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2,4-Dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones with Antianxiety and Antidepressant Activity

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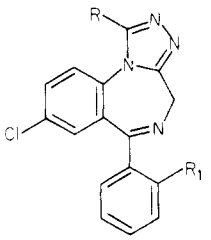
A series of 2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones was prepared and evaluated for central nervous system activity. It was found that the 2-methyl-substituted analogues had interesting activity in tests useful for detecting anxiolytic agents, while N-2 substitution with ω-(dialkylamino)alkyl substituents give compounds with antidepressant potential as well as antianxiety activity.

Derivatives of the 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine system[1,2] such as alprazolam (1) and tri-



1, R = CH_3; R_1 = H
2, R = CH_3; R_1 = Cl
3, R = Me_2NCH_2; R_1 = H

azolam (2) have been shown to have clinically useful anxiolytic[3] and hypnotic[4] activity. It has also been found that appropriate modifications of this system produce compounds with qualitatively different pharmacologic profiles. In particular, the 1-(aminoalkyl) derivatives (viz., 3) have a pharmacologic profile, which suggests that they may have a useful combination of antidepressant and antianxiety activities.[5] We have, therefore, been encouraged to investigate other modifications of this system in the hope of finding compounds with other interesting and potentially useful effects on the central nervous system. This article will deal with the 2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one system.

Compounds prepared in this study are presented in Table I. The chemistry will be illustrated for one representative of each reaction type. Our synthesis[6-8] of 8-chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepin-1-one (4) was accomplished in two steps. 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione[9] (5) was first condensed with ethyl carbazate in refluxing ethanol to give 6, which was subsequently warmed above its melting point (200–205 °C) to give the cyclic product 4. Alternatively 4, could be prepared in 80% yield from 1-bromo-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (7)[10-12] by hydrolysis with 85% phosphoric acid. A variety of 2-substituted derivatives were prepared by the reaction of 4 with either sodium hydride or thallous ethoxide and an appropriate alkyl halide. The 2-methyl derivative (8) was also prepared in 69% yield by the reaction of 4 with diazomethane in a mixture of methanol and methylene chloride. Several aminoalkyl derivatives were conveniently prepared in two steps by first alkylating 4 with a 1-bromo-ω-chloroalkane and subsequently allowing the resulting ω-chloroalkane to react with an appropriate amine. For example, 8-chloro-2,4-dihydro-2-[2-(4-methyl-1-piperazinyl)ethyl]-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (9) was prepared by the potassium iodide catalyzed reaction of 10 with 1-methylpiperazine in DMF at 60 °C.

Results and Discussion

The pharmacological data for the 2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones are presented in Table II.[13] Comparative data for diazepam (30), imipramine hydrochloride (31) and the 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine 3 are also recorded for comparison.

8-Chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepin-1-one (4) was an antagonist of nicotine- and pentylenetetrazol-induced convulsions (TE and P respectively). Methylation at N-2 potentiated activity in these tests and, in addition, the compound 8 gained activity in the end points (B, γ-B, and HS) which are associated with antianxiety activity. Chloro substitution at the 2 position of the C-6 phenyl moiety of compounds 4 and 8 potentiated the activities of both compounds in these tests (compare 12 with 4 and 13 with 8). ω-(Dialkylamino)alkyl substitution at N-2 of both 4 and 12 gave analogues that usually retained activity in the antianxiety end points. In addition, several of these compounds had an indication of

(1) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, 14, 1078 (1971).
(2) K. Meguro, H. Tawada, H. Miyano, Y. Sato, and Y. Kuwada, *Chem. Pharm. Bull.*, 21, 2383 (1973).
(3) T. M. Itil, N. Polvan, S. Egilmez, B. Saletu, and J. Marasa, *Curr. Ther. Res. Clin. Exp.*, 15, 603 (1973).
(4) R. I. H. Wang and S. L. Stockdale, *J. Int. Med. Res.*, 1, 600 (1973).
(5) J. B. Hester, A. D. Rudzik, and P. VonVoigtlander, *J. Med. Chem.*, 23, preceding paper in this issue (1980).
(6) Preliminary communication: J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971).
(7) J. B. Hester, Jr., U.S. Patent 3708592 (1973).
(8) A somewhat different synthesis has also been described: K. Meguro and Y. Kuwada, Deutsche Offenlegungsschrift 2056174 (1971).
(9) G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, 29, 231 (1964).
(10) A. Walser, T. Flynn, and R. I. Fryer, *J. Heterocycl. Chem.*, 12, 717 (1975).
(11) J. B. Hester, Jr., U.S. Patent 3709899 (1973).
(12) J. B. Hester, Jr., and P. VonVoigtlander, *J. Med. Chem.*, 22, 1390 (1979).
(13) A discussion of our screening procedure and the information contributed by the individual test systems has been presented in ref 5.

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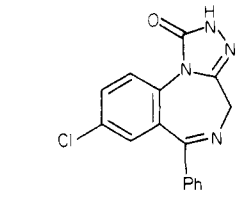

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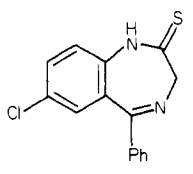

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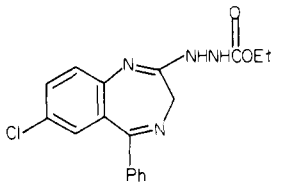

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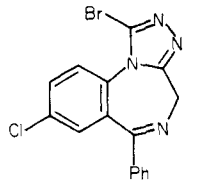

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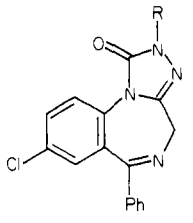


8, R = CH_3
9, R = CH_2CH_2-c-$N(CH_2CH_2)_2N$-CH_3
10, R = CH_2CH_2Cl

antidepressant potential. (Compare, for example, the activities of **21** and **26** in AG and OX, respectively, with the corresponding activities of **31**.) Another pharmacologically interesting series was produced by ω-(1-piperazinyl)alkyl substitution at N-2 of compounds **4** and **12**. In this series, the 4-alkyl-1-piperazinyl derivatives (viz. **9**, **19**, and **25**) were active on both antianxiety and antidepressant end points. The 4-(2-hydroxyethyl)-1-piperazinyl derivative (**29**) was also active on the antianxiety end points P, B, γ-B, and HS and on nicotine-induced TE and D. Activity was lost, however, by phenyl substitution on the 4 position of the 1-piperazinyl moiety (viz. **28**).

Experimental Section

Melting points were taken in a capillary tube and are corrected. The structures were supported by IR, UV, and NMR spectra. IR spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer and UV spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. NMR spectra were recorded on a Varian Model A-60A or XL 100 spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. The analytical results obtained were within ±0.4% of the theoretical values if not otherwise stated. The silica gel used for chromatography was obtained from E. Merck AG, Darmstadt, Germany. Skellysolve B (Sk B) is a commercial hexane, bp 60–70 °C, made by Skelly Oil Co., Kansas City, Mo.

3-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)carbazic Acid Ethyl Ester (6). Procedure A. A mixture of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione[9] (1.43 g, 0.005 mol), ethyl carbazate (1.29 g, 0.015 mol), and absolute EtOH (50 mL) was refluxed for 24 h with a slow stream of N_2 bubbling through the mixture. The mixture was concentrated and the residue was crystallized from CH_2Cl_2–EtOAc to give 1.38 g (77%) of **6**, mp 195.5–197.5 °C dec. The analytical sample had mp 198–199 °C dec; UV (EtOH) λ_{max} 213 nm (ε 30600), 229 (27750), 258 (28050), 339 (2050). Anal. ($C_{18}H_{17}ClN_4O_2$) C, H, Cl, N.

3-[7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]carbazic Acid Ethyl Ester (11). Compound **11** was prepared[14] in 90% yield by procedure A from 7-chloro-1,3-dihydro-5-(*o*-chlorophenyl)-2*H*-1,4-benzodiazepine-2-thione.[9] The analytical sample had mp 191–192 °C. Anal. ($C_{18}H_{16}Cl_2N_4O_2$) C, H, Cl, N.

8-Chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepin-1-one (4). **Procedure B.** Compound **6** (0.50 g, 0.0014 mol) was heated under N_2 at 197–207 °C for 15 min. The cooled melt was crystallized from EtOH to give 0.17 (mp 253.5–255 °C) and 0.11 g (mp 250.5–254 °C) of **4**. The analytical sample had mp 255–256 °C; UV (EtOH) λ_{max} 214 nm (ε 34800), 250 (15600), inflection 305 nm (1560); IR (Nujol) 3240, 3180, 3060 cm^{-1} (NH/=CH), 1710, 1690 (C=O/C=N); NMR [$(CD_3)_2SO$] δ ~4.36, 4.87 (2 br s, C-4 H_2).

8-Chloro-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepin-1-one (4). **Procedure C.** A stirred mixture of 1-bromo-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**7**)[10-12] (1.0 g, 0.00268 mol) and 85% phosphoric acid (30 mL) under nitrogen was warmed to 118 °C during 1 h 40 min and kept at 118–121 °C for 5 h. The cooled mixture was poured into a mixture of ice and water (400–500 mL). This mixture was made slightly alkaline with 50% NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from CH_2Cl_2–EtOH to give 0.671 g of **4**, mp 255.5–257.5 °C. The mixture melting point with an authentic sample was undepressed.

8-Chloro-2-[2-(diethylamino)ethyl]-2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (15). **Procedure D.** A solution of **4** (1.56 g, 0.005 mol) in dry DMF (40 mL) was treated with 0.232 g (0.0055 mol) of a 57% suspension of NaH in mineral oil and stirred at ambient temperature for 1 h. It was then cooled in an ice bath, treated with 0.67 g (0.0055 mol) of 2-(diethylamino)ethyl chloride dissolved in xylene (2 mL), and stirred at ambient temperature for 18 h. The mixture was concentrated to dryness in vacuo. The residue was mixed with water and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was crystallized from Et_2O at 0 °C to give 0.62 (mp 95–100 °C) and 0.31 g (mp 95–98 °C) of **15**. The analytical sample was crystallized from EtOAc–Skelly B and had mp 98.5–100.5 °C; UV (EtOH) λ_{max} 215 nm (ε 42500), inflections 249 nm (ε 18050), 280 (4950), 303 (2000); IR (Nujol) 1710 cm^{-1} (C=O).

8-Chloro-2,4-dihydro-2-methyl-6-phenyl-1*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepin-1-one Hydrochloride (8). **Procedure E.** A stirred solution of compound **4** (0.500 g, 1.68 mmol) in CH_2Cl_2 (10 mL) and MeOH (10 mL) was cooled in an ice bath and treated with an excess of an ethereal solution of diazomethane. The mixture was allowed to remain in the ice bath for 40 min, treated with HOAc to decompose the excess diazomethane, and concentrated in vacuo. The residue was suspended in dilute NaOH and extracted with CH_2Cl_2. The extract was washed with water, dried (K_2CO_3), and concentrated. The residue was chromatographed on silica gel (30 g) with 60% EtOAc–cyclohexane. The resulting oil was acidified with ethereal hydrogen chloride and crystallized from MeOH–EtOAc to give 0.403 g of **8**·HCl, mp 223–258.5 °C dec. The IR spectrum (Nujol) of this material was identical with that of the authentic sample.

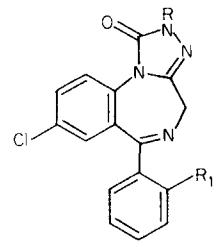
8-Chloro-6-phenyl-2,4-dihydro-2-[2-(diethylamino)-ethyl]-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (15). **Procedure F.** To a solution of 9.3 g (0.03 mol) of **4** in 150 mL of DMF, under N_2, was added 2.3 mL (0.03 mol) of TlOEt. This mixture was stirred for 10 min and treated dropwise with 8 mL (0.03 mol) of 2-(diethylamino)ethyl chloride. This was stirred for 1 h at 25 °C and filtered. The solid was washed with DMF, and the combined DMF solution was concentrated to a small volume under reduced pressure and diluted with ice–water. The resulting orange solid was collected by filtration, dried, and recrystallized from EtOAc–Skellysolve B to give 8 g of **15**, mp 98–100 °C.

8-Chloro-6-phenyl-2,4-dihydro-2-[2-(diethylamino)-ethyl]-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (15). **Procedure G.** A stirred solution of **12** (3.45 g, 0.01 mol) in DMF (100 mL) was treated with NaH (0.463 g of a 57% mineral oil suspension, 0.011 mol) and warmed on the steam bath for 30 min.

(14) Prepared in these laboratories by R. B. Moffett and B. V. Kamdar.

(15) Two of the 2-aminoalkyl derivatives of **4** have been reported previously: K. Meguro and Y. Kuwada, U.S. Patent 3846421 (1974).

Table I. Physical and Analytical Data for the 2,4-Dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones



no.	R	R_1	yield, %	procedure	mp, °C	recrystn solvent	formula	analyses
4	H	H	64.4	B	255–256	EtOH	$C_{16}H_{11}ClN_4O$	C, H, Cl, N
			80.6	C				
8	CH_3	H	33.7	D[g]	224–235[ii]	MeOH–EtOAc	$C_{17}H_{14}Cl_2N_4O$[d]	C, H, Cl, N
			69.5	E				
8	CH_3	H			139.8–144.5		$C_{17}H_{13}ClN_4O$[hh]	C, H, Cl, N
9	CH_3-c-N(CH_2CH_2)$_2$N-(CH_2)$_2$	H	25	H	118–125	CH_2Cl_2–EtOAc–Sk B	$C_{23}H_{25}ClN_6O$	C, H, Cl, N
10	$ClCH_2CH_2$	H	42	D[q]	164–169	CH_2Cl_2–EtOAc	$C_{18}H_{14}Cl_2N_4O$	
12	H	Cl	80	B[c]	204–205	EtOH	$C_{18}H_{16}Cl_2N_4O_2$[a]	H, Cl, N; C[b]
13	CH_3	Cl	30.6	F[c,g]	82–84	Et_2O–Sk B	$C_{17}H_{12}Cl_2N_4O$	C, H, Cl, N
14	$Et_2N(CH_2)_2$	Cl	45	F	253.5–255	EtOH	$C_{22}H_{24}BrCl_2N_5O$[f]	C, H, Br, Cl; N[e]
15	$Et_2N(CH_2)_2$	H	45.4	D	98.5–100.5	EtOAc–Sk B	$C_{22}H_{24}ClN_5O$	H, Cl, N; C[h]
			65.1	F[c]				
16[ff]	$Me_2N(CH_2)_2$	H	55.1	G[i]	263–265	MeOH–$CHCl_3$	$C_{20}H_{21}BrClN_5O$[f]	C, H, Br, Cl, N
17[gg]	$Me_2N(CH_2)_3$	H	50.8	D[j]	281–282	MeOH–$CHCl_3$	$C_{21}H_{23}BrClN_5O$[f]	C, H, Br, Cl, N
18	$Me_2NCH_2CH(CH_3)CH_2$	Cl	27.4	G[k]	199–205	MeOH–EtOAc	$C_{22}H_{27}Br_2Cl_2N_5O_2$[p]	C, H, Br, Cl, N
19	CH_3-c-N(CH_2CH_2)$_2$N-(CH_2)$_3$	Cl	20.3	G[m]	279–285[ii]	MeOH–EtOAc	$C_{24}H_{28}Cl_4N_6O \cdot 0.5H_2O$[n]	C, H, Cl, N
20	$Et_2N(CH_2)_3$	Cl	45.3	G	230–236	MeOH–EtOAc	$C_{23}H_{27}Br_2Cl_2N_5O \cdot 0.25EtOAc$[p]	H, Br, N, EtOAc, C, Cl[o]
21	$Me_2N(CH_2)_3$	Cl	44.6	G[j]	257–260	MeOH–$CHCl_3$–EtOAc	$C_{21}H_{22}BrCl_2N_5O$[f]	C, H, Br, Cl, N
22	$ClCH_2CH_2$	Cl	76.2	D[r]	123–127	EtOAc–Sk B	$C_{18}H_{13}Cl_3N_4O$	
23	$Cl(CH_2)_4$	Cl	90.3	D[s]			$C_{20}H_{17}N_4Cl_3O$	
24	$Cl(CH_2)_3$	Cl	65.8	D[t]	124.5–129	EtOAc–Sk B	$C_{19}H_{15}Cl_3N_4O$	
25	CH_3-c-N(CH_2CH_2)$_2$N-(CH_2)$_2$	Cl	65.1	H[u]	278.5–281[ii]	MeOH–EtOAc	$C_{23}H_{26}Cl_4N_6O \cdot 0.5H_2O$[v]	C, H, Cl, N, H_2O
26	$Et_2N(CH_2)_4$	Cl	24.0	H[x]	211–225[ii]	MeOH–EtOAc	$C_{24}H_{29}Br_2Cl_2N_5O \cdot 0.5EtOAc$[y]	C, H, Br, Cl, N, EtOAc
27	$MeNH(CH_2)_3$	Cl	13.7	H[z]	265–275[ii]	MeOH–EtOAc	$C_{20}H_{21}Br_2Cl_2N_5O$[bb]	C, H, Br, N; Cl[aa]
28	Ph-c-N(CH_2CH_2)$_2$N-(CH_2)$_3$	Cl	43.8	H[cc]	157–159	MeOH	$C_{29}H_{28}Cl_2N_6O$	C, H, Cl; N[dd]
29	$HOCH_2CH_2$-c-N(CH_2CH_2)$_2$N-(CH_2)$_3$	Cl	59.5	H[ee]	284–287	MeOH–EtOAc	$C_{25}H_{30}Cl_4N_6O$[w]	C, H, Cl, N

[a] EtOH solvate. [b] C: calcd, 55.26; found, 54.79. [c] Reference 14. [d] Hydrochloride. [e] N: calcd, 13.33; found, 13.81. [f] Hydrobromide. [g] Reaction with CH_3I; purified by chromatography on silica gel with 50% EtOAc–cyclohexane. [h] C: calcd, 64.46; found, 63.97. [i] Reaction with 2-(dimethylamino)ethyl chloride. [j] Reaction with 3-(dimethylamino)propyl chloride. [k] Reaction with 3-(dimethylamino)-2-methylpropyl chloride; product purified by silica gel chromatography with 3% MeOH–$CHCl_3$. [l] Dihydrobromide hydrate. [m] Reaction with 3-(4-methyl-1-piperazinyl)propyl chloride. [n] Dihydrochloride hemihydrate. [o] C: calcd, 44.88; found, 44.40. Cl: calcd, 11.04; found, 10.61. [p] Dihydrobromide, EtOAc solvate. [q] Reaction with 1-bromo-2-chloroethane; product purified by silica gel chromatography with 2.5% MeOH–$CHCl_3$. [r] Reaction with 1-bromo-2-chloroethane; product purified by silica gel chromatography with 30% EtOAc–cyclohexane. [s] Reaction with 1-bromo-4-chlorobutane; the oily product was purified by silica gel chromatography with 30% EtOAc–Skelly B and characterized by IR, UV, NMR, and high-resolution mass spectra. [t] Reaction with 1-bromo-3-chloropropane; product purified by silica gel chromatography with 30% EtOAc–Skelly B. [u] Reaction of 22 with 1-methylpiperazine at 90 °C for 21 h; product purified by silica gel chromatography with 2% Et_3N–15% MeOH–83% EtOAc. [v] Dihydrochloride hemihydrate. [w] Dihydrochloride. [x] Reaction of 23 with diethylamine at 50 °C for 18 h. [y] Dihydrobromide, EtOAc solvate. [z] Reaction of 24 with methylamine in 1-methylpyrrolidinone at 25 °C. [aa] Cl: calcd, 12.26; found, 11.30. [bb] Dihydrobromide. [cc] Reaction of 24 with 1-phenylpiperazine at 25 °C for 20 h and 50 °C for 18 h; purified by silica gel chromatography with 2.5% MeOH–$CHCl_3$. [dd] N: calcd, 15.35; found, 15.84. [ee] Reaction of 24 with 4-(2-hydroxyethyl)piperazine at 25 °C for 20 h and 50 °C for 12 h; purified by silica gel chromatography with 2% Et_3N–18% MeOH–80% EtOAc. [ff] Literature mp of oxalate salt 161–162.5 °C (ref 15). [gg] Literature mp of oxalate salt 163–166 °C (ref 15). [hh] Free base. [ii] Decomposition.

Table II. Pharmacological Data[a]

no.	nicotine TE	nicotine D	pentylene-tetrazole (P)	bicucullin (B)	γ-butyro-lactone (γ-B)	hypoxic stress (HS)	yohimbine (Y)	oxo-tremorine (OX)	apomorphine gnawing (AG)
3	0.11	0.13	0.9	0.7	1.6	5	12.5	5.3	5.3
4	1.4	1.6	5.6	40	6	>50	>50	>50	>50
8[c]	1.0	1.1	2.5	2	0.5	10	>50	>50	>50
8[d]	0.63	0.63	b	3	2	>50	>50	>50	>50
9	8	8	8.8	17.7	5.3	10.5	>50	14.9	>50
12	0.025	0.025	0.08	1	0.4	>50	>50	>50	>50
13	0.002	0.002	0.14	b	b	2.2	b	b	b
14	0.09	0.1	0.45	0.7	0.4	4	>100	>100	>100
15	1.3	1.3	4.0	10	1	>50	>50	>50	>50
16	0.89	1.4	3.2	6	5	30	>100	>100	>100
17	3.6	3.6	32	40	10	>50	>50	>50	>100
18	1.0	1.1	b	7	2	40	>50	>50	>50
19	0.4	0.5	3.7	>25	3.7	>30	25	25	>25
20	1.1	1.3	8.8	>50	5.3	10	>50	>25	>50
21	0.9	1.1	6.3	14.9	2.2	>50	>50	>50	7.4
25	b	b	0.3	3.1	0.2	3.1	>25	12.5	>25
26	0.8	0.8	4.4	>12.5	12.5	7	>12.5	10.5	>12.5
27	1.4	1.4	14.9	>50	25	9	>50	>50	>50
28	40	40	>50	>50	50	>50	>50	>50	>50
29	0.5	0.56	6.3	12.5	2	20	>25	>25	>30
30[e]	0.28	0.28	0.1	2.6	0.035	0.2	>50	>50	>50
31[f]	7.0	7.0	>50	21	18	>50	4	1	1

[a] Values are ED_{50} values expressed in mg/kg. [b] Not tested. [c] HCl salt. [d] Free base. [e] Diazepam, obtained from Hoffman-LaRoche, Inc. [f] Imipramine hydrochloride.

A solution of 3-(diethylamino)propyl chloride (1.64 g, 0.011 mol) in DMF (50 mL) was then added to the hot solution, and heating was continued for 1.5 h. The mixture was concentrated in vacuo, and the residue was mixed with water and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (400 g) with 5% MeOH–95% $CHCl_3$. The product thus obtained was dissolved in EtOAc and acidified with ethanolic hydrogen bromide. The salt was recrystallized from MeOH–EtOAc to give 2.91 g of **20**, mp 234–238 °C. The analytical sample had mp 230–236 °C.

8-Chloro-2,4-dihydro-2-[2-(4-methyl-1-piperazinyl)-ethyl]-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-one (9). Procedure H. A stirred solution of **10** (3.73 g, 0.01 mol), KI (3.32 g, 0.02 mol), and 1-methylpiperazine (2.0 g, 0.02 mol) in dry DMF (30 mL) was heated at 60 °C for 6 days, under N_2. The solution was mixed with brine and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was crystallized from EtOAc and recrystallized from CH_2Cl_2–EtOAc–Skelly B to give 0.71 (mp 118–125 °C) and 0.37 g (mp 120–125 °C) (soften at 115 °C) of **9**. The analytical sample had mp 118–125 °C.

Pharmacology. Methods. 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 intraperitoneally to groups of four or six mice per dose at multiple dose levels distributed at 0.3 log intervals. Procedures for measuring the effect of test compounds on the antagonism of nicotine-induced tonic–extensor convulsions (TE) and death (D), bicucullin-induced tonic–extensor convulsions (B), pentylenetetrazole-induced clonic convulsions (P), and oxotremorine-induced hypothermia (OX); on the potentiation of γ-butyrolactone-induced sleep (γ-B), apomorphine-induced gnawing (AG), and yohimbine-induced toxicity in aggregated mice (Y); and on the prolongation of hypoxic survival time (HS) have been described previously.[1,5,16] ED_{50} values were calculated by the method of Spearman and Karber.[17]

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(16) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. Devanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, 7, 415 (1964).
(17) D. J. Finney, "Statistical Methods in Biological Assay", Hafner Publishing Co., New York, 1952.

Orally Active Cephalosporins and Penicillins

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A number of orally active cephalosporins and penicillins with interesting biological activity were synthesized. Two of these, 7-[[[3,4-(methylenedioxy)phenyl]glycyl]amino]deacetoxycephalosporanic acid and 7-[[2-(2,3-dihydro-5-benzofuranyl)glycyl]amino]deacetoxycephalosporanic acid were considerably more active than cephalexin both in vitro and in vivo against staphylococcal and streptococcal infections.

In our search for an orally active cephalosporin, we became involved with a series of β-lactam antibiotics in which some compounds exhibited interesting microbiological activity. The compounds synthesized differ from the usual penicillins, such as ampicillin and carbenicillin, and cephalosporins, such as cephalexin and cefamandole,

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