1 2



3

Pharmacology.

Most of these benzodiazepines were screened in a battery of tests (3) designed to pick up central nervous system activity. The results are given in Table II. It will be seen that most of these compounds are only moderately active, *i.e.* less than the standard compound diazepam. However, one compound **11**, is highly active, more active than diazepam but less active than triazolam or alprazolam, two of our benzodiazopines (**4** and **5**) now undergoing clinical trial. Two compounds, **15** and **18**, were screened in different CNS tests (1) but were nearly inactive.

EXPERIMENTAL

8-Chloro-6-phenyl-1-(3,4,5-trimethoxyphenyl)-4*H*-*s*-triazolo[4,3-*a*]benzodiazepine (**4**).

A solution of 2.87 g. (0.01 mole) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione and 6.78 g. (0.03 mole) of 3,4,5-trimethoxybenzoic acid hydrazide in 150 ml. of *n*-butyl alcohol under nitrogen, was stirred at reflux for 21 hours. After evaporation *in vacuo*, the residue was well shaken with water which was decanted from the gummy product. This residue was dried and boiled with 300 ml. of ether giving a crystalline material. Recrystallization from methanol yielded 3.55 g. (77%) of a white solid, m.p. 210-212°. Ir and nmr spectral data support the structure.

8-Chloro-1-(methyl-2-pyrrodidinyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*] [1,4]-benzodiazepine (**5**).

A solution of 11 ml. of hydrazine hydrate in 18 ml. of methanol was heated to reflux and 3.4 g. (0.0024 mole (of ℓ-1-methylproline methyl ester was slowly added. Refluxing was continued for 3 hours and the solvent was removed *in vacuo* giving crude ℓ-1-methylproline hydrazide. A sample was distilled from a short path apparatus, [α]**D**-122°. Ir and ms spectral data showed this to be the expected hydrazide but analysis indicated it was not pure.

A solution of 1.72 g. (0.012 mole) of this crude hydrazide and 2.87 g. (0.01 mole) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione in 30 ml. of 1-butanol was refluxed for 23 hours and evaporated *in vacuo*. The product was chromatographed on silica gel and eluted with 3% methanol in chloroform giving 1.3 g. of solid which was recrystallized from ethyl acetate yielding 0.7 g. of white crystals, m.p. 156-157°, [α]**D**-1°. Ir, nmr and ms spectral data support the structure.

7-Chloro-2-[[2-(dimethylamino)ethyl]amino]-5-phenyl-3*H*-1,4-benzodiazepine Dihydrochloride (**6**).

A solution of 14.34 g. (0.05 mole) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione and 8.82 g. (0.1 mole) of *N,N*-dimethyl-1,2-ethanediamine in 225 ml. of tetrahydrofuran, under nitrogen, was stirred at room temperature for 18 hours and evaporated *in vacuo*. The residue was dissolved in 150 ml. of 2-propanol, filtered and acidified with ethanolic hydrogen chloride giving a white solid which was recrystallized from acetic acid yielding 14.7 g. of fluffy white crystals,

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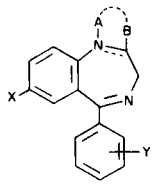
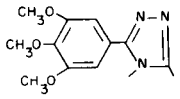
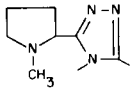
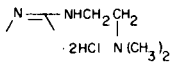
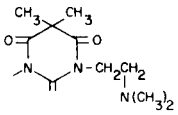
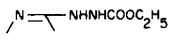
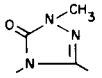
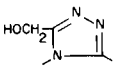
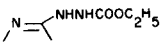
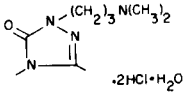
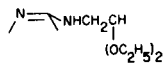
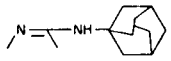
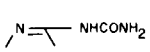
Table I

Chemical Properties



Compound No.	X	Y		M.p. °C	Molecular Formula	Analysis (a) C	H	Cl	N
4	Cl	H		210-212	$C_{25}H_{21}ClN_4O_3$	64.66 (65.11)	4.56 (4.59)	7.61 (7.69)	12.10 (12.20)
5	Cl	H		156-157	$C_{21}H_{20}ClN_5$	67.03 (66.75)	5.38 (5.34)	9.58 (9.38)	18.76 (18.53)
6	Cl	H		269-270 dec.	$C_{19}H_{23}Cl_3N_4$	54.94 (55.15)	5.62 (5.60)	25.73 (25.70)	13.33 (13.54)
7	Cl	H		173.5- -174.5	$C_{24}H_{25}ClN_4O_2$	65.98 (65.97	5.74 (5.77)	8.28 (8.11)	12.53 (12.82)
8	H	o-Cl		226-228	$C_{16}H_{16}ClN_4O_2$ (b)	59.63 (59.88)	4.92 (5.11)	9.57 (9.30)	16.07 (15.91)
9	H	o-Cl		251-252	$C_{16}H_{11}ClN_4O$	61.91 (61.85)	3.63 (3.57)	11.39 (11.41)	18.15 (18.02)
10	H	o-Cl		157-159	$C_{17}H_{13}ClN_4O$	62.82 (62.87)	3.82 (4.03)	10.84 (10.91)	16.76 (17.25)
11	H	o-Cl		196-197	$C_{17}H_{13}ClN_4O$	62.46 (62.87)	3.91 (4.03)	10.92 (10.91)	17.01 (17.25)
12	Cl	m-OCH_3		225-236 dec.	$C_{16}H_{13}ClN_2OS$ (c)	60.44 (60.66)	4.15 (4.14)	11.31 (11.20)	8.87 (8.84)
13	Cl	m-OCH_3		177.5- 178.5	$C_{19}H_{19}ClN_4O_3$	58.85 (58.99)	5.06 (4.95)	9.77 (9.17)	14.55 (14.49)
14	Cl	m-OCH_3		226-227	$C_{17}H_{13}ClN_4O_2$	59.96 (59.92)	3.97 (3.84)	10.38 (10.41)	16.47 (16.44)
15	Cl	m-OCH_3		227-228	$C_{22}H_{28}Cl_3N_5O_3$	51.56 (51.12)	5.38 (5.46)	20.24 (20.58)	13.28 (13.55)
16	Cl	H		131-132	$C_{21}H_{24}ClN_3O_2$	65.31 (65.36)	6.30 (6.27)	9.25 (9.19)	10.87 (10.89)

17	Cl	H	 1/2 EtOAc	224-225 (d)	$C_{27}H_{30}ClN_3O$ (d)	72.92 (72.39) (e)	6.92 (6.75)	7.92 (7.92)	9.24 (9.38)
18	Cl	H		217-220	$C_{16}H_{13}ClN_4O$	61.42 (61.44)	4.07 (4.19)	11.72 (11.34)	17.95 (17.92)

(a) Values in parentheses are calculated. (b) Nmr showed the sample, recrystallized from dimethylformamide, contained about 1/3 mole of this solvent. The calculated values are corrected for this. (c) Thanks to Paul E. Marlatt and M. E. Moerman, of our Chemical Research Preparations Unit, for preparation of this compound. *Anal.* S, 9.85 (10.12). (d) Sintered or melted at 164-165° with effervescence, resolidified, and remelted at 224-225°. The calculated values include one half moleule of ethyl acetate. (e) More satisfactory values could not be obtained.

Table II

Pharmacological Properties
ED_{50} (mg./kg.) in Mice (a)

Compound No. (b)	Traction	Chimney	Dish	Pedestal	Nicotine Antagonism	Thiosemicarbazide Antagonism	Potentiation
4	>200	142	40	42	>200		
5	>100	71	71	>100	11.5		
6	100	11	15	40	8	8	15
7	>100	80	71	>100	80		
8	>100	>100	71	74	>100		
9	>100	4	2.2	4	2.3	0.8	36
10	>100	11	1.4	4.5	1.8	0.9	>100
11	80	0.45	0.32	0.4	0.089	0.14	>100
12	>100	89	71	71	89		
13	>100	22.5	63	80	23.5	32	22.5
14	>100	20	56	56	5.6	18	25
16	126	40	20	50	25	23	
17	>200	50	9	14	>200		
2	>200	23	35	35	142	>50	
19	>200	>200	28	50	112		
20	>200	28	16	>200	>200		
21	>200	63	16	18	112		
Diazepam	7	2	0.7	1.3	0.28	0.7	0.9
Triazolam	0.6	0.056	0.1	0.13	0.0013	0.028	0.63
Alprazolam	0.6	0.11	0.032	0.25	0.02	0.16	0.16

(a) Procedures for these tests have been described previously (3). (b) Number from Table I or Experimental Section.

m.p. 269-270° dec. Ir, nmr and ms spectral data support the structure.

9-Chloro-4-[2-(dimethylamino)ethyl]-2,2-dimethyl-7-phenylpyrimido-[1,2-*a*][1,4]benzodiazepine-1,3(2*H*,4*H*)dione (**7**).

A mixture of 4.14 g. (0.1 mole) of **6**, 7.9 ml. (0.57 mole) of triethylamine, and 125 ml. of tetrahydrofuran, under nitroen, was cooled to -80°, and 3.54 g. (0.021 mole) of dimethylmalonyl dichloride was added. After standing at room temperature for 17 hours and refluxing for 6.5 hours, the mixture was concentrated, shaken with ice water, basified with sodium hydroxide and extracted with ether. The extract was washed with water, saturated sodium chloride, and dried over sodium sulfate. Filtration and evaporation gave a gum which crystallized from ether-pentane yielding 2.1 g. (48%) of solid, m.p. 170-173 °. Recrystallization from 2-propanol gave 1.75 g. of yellow crystals, m.p. 173.5-174.5°. Ir, nmr and ms. spectral data support the structure.

Ethyl 3-[5-(*o*-Chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]carbazate (**8**).

A mixture of 33 g. (0.11 mole) of 5-(*o*-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (**4**), 31.5 g. (0.36 mole) of ethyl carbazate, and 1200 ml. of ethanol was refluxed for 24 hours while a slow stream of nitrogen was passed into the mixture. Evaporation *in vacuo* gave 47 g. of a white crystalline solid, m.p. 226-228°. A sample for analysis was recrystallized from dimethylformamide, m.p. 214-215°. Ir and nmr spectral data supported the structure but showed it to contain about 1/3 mole of this solvent.

6-(*o*-Chlorophenyl)-2,4-dihydro-1*H*-5-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (**9**).

A 25 g. (0.07 mole) sample of crude **8** was heated under nitrogen at 250-270° for 30 minutes. The product was crystallized from ethanol yielding 17.5 g. (80%(of yellow crystals, m.p. 251-252°. Ir and nmr support the structure.

6-(*o*-Chlorophenyl)-2,4-dihydro-2-methyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzo diazepin-1-one (**10**).

A mixture of 6.2 g. (0.02 mole) of **9**, 1.6 ml. (0.02 mole) of thallous ethoxide and 100 ml. of dimethylformamide, under nitrogen, was stirred at room temperature for 10 minutes, and 1.6 (0.02 mole) of methyliodide was added dropwise. Stirring was continued for 4 hours; the solution was filtered, concentrated *in vacuo* and diluted with water. The product was

extracted with water, saturated sodium chloride, and dried over sodium sulfate. After filtration and evaporation the residue was crystallized from cyclohexane yielding 2.2 g. (37%) of yellow crystals, m.p. 157-159°. Ir and nmr spectral data support the structure; ir (Nujol): 1715 (NH), 1615, 1600, 1585, 1490 (C=N/C=O), 1320 (NH/other), 780 765, 750 (arom. CH/other); nmr (deuteriochloroform): δ 3.53 (s, CH_3), 4.67 (s, 2, 3-CH_2), between 6.9 and 7.8 (m, 8, arom. H's); M^+ 324 (1 Cl).

6-(*o*-Chlorophenyl)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-1-methanol (**11**).

A mixture of 8.6 g. (0.03 mole) of 5-(*o*-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (**4**), 6.66 g. (0.09 mole) of hydroxyacethydrazide and 300 ml. of *n*-butyl alcohol under nitrogen, was refluxed for 15 hours. The mixture was filtered, evaporated *in vacuo*, and mixed with water and ether. A solid remained insoluble in both layers. It was collected, washed with ether and dried giving 8 g. of a nearly white solid. Crystallization from ethyl acetate yielded 6 g. (62%) of white crystals, m.p. 196-197°. Ir and nmr spectral data support the structure. H. Allgeier and A. Gagneux (6) report m.p. 235-237°.

7-Chloro-1,3-dihydro-5-(*m*-methoxyphenyl)-2*H*-1,4-benzodiazepine-2-thione (**12**).

A solution of 140 g. (0.466 mole) of 7-chloro-1,3-dihydro-5-(*m*-methoxyphenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**7**) and 107.9 g. (0.485 mole) of phosphorus pentasulfide in 8.6 l. of pyridine, under nitrogen, was stirred under reflux for 1 hour. The solution was reduced to one half its volume by distillation under reduced pressure, cooled, and mixed with 4.3 l. of 17% aqueous sodium carbonate solution. The product was extracted with chloroform, washed with water, and dried over sodium sulfate. After filtration and evaporation *in vacuo*, the residue was triturated with 4 l. of chloroform-methanol (1:1) at the boiling point, and cooled giving 102 g. of a light yellow solid. An additional 16 g. of product was obtained from the filtrate. Repeating the trituration with chloroform-methanol yielded 95 g. (80%) of a light yellow solid, m.p. 240° dec., estimated by tlc (silica gel, 5% methanol in chloroform) to be 95% pure. A sample for analysis was obtained by recrystallization from methanol yielding white fluffy crystals, m.p. 225-236° dec. Ir and nmr spectral data support the structure.

Ethyl 3-[7-Chloro-5-(*m*-methoxyphenyl)-3*H*-1,4-benzodiazepin-2-yl]carbazate (**13**).

This was prepared as for **8** above from 19.28 g. (0.06 mole) of **12**, 18.74 g. (0.18 mole) of ethyl carbazate, and 450 ml. of ethanol. The product crystallized from ethanol-ether yielding 16.1 g. (69%) of white crystals, m.p. 177.5-178.5°. Ir, nmr and ms spectral data support the structure.

8-Chloro-2,4-dihydro-6-(*m*-methoxyphenyl-1*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepin-1-one (**14**).

A 5 g. (0.013 mole) sample of **13** was heated at 210° under nitrogen for 15 minutes, cooled and crystallized from ethanol yielding 3.12 g. (71%) of tan needles, m.p. 224-227°. A sample for analysis was recrystallized from acetone, m.p. 226-227°. Ir, nmr and ms support the structure.

8-Chloro-2,4-dihydro-2-[3-(dimethylamino)propyl]-6-(*m*-methoxyphenyl)-1*H*-*s*-triazolo-4,3-*a*][1,4]benzodiazepin-1-one Dihydrochloride Hydrate (**15**).

A mixture of 3.4 g. (0.01 mole) of **14**, 0.5 g. (0.011 mole) of 50% sodium hydride in mineral oil and 60 ml. of dimethylformamide, under nitrogen, was stirred at 80° for 2.5 hours. After cooling, 3.4 ml. of a benzene solution containing 0.02 moles of 3-(dimethylamino)propyl chloride was added and the mixture was stirred at 70° for 5 hours, and at room temperature for 2 days. After removing the solvent under high vacuum, the residue was dissolved in chloroform and extracted with cold dilute hydrochloric acid. The acid solution was basified with sodium hydroxide, extracted with chloroform, dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 3% methanol in chloroform. The oily free base was converted to the hydrochloride with ethereal hydrogen chloride and crystallized from a mixture of methanol and 2-propanol, yielding 0.16 g. (3.1%) of yellow needles, m.p. 227-228°. Karl Fischer analysis showed this to be hydrated. Ir, nmr and ms spectral data support the structure.

7-Chloro-2-(2,2-diethoxyethylamino)-5-phenyl-1,4-benzodiazepine (**16**).

A solution was prepared by cautiously adding 1.2 ml. (2.19 g., 0.011 mole) of titanium tetrachloride to 65 ml. of tetrahydrofuran. This solution was added with stirring to an ice-cold solution of 5.42 g. (0.02 mole) of **1** and 25 ml. of aminoacetaldehyde diethylacetal in 200 ml. of tetrahydrofuran under nitrogen. After stirring for 18 hours at room temperature, 15 ml. of water was added. The gelatenous titanium dioxide was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was triturated with water, which was decanted leaving a gummy mixture of starting material and product. Two crystallizations from cyclohexane, filtering off insoluble starting material from the hot solution each time, and cooling yielded 3.65 g. (47%) of a nearly white solid, m.p. 131-132°. Ir, uv, nmr and ms spectral data support the structure.

2-(1-Adamantylamino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine Ethyl Acetate Solvate (2:1) (**17**).

This compound was prepared as described for **16** from 13.5 g. (0.05 mole) of **1**, 30.5 g. (0.2 mole) of 1-adamentanamine, 10.5 g. of titanium tetrachloride, and 780 ml. of tetrahydrofuran. The reaction was very slow and after refluxing for 5 days and standing at room temperature for 6 months, tlc (silica gel, 20% methanol in benzene) indicated only about 50% reaction. The crude product was heated to 100° (0.05 mm) in an evaporator to remove 1-adamantanamine, boiled with ethyl acetate and filtered from the starting material. The filtrate was chromatographed on silica gel eluting with 50% ethyl acetate-cyclohexane. The product fraction, showing one spot on tlc (silica gel, 50% ethyl acetate-cyclohexane) as recrystallized from ethyl acetate yielding 3.7 g. (16.5%) of nearly white crystals, m.p. 224-225° after effervescence at 164-165°. After drying overnight at 100°/<0.1 mm, a melt solvate showed the compound still contained about one-half molecule of ethyl acetate. Ir, nmr and ms spectral data support the structure; ir (Nujol): 3310,3280,3060 (NH/=CH), 1735 (ethyl acetate), 1610,1595,1570,1550 (C=N)/C=C), 1240, 1215, 1120, 1095 (C-N/other), 825,780,695 (arom. CH/other); nmr (deuteriochloroform): δ 1.22 (t, 1.5, CH_2CH_3 of 1/2 ethyl acetate), 1.53 and 1.85 (two aparent s's of adamantly), about 4 (broad s, 2, c-CH_2), 4.15 (q, 1, CH_2 of 1/2 ethyl acetate), 5.48 (s, 1, NH), between 7.0 and 7.8 (m, 8, arom. H's); ms: m/e at 402 ($M^{\pm}$ -H), 135 (adamantly), (1 Cl).

N-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl) urea (**18**).

To a cooled solution of 1.18 g. (0.006 mole) of silicon tetraisocyanate in 50 ml. of tetrahydrofuran, under nitrogen, was slowly added a slurry of 4.04 g. (0.015 mole) of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**3**). After stirring under reflux for 2 hours, a mixture of 45 ml. of 2-propanol and 5 ml. of water was added and refluxing was continued for 30 minutes. The mixture was filtered hot through Celite and the filtrate was evaporated *in vacuo*. The residue was slurried with methylene chloride and the product collected giving 2.64 g. (56%) of white solid, m.p. 214-217°. A sample for analysis was recrystallized from methanol-methylene chloride,, m.p. 217-220°. Ir, uv and nmr spectral data support the structure.

7-Chloro-2,3-dihydro-2-oxo-5-phenyl-*N*-(trichloroacetyl)-1*H*-1,4-benzodiazepine-3-carboxamide (**2**).

A solution of 5.42 g. (0.02 mole) of **1** and 13.15 g. (0.07 mole) of trichloroacetylisocyanate in 75 ml. of tetrahydrofuran was allowed to stand at room temperature, under nitrogen, for 18 hours. The solution was evaporated *in vacuo*; toluene was added and evaporated, and the residue was crystallized from ether, giving 10.94 g. of a yellow solid, m.p. 190-220°. This solid was boiled with 150 ml. of 2-propanol and filtered hot. The insoluble product weighed 7.3 g. (80%), m.p. 225-228° dec. Recrystallization from acetonitrile gave 5.5 g. (60%) of white silky

needles, m.p. 231.5-233° dec. Ir, nmr and ms support the proposed structure; ir (Nujol): 3290 (NH), 1790, 1725, 1690 (C=O), 1690, 1575, 1485, 1465 (C=C/C=N/other), 1330, 1225 (C-N/other), 835,820,700,670 (arom. CH/other); nmr (DMF-d_7): δ 4.96 (s, 1, 3-CH), between 7.35 and 7.95 (m, 8, arom. H's), 11.1 (s, 1, NH); ms: M^+ 459 (4 Cl).

Anal. Calcd. for $C_{18}H_{11}Cl_4N_3O_3$: C, 47.09; H, 2.42; Cl, 30.89; N, 9.15. Found: C, 47.21; H, 2.66; Cl, 30.70;N, 9.14.

To confirm the structure, a 0.1 g. sample in 2 ml. of dimethylformamide was hydrolyzed with 1 ml. of 5% aqueous sodium hydroxide and recrystallized from methanol giving a white solid, m.p. 256-258° dec., reported for **3**, m.p. 255-256° (9). Ir, nmr and ms support the structure (**3**).

Anal. Calcd. for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; Cl, 11.30; N, 13.39. Found: C, 60.96; H, 3.81; Cl, 11.40; N, 12.95.

2-Amino-4-chloro-*N*-phenacylbenzamide (**19**).

To a stirred solution of 15 g. (0.087 mole) of α-aminoacetophenone hydrochloride in 100 ml. of water was added 17.3 g. (0.087 mole) of 4-chloroisatoic anhydride (8) followed by 4.7 g. of sodium carbonate. After stirring overnight at room temperature, the mixture was filtered, the solid was washed with water and dried giving 26.5 g. of an orange compound, m.p. 146-150°. Recrystallization from benzene yielded 15 g. (68%) of yellow crystals, m.p. 164-166°. Ir and nmr spectral data support the structure.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; Cl, 12.28; N, 9.70. Found: C, 62.63; H, 4.56; Cl, 12.43 N, 10.04.

8-Chloro-3,4-dihydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (**20**).

A mixture of 5.9 g. (0.02 mole) of **19** in 150 ml. of xylene was refluxed for 5 hours with stirring while the liberated water was removed by a Dean-Stark separator. The mixture was filtered hot and cooled to 0° giving 2.5 g. (82%) of white crystals, m.p. 202-204°. Recrystallization from xylene raised the melting point to 204-206°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; C, 13.10; N, 10.34. Found: C, 66.58; H, 4.15; Cl, 13.42; N, 10.44.

8-Chloro-5-methoxy-2-phenyl-3*H*-1,4-benzodiazepine (**21**).

To an ice-cold suspension of 1.35 g. (0.055 mole) of **20** in 30 ml. of dry methylene chloride was added 1 g. (0.005 mole) of trimethyloxonium fluoroborate in 20 ml. of methylene chloride, and the mixture was stirred at room temperature for 18 hours. Ice and 50% aqueous potassium carbonate was added and the layers separated. The aqueous layer was extracted with more methylene chloride and the organic solutions were dried over sodium sulfate. Filtration and evaporation gave an oil which crystallized on standing. Recrystallization from petroleum ether yielded 0.45 g. (38%) of white crystals, m.p. 105-106°. Ir and nmr spectral data support the structure.

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.50; H, 4.60; Cl, 12.45; N, 9.83. Found: C, 66.94; (10), H, 4.71; Cl, 12.35; N, 9.58.

8-Chloro-5-hydrazino-2-phenyl-3*H*-1,4-benzodiazepine (**22**).

A solution of 0.284 g. (0.001 mole) of **21** and 2 ml. of hydrazine hydrate was stirred at room temperature for 2.5 hours and evaporated *in vacuo*. The residue was crystallized from ethyl acetate-hexane giving 0.10 g. (35%) of yellow crystals, m.p. 162-164°. Ir and nmr spectral data support the structure.

Anal. Calcd. for $C_{15}H_{13}ClN_4$: C, 63.28; H, 4.60; Cl, 12.45; N, 19.66. Found C, 63.49; H, 4.64; Cl, 12.52; N, 19.59.

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