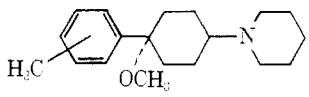
Table XI. *cis*-1-(4-Methoxy-4-tolylcyclohexyl)piperidine *p*-Toluenesulfonates



Compd no.	Isomer	Yield, %	Mp, °C	Formula
15a	Ortho	56	171–172	$C_{26}H_{37}NO_4S$
15b	Meta	58	182–184	$C_{26}H_{37}NO_4S$
15c	Para	58	180–181	$C_{26}H_{37}NO_4S$

was then removed at oil pump vacuum and the residue dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness.

A solution of the residual oil in 30 ml of THF was added with stirring over 40 min to 1.5 g of $LiAlH_4$ in 15 ml of THF. Following an additional 5 hr of stirring the mixture was cooled in ice and treated in turn with 1.5 ml of H_2O, 1.5 ml of 15% NaOH, and 4.5 ml of H_2O. The inorganic gel was collected on a filter and the filtrate taken to dryness. This last residue was dissolved in Et_2O and treated with 1 equiv of 4.9 *N* HCl in Et_2O. The precipitated salt was purified by recrystallization (no heat) from MeOH-Et_2O.

4-Aryl-4-methoxycyclohexanone Oximes (Table VII). A mixture of 0.017 mol of the ketone, 3.75 g of NH_2OH·HCl, and 7.5 ml of 45% KOH in 70 ml of EtOH was heated at reflux for 4 hr. The solvent was removed *in vacuo* and the residue taken up in H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was purified by recrystallization.

4-Aryl-4-methoxycyclohexanone Oxime Acetates (Table VIII). A solution of 0.017 mol of the oxime and 15 ml of Ac_2O in 30 ml of pyridine was allowed to stand at room temperature for 18 hr. The mixture was poured into ice-H_2O and the precipitated gum extracted with Et_2O. The organic layer was washed with ice-cold 2.5 *N* HCl, H_2O, $NaHCO_3$, and brine. The solid which remained when this solution was taken to dryness was purified by recrystallization.

***trans*-4-Aryl-4-methoxycyclohexylamine Hydrochlorides (Table IX).** To an ice-cold solution of 0.0156 mol of the oxime acetate in 20 ml of THF there was added dropwise with good stirring 46 ml of 1 *N* B_2H_6 in THF. Following 18 hr in the cold, 1 ml of H_2O was added dropwise. When effervescence ceased the solvent was removed *in vacuo*. The residue was stirred for 1 hr with 100 ml each of 0.5 *N* HCl and Et_2O. The organic layer was separated and extracted twice with 30 ml of 0.5 *N* HCl. The aqueous portions were combined and made strongly basic and the precipitate was extracted with Et_2O. The organic layer was washed with brine and concentrated. This last solution was treated with 2.0 ml of 4.9 *N* HCl in Et_2O and the precipitated solid collected on a filter. This last solution was purified by recrystallization (no heat) from MeOH-Et_2O.

4′-Fluoro-4-[(4-methoxy-4-arylcyclohexyl)amino]butyrophenone Hydrochlorides (Table X). To a solution of 9.7 mmol of the amine hydrochloride in 45 ml of DMF there was added 0.41 g of 57% NaH. Following 1 hr of stirring, 1.65 g of KI, 2.76 g of K_2CO_3, and 2.46 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene ketal was added. Following 17 hr of heating at 90°, the solvent was removed at oil pump vacuum. The residue was dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness. To a solution of the residue in 30 ml of MeOH, there was added 15 ml of 2.5 *N* HCl. At the end of 1 hr the bulk of the solvent was removed *in vacuo* and the precipitated solid collected on a filter. This product was purified by recrystallization (no heat) from MeOH-Et_2O.

***cis*-1-(4-Methoxy-4-tolylcyclohexyl)piperidine *p*-Toluenesulfonates (Table XI).** To 6.7 mmol of the amine hydrochloride in 29 ml of EtOH there was added 1.7 ml of 4.18 *N* NaOMe in MeOH. Following 1 hr of stirring, 1.02 ml of 1,5-diiodopentane and 1.68 g of K_2CO_3 were added and the mixture was brought to reflux. At the end of 17 hr the solvent was removed *in vacuo* and the residue partitioned between H_2O and Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. To a solution of the residue in Et_2O there was added 1 equiv of *p*-TSA in Et_2O. The resulting salt was recrystallized from CH_2Cl_2-EtOAc.

References

(1) D. Lednicer, D. E. Emmert, R. Lahti, and A. D. Rudzik, *J. Med. Chem.*, 15, 1235 (1972).
(2) D. Lednicer, D. E. Emmert, R. Lahti, and A. D. Rudzik, *ibid.*, 15, 1239 (1972).
(3) P. A. J. Jansen, "Psychopharmacological Agents," Vol. 11, M. Gordon, Ed., Academic Press, New York, N. Y., 1967, p 199.
(4) P. A. J. Jansen and C. A. M. Van der Eycken, "Drugs Affecting the Central Nervous System," A. Burger, Ed., Marcel Dekker, New York, N. Y., 1968, p 25.

Central Nervous System Depressants. 11. Benzodiazepines with Ureas in the 2 Position†

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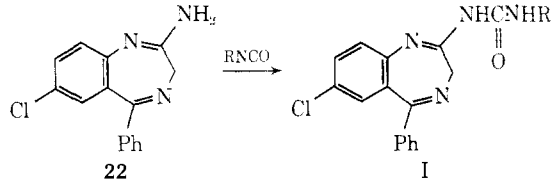
Twenty-one 2-ureidobenzodiazepines have been prepared. These included acyclic ureas with N′-Me, cyclopropyl, $COCH_3$, CH_2COOEt, COOEt, and CH_2CH_2Cl, cyclic ureas, [1,2-*a*]-*s*-triazinodiones, and 2-imidazolidinones. These were prepared from 2-amino-3*H*-1,4-benzodiazepines and isocyanates, followed by cyclization of the appropriate acyclic ureas. The acyclic ureas and imidazolidinones had a rather low order of CNS depressant activity but some of the triazinodiones (notably 12) showed considerable interest.

In the preceding paper[1] we reported a series of 1,4-benzodiazepines with carbamoyl groups in the 1 position. Several were quite active anxiolytic agents. Since these are actually ureas, it seemed desirable to prepare benzodiazepines with ureas in other positions, especially the 2 position (I). These were prepared by the action of an isocyanate on a 2-amino-1,4-benzodiazepine.

Recently it came to our attention that workers at Takeda Chemical Industries[2] in Japan had made analogous compounds. Only one (I, R = CH_3) was identical with

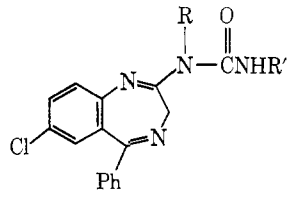


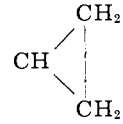
22 I

ours. In our hands these open-chain ureas showed a rather low order of CNS activity. However, it was found that the carbethoxy ureas (I, R = COOEt) could be cyclized by heating to the triazinodiones (*e.g.*, 11), which could be methylated in the 2, 4, and 5 positions. Some of these

† Presented in part at the Seventh Great Lakes Regional Meeting of the American Chemical Society, Kalamazoo, Mich., June 7, 1973.

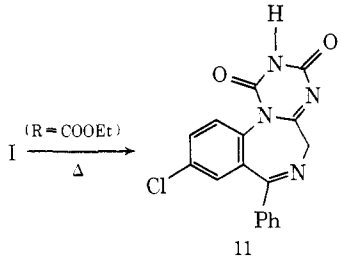
Table I. Acyclic Ureas



No.	Ph	R	R′	% yield[a]	Recrystn solvent	Mp, °C[b]	Formula[c]
1	C_6H_5	H	CH_3	86	EtOH	211–215[d]	$C_{17}H_{15}ClN_4O$
2	C_6H_5	CH_3[e]	CH_3	94	*i*-PrOH	235–243	$C_{18}H_{17}ClN_4O$
3	C_6H_5	H		92	$CH_3O(CH_2)_2OH$	208.5–211	$C_{19}H_{17}ClN_4O$
4	C_6H_5	H	$COCH_3$[f]	12	EtCOMe[g]	188–190	$C_{18}H_{15}ClN_4O_2 \cdot 0.62C_4H_8O$
5	C_6H_5	H	CH_2COOEt	77	EtOH	195–198	$C_{20}H_{19}ClN_4O_3$
6	C_6H_5	H	COOEt[f,h]	73	EtOH	179–180.5	$C_{19}H_{17}ClN_4O_3$
7	*o*-ClC_6H_5	H	COOEt[f,h]	81[i]	EtOH	176–178	$C_{19}H_{16}Cl_2N_4O_3$
8	C_6H_5	H	CH_2CH_2Cl	70	EtOH	164–167	$C_{18}H_{16}Cl_2N_4O$
9	C_6H_5	CH_3[e]	CH_2CH_2Cl	72	*i*-PrOH[j]	112–116	$C_{19}H_{18}Cl_2N_4O$
10	o-ClC_6H_4	H	CH_2CH_2Cl	72	EtOH	155–158	$C_{18}H_{15}Cl_3N_4O$

[a] Yields are based on the 2-aminobenzodiazepine and are reported for material melting not less than 2° below the highest melting point obtained. [b] Melting points are probably with decomposition. [c] Compounds were analyzed for all elements except oxygen.§ [d] Meguro, *et al.*,[2] report mp 209–210° dec. [e] Prepared from 7-chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine.[4c] [f] The reaction was run at −70° followed by slow warming to room temperature. [g] The product was crystallized from *i*-PrOH followed by recrystallization from EtCOMe. It showed only one spot on tlc (SiO_2, 5% MeOH in $CHCl_3$) but even after drying at 100° (0.5 mm) for 4 hr it was found, by melt solvate, to contain 11.2% (equivalent to 0.62 molecules) of EtCOMe. The analysis was calculated on this basis: C, H, and Cl were within 0.4% of calcd; N: calcd, 14.02; found, 14.67. [h] Prepared using EtOCONCO;[6] G. H. Youngdale, *et al.*, *J. Med. Chem.*, **7**, 415 (1964). [i] Crystallized by trituration with Et_2O and recrystallized from EtOH. [j] Crystallized first from benzene–pentane, then from cyclohexane, and finally from *i*-PrOH.

showed high CNS activity which is reminiscent of the analogous 1-carbamoyl compounds[1] and the *s*-triazolobenzodiazepines.[3] Another type of cyclic urea, imidazolidinone (*e.g.*, **18**), was prepared by cyclization, with base, of the *N′*-chloroethyl ureas. These were less active than the triazinodiones. Examples of 2-ureidobenzodiazepines were also made without the chlorine in the 5 position and with an *o*-chlorine in the Ph ring. Tables I–III list the chemical properties of these ureas and Table IV, the pharmacology. 2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**22**), used as a starting material for many of these compounds, is well known in the literature. It has been prepared by several methods[4] but we prepared it by the reaction of NH_3 on 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione. This method‡ is analogous to that used by Archer and Sternbach[5] for the 2-piperidino compound.



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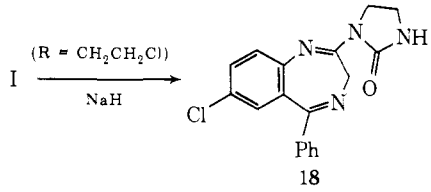

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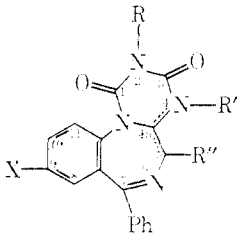
‡ Devised by the late Dr. A. R. Hanze in these laboratories.

Pharmacology. These benzodiazepine compounds were tested in a variety of test systems in comparison with diazepam (Table IV). The open-chain ureas, compounds **1–10**, in general showed little CNS activity. The most active was **7** which showed potencies on the various tests from 1/20 to nearly equal to those of diazepam. Likewise, the imidazolidinone compounds **18–21**, which are simply cyclic ureas, were less active than diazepam, the most potent being **19**. Of greater interest were the triazinodiones **11–17**, several of which were at least equipotent to diazepam on some end points. Compound **12** was the most active of the series being equal to diazepam on all end points measured except for the antagonism of pentylenetetrazole-induced clonic convulsions and the potentiation of ethanol narcosis where it is approximately one-third as active as diazepam. The activity of **12** in traction and strychnine tests as well as its potency in suppressing simple reflexes (dish and pedestal) may indicate potent muscle relaxant activity. Since it is less potent than diazepam on potentiating ethanol narcosis, a test used to measure potential sedative or depressant activity, this compound may produce muscle relaxation at doses which do not produce overt depression. Further test of this hypothesis must await clinical trial.

Substitution of a chlorine in the ortho position of the 5-phenyl of these benzodiazepines markedly increased the activity, especially on the convulsive end points (nicotine, pentylenetetrazole, and thiosemicarbazide antagonism). Note activities of **7** *vs.* **6**, **10** *vs.* **8**, and **14** *vs.* **11**.

On the basis of limited data, a methyl group on the 2 position of the triazinodione ring would seem to be desirable but a methyl on the 4 position (with shift of the double bond) detrimental; **12** is more potent than **11** which is more potent than **13**.

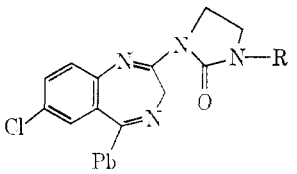
Table II. Triazinodiones



No.	Ph	X	R[a]	% yield[b]	Recrystn solvent	Mp, °C[c]	Formula[d]
11	C_6H_5	Cl	H	40	EtOAc	224–233	$C_{17}H_{11}ClN_4O_2 \cdot 0.5C_4H_8O_2$
12	C_6H_5	Cl	CH_3	60	PhH–C_6H_{12}	211–213[e]	$C_{18}H_{13}ClN_4O_2 \cdot {}^1/_3C_6H_{12}$
13	C_6H_5	Cl	H[f]	65	EtOH	243–245	$C_{18}H_{13}ClN_4O_2$[g]
14	o-ClC_6H_4	Cl	H	70	Xylene	238–240	$C_{17}H_{10}Cl_2N_4O_2$
15	o-ClC_6H_4	Cl	CH_3[f]	23	EtOAc	239–240	$C_{18}H_{14}Cl_2N_4O_2$
16	o-ClC_6H_4	Cl	CH_3[h]	11.5	*i*-PrOH	226–228.5	$C_{18}H_{14}Cl_2N_4O_2$
17	o-ClC_6H_4	H	H	24	$MeO(CH_2)_2OH$	225–232	$C_{17}H_{11}ClN_4O_2 \cdot C_3H_8O_2$

[a] Unless indicated R'' = H, there is no R', and the double bond is at 4–4a. [b] Yields are based on the acyclic carboethoxy urea if isolated; otherwise on the 2-aminobenzodiazepine. They are reported for material melting not less than 2° below the highest melting point obtained. [c] Melting points are probably with decomposition. [d] Compounds were analyzed for all elements except oxygen.§ [e] Nearly solvent free. See Experimental Section. [f] R' = CH_3, R'' = H, double bond at 4'–5. [g] Although tlc, ir, uv, nmr, mass spectra, and H, Cl, and N analyses showed this to be pure and the indicated structure, C analysis was slightly low (calcd, 61.24; found, 60.71). [h] R'' = CH_3 and the double bond is 4–4a.

Table III. 2-Imidazolidinones



No.	Ph	R	% yield[a]	Recrystn solvent	Mp, °C[b]	Formula[c]
18	C_6H_5	H	66	*i*-PrOH	245–247.5	$C_{18}H_{15}ClN_4O$
19	o-ClC_6H_4	H	31	EtOAc–Et_2O	197–199	$C_{18}H_{14}Cl_2N_4O$
20	C_6H_5	CH_3	82	*i*-PrOH	212–215	$C_{19}H_{17}ClH_4O$
21	C_6H_5	$(CH_2)_2N(CH_3)_2$	52	C_6H_{12}	129–130.5	$C_{22}H_{24}ClN_5O$

[a] Yields are reported for material melting not less than 2° below the highest melting point obtained. [b] Melting points are probably with decomposition. [c] Compounds were analyzed for all elements except oxygen.§

Experimental Section§

2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (22). A solution of 28.7 g (0.1 mol) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-[1,4]benzodiazepine-2-thione[5] in 500 ml of MeOH saturated with NH_3 was stirred at room temperature for 2.5 hr during which time crystals separated. The product was collected and dried yielding 20.1 g (75%) of white solid, mp 236–237.5° (Bell, Gochman and Childress[4b] report mp 236–237°). *Anal.* C, H, Cl, N.

2-Amino-7-chloro-5-(o-chlorophenyl)-3*H*-1,4-benzodiazepine (23). A suspension of 102 g (0.315 mol) of 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione[5] in 1.8 l. of MeOH was cooled to −70° and saturated with NH_3. On stirring the resulting solution, product separated and after 18 hr at room temperature was collected and dried yielding 43 g of white crystals, mp 228–230° dec. Concentration of the filtrate and recrystallization of the resulting second crop from MeOH–CH_2Cl_2 gave an additional 41 g, mp 222–226° (total yield 87.5%). *Anal.* C, H, Cl, N.

2-Amino-5-(o-chlorophenyl)-3*H*-1,4-benzodiazepine (24). This was prepared as described for **23** from 57.4 g (0.2 mol) of 5-(o-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione[5] yielding 50 g (92%) of white crystals, mp 238–241° dec. A sample recrystallized from MeOH–CH_2Cl_2 had mp 240–242° dec. *Anal.* C, H, Cl, N.

§ Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Ir (Nujol mull), usually nmr (in DMSO-d_6 or $CDCl_3$), and often mass spectra were obtained on pure compounds and were in accordance with the proposed structure. Data on several key examples are given. Where analyses were indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of theoretical values.

Method for Acyclic Ureas. 1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-3-cyclopropylurea (3). A mixture of 2.7 g (0.01 mol) of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine and 25 ml of THF was cooled under N_2 to 0° and 2 ml (0.024 mol) of cyclopropyl isocyanate[1] was slowly added with stirring. After stirring at room temperature for 3 hr and standing overnight, the mixture was evaporated *in vacuo* and recrystallized from *i*-PrOH giving 3.25 g (92%) of white solid, mp 208–210° dec. Recrystallization from 2-methoxyethanol gave 2.54 g of white crystals, mp 208.5–211° dec. The principal spectral bands are: ir (Nujol mull) 3240, 3170, 3060 (NH), 1715 (C=O), and 1625 cm^{-1} (C=N); nmr (DMSO-d_6) δ 0.6 (m, 4, cyclopropyl CH_2), 2.65 (m, 1, cyclopropyl CH), 4.1 (broad s, 2,3-CH_2), 9.25 (broad s, 1, NH), 10.1 (broad s, 1, NH), and between 7.15 and 7.6 (m's, 8, arom H's).

9-Chloro-7-phenyl-*s*-triazino[1,2-*a*][1,4]benzodiazepine-1,3-(2*H*,5*H*)-dione Ethyl Acetate Solvate (2:1) (11). A solution of 7.28 g (0.019 mol) of **6** in 300 ml of xylene was stirred under reflux under N_2 with a short air-cooled condenser for 8 hr. After cooling, the solvent was removed *in vacuo* and the residue was recrystallized twice from EtOAc yielding 2.9 g of white fluffy needles. This was dried at 100° (0.05 mm) for 19 hr, mp 224–233° with sintering from 120° up. Tlc (SiO_2, 60% EtOAc in cyclohexane) showed only one spot, but melt solvate showed 11.9% EtOAc (calcd for 0.5EtOAc, 11.5%). The principal spectral bands are: ir (Nujol mull) 3180, 3070 (NH/=OH), 1755, 1705, 1680 (C=O), and 1610, 1590, 1485 cm^{-1} (C=C/C=N); nmr ($CDCl_3$) δ 1.17 (t, 1.5, CH_2CH_3), 1.90 (s, 1.5, $COCH_3$), 3.97 (q, 1, OCH_2CH_3), ab centered at 4.85 and 3.95 (2, J = −12 Hz, 5-CH_2), 11.5 (broad s, 1, NH), and between 7.18 and 7.7 (m's, 8, arom H's); mass spectrum $M^{\cdot+}$ 338 (1 Cl).

9-Chloro-2-methyl-7-phenyl-*s*-triazino[1,2-*a*][1,4]benzodiazepine-1,3(2*H*,5*H*)-dione and Cyclohexane Solvate. (12). To a stirred solution of 1.92 g (0.005 mol) of **11** in 25 ml of DMF under

Table IV. Pharmacology[a]

No.[b]	Tr_{50}[c]	Ch_{50}[c]	D_{50}[c]	P_{50}[c]	Nicotine (TE) antag[c]	Thiosemicarbazide antag[d]	Strychnine antag[d]	Electroshock antag[d]	Pentylenetetrazole antag[e]	EtOH potentiation[f]
1	142	45	29	40	4.5	28	>50	>50		
2	>100	22	16	25	6.3	45	>50	>50	>50	>50
3	>200	159	40	159	>200					
4	32	14	18	>25	10	12	>50	>50		18
5	>200	112	12.5	12.5	>200	>50	>50	>50	>50	>50
6	>200	71	18	40	50	25	>50	>50	>50	>50
7	142	20	3.6	4.5	5	0.9	63	>200	12	18
8	>200	112	142	159	159	>50	>50	>50		
9	142	22	11	11	18	3.6	>50	>50	>50	28
10	200	20	40	56	16	9	>200	>200	18	89
11	32	12	16	18	9	10	36	>100	14	9.0
12	6.3	1.8	0.23	0.23	0.36	0.8	5.6	40	2.8	3.1
13	>200	23	11	159	63					
14	50	9	0.5	5	0.63	0.13	36	>50	3.1	6.0
15	71	11	2	4.5	8	0.7	>50	>50	23	32
16	20	8	1.0	13	1.3	0.36	13	>100	11	5.0
17	>200	112	9	40	28	56	>100	>100	>100	>100
18	79	32	10	18	16	6.3	36	>50	20	
19	>100	1.2	5	20	7	13	>25	>25	16	>25
20	>200	32	32	178	126					
21	126	32	20	45	5			112	32	
22	200	28	5	14	7	40	>50	>50	>200	50
23	>50	16	3.2	12	2.0	3.5	>50	>50	6.3	36
24	>100	63	56	80	>100					
Diazepam[g]	7.0	2.0	0.7	1.3	0.28	0.7	8.0	50	0.8	0.9

[a] Carworth Farms male, albino mice (CF-1), weighing 18–22 g, were used for all studies reported here. The test compounds were dissolved or suspended in 0.25% aqueous methylcellulose solution and administered ip. Values are ED_{50}'s expressed in mg/kg. [b] No. from Tables I–III, and for intermediate 2-aminobenzodiazepines (no. **22–24**) see Experimental Section. [c] Procedures for measuring the effects of the compound on overt behavior, traction (Tr_{50}), chimney (Ch_{50}), dish (D_{50}), pedestal (P_{50}), and antagonism of nicotine-induced tonic extensor convulsions (TE) have been described previously: G. H. 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). [d] Procedures for the antagonism of thiosemicarbazide (TSC), electroshock convulsions, and strychnine lethality have been described: H. H. Keasling, E. L. Schumann, and W. Veldkamp, *ibid.*, **8**, 548 (1965). [e] Procedures for measuring antagonism of pentylenetetrazole-induced convulsions have been described: J. B. Hester, A. D. Rudzik, and B. V. Kamdar, *ibid.*, **14**, 1078 (1971). [f] Procedures for measuring potentiation of ethanol narcosis have been described: J. B. Hester, A. D. Rudzik, H. H. Keasling, and W. Veldkamp, *ibid.*, **13**, 23 (1970). [g] The authors thank Hoffman-LaRoche, Inc., for a sample.

N_2 was added 0.38 ml (1.25 g, 0.005 mol) of TlOEt. To the resulting dark red solution was added dropwise 0.312 ml (0.005 mol) of MeI. After stirring at room temperature for 4 hr the solution was filtered from solid TlI which was well extracted with DMF. The solution was poured into water and the product extracted with ether. The ether solution was washed (H_2O), dried (Na_2SO_4), and evaporated giving solid which was recrystallized from *i*-PrOH and then from benzene–cyclohexane. The product was dried at 60° (0.5 mm) giving 0.6 g of solid, mp 120–167° dec. This was shown by nmr to contain about one-third molecule of cyclohexane. The analysis was calculated on this basis. An additional 0.52 g of product was obtained from the filtrates by fractional crystallization from PhH–cyclohexane. After drying at 100° (0.1 mm), nmr showed it to be nearly free of solvent, mp 211–213°. Tlc (SiO_2, 5% MeOH in PhH) showed only one spot. The principal spectral bands are: ir (Nujol mull) 1745, 1690 (C=O) and 1625 cm^{-1} (C=O/C=N); uv (EtOH) 219 mμ (ε 28,900), 249 (14,050), 265 (sl sh, 10,350), 290 (sl sh, 3400), 380 (244); nmr ($CDCl_3$) δ 1.4 (s, trace of cyclohexane), 3.33 (s, 3, NCH_3), ab centered at 5.0 and 4.05 (2, J = −12 Hz, 5-CH_2), and between 7.2 and 7.8 (m's, 8, arom H's).

9-Chloro-4-methyl-7-phenyl-*s*-triazino[1,2-*a*][1,4]benzodiazepine-1,3(2*H*,4*H*)-dione. (13). A solution of 5.68 g (0.02 mol) of 7-chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine[4c] in 200 ml of THF was cooled under N_2 to −70° and 10 ml (0.08 mol) of EtOCONCO[6] was slowly added with stirring. The solution was allowed to warm to room temperature and stirred for 23 hr, filtered, evaporated *in vacuo*, and purged with $PhCH_3$, giving a crystalline residue which was shown by tlc, nmr, and ir to be mostly 1-carbethoxy-3-(7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-3-methylurea but contained a little starting material.

This was dissolved in 50 ml of xylene and stirred under reflux, under N_2, for 20 hr. After filtration the solution was cooled giving 5.23 g of yellow crystals, mp 236–241°. This was recrystallized from 80% EtOH yielding 4.6 g (65%) of yellow crystals, mp 243–245°. The principal spectral bands are: ir (Nujol mull) 3190, 3120, 3080 (NH/OH), 1725, 1700 (C=O), and 1615 cm^{-1} (C=N/C=C); uv (EtOH) 225 mμ (ε 27,880), 272 (16,900), 379 (6760); nmr ($CDCl_3$ + DMSO-d_6) δ 3.12 (s, 3, N-CH_3), 6.46 (s, 1, 5-=CH), 11.5 (broad s, 1, NH), and between 7.0 and 7.8 (m's, 8, arom H's); mass spectrum M·+ 352 (1 Cl).

9-Chloro-7-(o-chlorophenyl)-*s*-triazino[1,2-*a*][1,4]benzodiazepine-1,3(2*H*,5*H*)-dione (14). This was prepared as described for **11** from 0.63 g (0.0015 mol) of **7** yielding 0.39 g (69.5%) of fluffy needles, mp 247–251° (dec with darkening from 237° up). This seemed essentially pure by tlc, ir, and nmr. A sample was recrystallized from THF–H_2O giving a crystalline solvate. The solvent was removed by boiling with xylene, mp 250–254° (dec as above). The principal spectral bands are: ir (Nujol mull) 3160, 3060 (NH/=OH), 1745, 1685 (C=O), and 1605, 1585 cm^{-1} (C=N/C=C); uv (EtOH) 215 mμ (sl sh, ε 33,150), 246 (sl sh, 13,250), 292 (sl sh, 1600); nmr (DMSO-d_6) δ ab centered at 4.2 and 4.83 (2, J = −11 Hz, 5-CH_2), 705 (broad s, 1, NH), and between 7.0 and 7.8 (m's, 7, arom H's); mass spectrum M·+ 372 (2 Cl).

9-Chloro-7-(o-chlorophenyl)-2,4-dimethyl-*s*-triazino[3,2-*a*][1,4]benzodiazepine-1,3(2*H*,4*H*)-dione (15) and 9-Chloro-7-(o-chlorophenyl)-2,5-dimethyl-*s*-triazino[1,2-*a*][1,4]benzodiazepine-1,3(2*H*,5*H*)-dione (16). To a solution of 1.49 g (0.004 mol) of **14** in 25 ml of DMF, under N_2, was added with stirring 0.302 ml (1.0 g, 0.004 mol) of TlOEt. The solution became dark red and after a few minutes 0.5 ml (0.008 mol) of MeI was added. The mixture was stirred until the red color had faded and was filtered from TlI. The solid was extracted with DMF, and the combined DMF solution was evaporated *in vacuo* and diluted with H_2O. The resulting solid was collected and dried giving 1.2 g of a mixture of products. Crystallization from EtOAc yielded 0.25 g of light yellow crystals, mp 237–239°. Recrystallization from EtOAc raised the mp to 239–240°. The filtrate from the first crystallization was chromatographed on 100 g of SiO_2 eluting with 40-ml portions of 50% EtOAc in cyclohexane. Fractions 4–8 were evapo-

rated, combined with the filtrate from the second crystallization, and recrystallized from EtOAc giving 0.22 g of yellow crystals, mp 237–239°. This was found by ir, nmr, and uv spectra to have the structure 15. The principal spectral bands are: ir (Nujol mull) 1725, 1685 (C=O) and 1620, 1590, 1580 cm^{-1} (C=N/C=O); uv (EtOH) 220 mμ (ε 32,050), 265 (13,250), 374 (5150); nmr ($CDCl_3$) δ 3.22 and 3.24 (2 s, 6, NCH_3), 6.42 (s, 1, 5-=CH), and between 6.75 and 7.55 (m's, 7, arom H's).

Column fractions 10–17 were evaporated giving 0.2 g of nearly white solid. This was recrystallized from *i*-PrOH yielding 0.18 g of white needles, mp 226–228.5°. Ir, nmr, and analysis showed this to have the structure 16. The principal spectral bands are: ir (Nujol mull) 1740, 1675 (C=O) and 1610, 1590, 1570 cm^{-1} (C=N/C=C); nmr ($CDCl_3$) δ 1.8 (d, 3, 5-CH_3), 3.39 (s, 3, NCH_3), 4.14 (q, 1, 5-CH), and between 7.05 and 7.65 (m's, 7, arom H's).

7-(*o*-Chlorophenyl)-*s*-triazino[1,2-*a*][1,4]benzodiazepine-1,3(2*H*,5*H*)-dione 2-Methoxyethanol Solvate (17). This was prepared from 5.39 g (0.02 mol) of **24** essentially as described for **13** using diethylene glycol-dimethyl ether as a solvent for the first step. The intermediate 1-carbethoxy-3-[5-*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]urea failed to crystallize but tlc (SiO_2, 5% MeOH in $CHCl_3$) showed mostly one spot. It was used in the second step without purification. Crude **17** crystallized from the xylene solution during reflux. It was collected and recrystallized first from MeOH and then from 2-methoxyethanol and dried at 100° (0.02 mm) for 6 hr giving 2.95 g of solid, mp 225–232°. This was found by nmr to contain one molecule of 2-methoxyethanol. The principal spectral bands are: ir (Nujol mull) 3250, 3060 (NH_2/OH), 1705 (C=O), and 1615, 1595, 1570 cm^{-1} (C=N/C=C); nmr (DMSO-d_6) δ 3.25 (s, 3, OCH_3), between 3.0 and 3.8 (m's, 5, OCH_2CH_2OH), ab centered at 4.3 and 4.8 (2, J = −11 Hz, 5-CH_2), and between 6.8 and 7.8 (m's, 8, arom H's).

1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-2-imidazolidinone (18). To a solution of 7.5 g (0.02 mol) of **8** in 100 ml of THF under N_2 was added portionwise with stirring 3.0 g (0.07 mol) of 56% NaH in mineral oil. After stirring at room temperature for 18 hr the mixture was concentrated *in vacuo*, mixed with water and pentane, and neutralized with AcOH. The solid was collected, washed (H_2O and pentane), and dried giving 6.66 g of crystalline solid, mp 217–227° dec. Recrystallization from *i*-PrOH yielded 4.45 g (65.5%) of white crystals, mp 245–247.5°. The principal spectral bands are: ir (Nujol mull) 3220, 3120 (NH), 1710 (C=O), and 1605, 1580 cm^{-1} (C=N/C=C); nmr ($CDCl_3$) δ 3.46 (t, 2, CH_2), 4.05 (t, 2, CH_2), 3-CH_2 too broad to locate, 6.23 (broad s, 1, NH), and between 7.1 and 7.7 (m's, 8, arom H's); mass spectrum $M^{\cdot+}$ 338 (1 Cl).

1-[7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]-2-imidazolidinone (19). This was prepared as described for **18** from 4.1 g (0.01 mol) of **10**. The crude product was dissolved in EtOAc, treated with decolorizing charcoal, filtered, concentrated, and diluted with Et_2O giving 1.16 g (31%) of white crystals, mp 197–199°. The principal spectral bands are: ir (Nujol mull) 3270, 3120 (NH), 1725 (C=O), and 1605, 1580 cm^{-1} (C=N/C=C); nmr ($CDCl_3$) δ 3.45 (t, 2, CH_2), 4.07 (t, 2, CH_2), 4.8 (broad s, 2, 3-CH_2), 6.5 (broad s, 1, NH), and between 7.0 and 7.6 (m's, 7, arom H's).

1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-3-methylimidazolidin-2-one (20). To a solution of 2.7 g (0.008 mol) of **18** in 50 ml of DMF, under N_2, was slowly added with stirring 0.602 ml (2.0 g, 0.008 mol) of TlOEt. After stirring for 15 min 0.62 ml (0.01 mol) of MeI was added dropwise. After stirring at room temperature for 18 hr the mixture was filtered and the solid TlI was extracted with DMF. The DMF solution was concentrated *in vacuo* and diluted with water. The resulting solid was collected, washed (H_2O), and dried giving 2.58 g of cream-colored solid showing only one spot on tlc (SiO_2, 5% MeOH in $CHCl_3$ or 60% EtOAc in cyclohexane). Recrystallization from *i*-PrOH yielded 2.32 g (82%) of light yellow crystals, mp 212–215° (after scintering at 195.5–199°). The principal spectral bands are: ir (Nujol mull) 1720 (C=O) and 1605, 1595, 1580 cm^{-1} (C=N/C=C); nmr ($CDCl_3$) δ 2.9 (s, 3, NCH_3), 3.38 (t, 2, CH_2), 3.95 (t, 2, CH_2), 3-CH_2 too broad to locate, and between 7.22 and 7.7 (m's, arom H's).

1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-3-[2-(dimethylamino)ethyl]-2-imidazolidinone (21). To a solution of 1.7 g (0.005 mol) of **18** in 25 ml of DMF, under N_2, was added with stirring 0.362 ml (0.005 mol) of TlOEt. A solid separated and 1.3 ml (0.65 g, 0.006 mol) of 4.6 *M* 2-(dimethylamino)ethyl chloride in xylene was added. After stirring at room temperature for 18 hr tlc (SiO_2, 20% MeOH in PhH) indicated the reaction was not complete so 1.3 ml more of the 2-(dimethylamino)ethyl chloride solution was added and stirring was continued for 4 days. The mixture was filtered, concentrated, diluted with H_2O, and extracted with $CHCl_3$. The extracts were washed (H_2O + NaCl solution) and dried (Na_2SO_4). Evaporation of the solution gave light brown gum which was crystallized from cyclohexane–pentane and recrystallized from cyclohexane yielding 1.07 g (52%) of fluffy white needles, mp 129–130.5°. The principal spectral bands are: ir (Nujol mull) 1710 (C=O) and 1600, 1580 cm^{-1} (C=N/C=C); nmr ($CDCl_3$) δ 2.22 [s, 6, $N(CH_3)_2$], 2.45 (t, 2, CH_2), 3.42 (t, 2, CH_2), 3.5 (t, 2, CH_2), 3.95 (t, 2, CH_2), 3-CH_2 too broad to locate, and between 7.1 and 7.7 (m's, arom H's); mass spectrum $M^{\cdot+}$ 409 (1 Cl).

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References

(1) R. B. Moffett and A. D. Rudzik, *J. Med. Chem.*, **15**, 1079 (1972).
(2) K. Meguro, Y. Kuwada, Y. Nagawa, and T. Masuda, *Netherlands Patent* 6,913,042 (1970); U. S. Patent 3,652,754 (1972).
(3) J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971); J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971).
(4) (a) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961); (b) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962); (c) R. I. Fryers, J. V. Earley, G. F. Field, W. Zally, and L. H. Sternbach, *J. Org. Chem.*, **34**, 1143 (1969).
(5) G. A. Archer and L. H. Sternbach, *ibid.*, **29**, 231 (1964).
(6) R. W. Lamon, *J. Heterocycl. Chem.*, **6**, 261 (1969).

Compounds Affecting the Central Nervous System. 4. 3β-Phenyltropane-2-carboxylic Esters and Analogs

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Modification of the structure of cocaine (1) by attachment of the aromatic ring directly to the 3 position of the tropane ring has resulted in a five- to sixtyfold increase in several biological parameters accompanied by a tenfold drop in local anesthetic activity and a fourfold lowering of intravenous toxicity.

Cocaine (1) has a variety of pharmacological actions, primary among them being strong CNS stimulation and local anesthetic action. These effects are accompanied by high toxicity and dependence liability. It was of considerable interest to see if modification of this molecule could result in a useful stimulant or antidepressant.