6-Phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines Which Have Central Nervous System Depressant Activity

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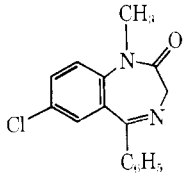
A series of 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines has been prepared by the reaction of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thiones with carboxylic acid hydrazides. Pharmacologic testing has demonstrated that this series has high CNS depressant activity with low concomitant toxicity.

The 1,4-benzodiazepine ring system has, during the past decade, been the object of intense investigation by medicinal chemists in search of compounds with useful anxiolytic activity.[1,2] In this manuscript we will describe a series of 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-



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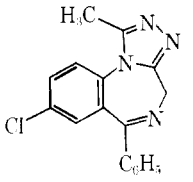

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benzodiazepines (*viz.* **2**)[3] which in our animal studies are extremely active, often exceeding the activity of the closest diazepam (**1**) analog by an order of magnitude. The toxicity is generally very low, so low that the LD_{50}'s have often been difficult to determine and have not been an important factor in the pharmacological evaluation of individual compounds.

Our discovery of the 6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepines resulted from a comprehensive study of the chemistry of electrophilic amide derivatives that could be derived from the 1,4-benzodiazepine system.[4] In particular the reaction of the known 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (**28**, Table II)[5] with acethydrazide in refluxing *n*-BuOH gave 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepine (**2**) in 69% yield. If the condensation was carried out under milder conditions, for example, in refluxing EtOH, cyclization was not complete and the intermediate, acetic acid 2-(7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazide (**18**), in addition to **2**, was isolated. Conversion of **18** to the triazole (**2**) was accomplished by thermal cyclization at 250°. The 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines listed in Table I were prepared by one of these methods from the appropriate acid hydrazide and 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (Table II).

Experimental Section

Chemistry.—Mps, taken in a capillary tube, are corrected. The structures of all compds were supported by ir, uv, and nmr spectra. Ir spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer, Uv spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian Model A60-A; chemical shifts were recorded in ppm downfield from Me_4Si. The silica gel used for chromatography was obtained from E. Merck A.G., Darmstadt, Germany. Skellysolve B (SkB) is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo.

1,3-Dihydro-5-phenyl-7-(trifluoromethyl)-2*H*-1,4-benzodiazepine-2-thione (20). Procedure A.—A modification of the lit.[5] was used for the prepn. A stirred mixt of 1,3-dihydro-5-phenyl-7-(trifluoromethyl)-2*H*-1,4-benzodiazepin-2-one[6] (89.7 g, 0.294 mole), dry pyridine (2300 ml), and P_2S_5 (72.4 g, 0.323 mole) was refluxed under N_2 for 30 min, cooled, and concd *in vacuo*. A suspension of the residue in ice water was extd with CH_2Cl_2. The ext was dried (K_2CO_3) and concd. The residue was crystd from CH_2Cl_2–EtOH to give 43.2 g, mp 228.5–229° dec, and 17.8 g, mp 229–230° dec, of **20**.

1-Methyl-6-phenyl-8-(trifluoromethyl)-4*H*-*s*-triazolo[4,3-*a*]-[1,4]benzodiazepine Hydrate (10). Procedure B.—A stirred mixt of **20** (64.9 g, 0.204 mole), acethydrazide (45.3 g, 0.612 mole), and MeOH (2500 ml) was refluxed under N_2 for 24 hr; during the first 2 hr N_2 was bubbled through the refluxing mixt. The mixt was concd *in vacuo*. A suspension of the residue in H_2O was stirred for 1 hr and filtd. The solid was dried at 30° *in vacuo* to give 64 g of crude acetic acid 2-(5-phenyl-7-trifluoromethyl-3*H*-1,4-benzodiazepin-2-yl)hydrazide. This material was heated in batches of 10–20 g at 200° under reduced pressure (12 mm) until the solid had melted and bubbling had become slow. The oily product was combined and stored at 4°. The cryst material which resulted was collected by filtn, washed with Et_2O, and dried to give 33.4 g of crude product. The mother liquor was chromatogd on silica gel (3 kg) with 5% MeOH–95% PhH to give addn product. The combined product was recrystd from wet CH_2Cl_2–Et_2O to give 2 crops: 25.2 g, mp 120.5–127.5°, and 12.8 g, mp 120–127° of **10**·hydrate. The anal. sample of anhyd **10** was obtd by recrystg some of this material from dry CH_2Cl_2–Et_2O and drying the resulting sample to const wt.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (2). Procedure C.—A stirred mixt of **28** (80.0 g, 0.279 mole), acethydrazide (55.0 g, 0.74 mole), and *n*-BuOH (2.5 l) was refluxed for 4 hr with a slow stream of N_2 bubbling through the reaction mixt. The mixt was concd *in vacuo*, and the residue was suspended in H_2O. The solid product was collected by filtn and dissolved in CH_2Cl_2. The soln was dried (K_2CO_3) and concd *in vacuo*. Crystn of the residue from CH_2Cl_2–EtOAc gave 45.5 g, mp 228–229°, and 14.3 g, mp 225–226° of **2**.

Acetic Acid 2-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-hydrazide (18).—A mixt of **28** (2.0 g, 0.0070 mole), acethydrazide (1.55 g, 0.021 mole), and abs EtOH (70 ml) was refluxed for 24 hr with a slow stream of N_2 bubbling through the mixt. The mixt was then concd to give a residue which was suspended in CH_2Cl_2 and filtd. Concn of the filt and crystn of the residue from EtOAc gave 0.65 of **18**, mp 196–197° dec. The anal. sample, mp 199–200° dec, was prepd by recrystg some of this material from CH_2Cl_2–EtOAc. *Anal.* ($C_{17}H_{15}ClN_4O$) C, H, Cl, N. Crystn of the solid from the CH_2Cl_2 filtn gave 0.73 g of a mixt of **18** and **2**.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (2) from 18.—A sample of **18** was heated under N_2 at 250° for a few min. Crystn of the cooled melt from EtOAc gave **2** which had mp 228–228.5°; uv (EtOH) end absorption, λ_{max} 222 mμ (ε 40,250), inflections 245 (15,350), 265 (6250), and 290

(1) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).

(2) R. C. Elderfield, *Heterocycl. Compounds*, **9**, 332 (1967).

(3) The synthesis of this ring system has recently been reported by K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970).

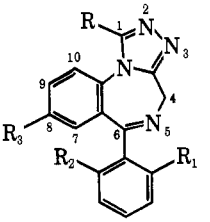
(4) For a preliminary discussion see J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *ibid.*, 1609 (1971).

(5) G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, **29**, 231 (1964).

(6) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR THE 6-PHENYL-4*H*-*s*-TRIAZOLO[4,3-*a*][1,4]BENZODIAZEPINES

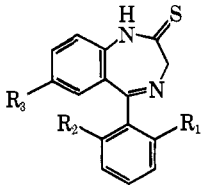


No.	R	R_1	R_2	R_3	Yield, %	Procedure	Mp, °C	Recrystn solvent	Formula	Analyses
2	CH_3	H	H	Cl	69	C	228–228.5	EtOAc	$C_{17}H_{13}ClN_4$	C, H, Cl, N
3	C_2H_5	H	H	Cl	37.2	B	231.5–232.5	MeOH–EtOAc	$C_{18}H_{15}ClN_4$	C, H, Cl, N
4	*n*-C_3H_7	H	H	Cl	39.3	B	176–176.5	EtOAc–SkB	$C_{19}H_{17}ClN_4$	C, H, Cl, N
5	C_6H_5	H	H	Cl	37.4	B	193.5–194.5	EtOAc	$C_{22}H_{15}ClN_4$	C, H, Cl, N
6	$CH_2C_6H_5$	H	H	Cl	68.6	C	192.5–193.5	EtOAc–SkB	$C_{23}H_{17}ClN_4$	C, H, Cl, N
7	$COOC_2H_5$	H	H	Cl	16.5	C	234–235 dec	EtOAc–SkB	$C_{19}H_{15}ClN_4O_2$	C, H, Cl, N
8	H	H	H	Cl	43.2	C	228–229[c]	EtOAc	$C_{16}H_{11}ClN_4$	C, H, Cl, N
9	CH_3	H	H	H	60.6	C	230–231	EtOAc	$C_{17}H_{14}N_4$	C, H, N
10	CH_3	H	H	CF_3	54.4	B	135–137	CH_2Cl_2–Et_2O	$C_{18}H_{13}F_3N_4$[a]	C, H, N, F
11	CH_3	H	H	NO_2	26	C	231.5–232.5	MeOH–EtOAc	$C_{17}H_{13}N_5O_2$	C, H, N
12	CH_3	H	H	SCH_3	53.3	C	193–194	EtOAc–SkB	$C_{18}H_{16}N_4S$	C, H, S, N[b]
13	CH_3	F	H	Cl	70	C[d]	203–204	EtOAc–SkB	$C_{17}H_{12}ClFN_4$	C, H, Cl, F, N
14	CH_3	Cl	H	Cl	43	C	223–225	*i*-PrOH	$C_{17}H_{12}Cl_2N_4$	C, H, Cl, N
15	CH_3	Cl	H	NO_2	70.8	C	229–231	*i*-PrOH	$C_{17}H_{12}ClN_5O_2$	C, H, Cl, N
16	CH_3	F	F	Cl	70	C[e]	278–279.5	EtOH	$C_{17}H_{11}ClF_2N_4$	C, H, Cl, F, N
17	CH_3	Cl	H	H	73	C	211.5–213	EtOAc	$C_{17}H_{13}ClN_4$	C, H, Cl, N

[a] This compound is hygroscopic. [b] N: calcd, 17.50; found, 17.94. [c] K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970) reported mp 226–227°. [d] Prepd in this laboratory by Elisabeth S. Cerda. [e] Prepd in this laboratory by Thomas L. Lemke.

TABLE II

PHYSICAL AND ANALYTICAL DATA FOR THE 1,3-DIHYDRO-5-PHENYL-2*H*-1,4-BENZODIAZEPINE-2-THIONES[a]



No.	R_1	R_2	R_3	Yield, %	Mp, °C	Lit. mp, °C	Recrystn solvent	Formula	Analyses	Reference[b]
19	H	H	H	34.4	234.4–235	256–257[c]	CH_2Cl_2–EtOH	$C_{15}H_{12}N_2S$	C, N, S, H[d]	
20	H	H	CF_3	64.5	223.5 dec		CH_2Cl_2–EtOH	$C_{16}H_{11}F_3N_2S$	C, H, F, N, S	*e*
21	H	H	NO_2	57.6	211–212 dec	209–214[c]	CH_2Cl_2–EtOH			
22	H	H	SCH_3	25	210–212 dec		*i*-PrOH	$C_{16}H_{14}N_2S_2$	C, H, N, S	*f*
23	F	H	Cl	73	227 dec	229–232[c]	EtOH–SkB			
24	Cl	H	Cl	34.5	240–241 dec	252–253[c]	EtOH			
25	Cl	H	NO_2	66	219–221 dec		EtOH	$C_{15}H_{10}ClN_3O_2S$	C, H, N, Cl, S	*g*
26	F	F	Cl	74.4	222.5–224		EtOH–H_2O	$C_{15}H_9ClF_2N_2S$	C, H, Cl, F, N	*h*
27	Cl	H	H	78	228–229		EtOH	$C_{15}H_{11}ClN_2S$	H, Cl, N, S, C[i]	*g*
28	H	H	Cl	41	236 dec	245–247[c]	CH_2Cl_2–EtOH			

[a] Prepd by procedure A. [b] Lit. ref to the starting 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one. [c] Ref 5. [d] H: calcd, 4.80; found, 4.34. [e] Ref 6. [f] E. Reeder and L. H. Sternbach, U. S. Patent 3,243,427 (1966). [g] L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963). [h] T. L. Lemke, The Upjohn Co. unpublished results; Belgium Patent 717,478 (1969) to Hoffman La Roche. [i] C: calcd, 62.94; found, 62.29.

(2850); nmr ($CDCl_3$) δ 2.62 (s, 3, CH_3), 4.11; 5.47 (d, 1, J = 13 Hz; d, 1, J = 13 Hz, C-4).

Pharmacology. Methods.—Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for all studies reported here. Unless otherwise indicated the test compds were dissolved or suspended in 0.25% aq methylcellulose soln and administered ip to groups of 6 mice per dose, at multiple dose levels distributed at 0.3 log intervals. Procedures for measuring the effect of test compds on overt behavior [loss of righting reflex (LRR) and traction (Tr); antagonism of nicotine-induced tonic-extensor convulsions (TE) and death (D); potentiation of EtOH and pentobarbital-induced narcosis; antagonism of thiosemicarbazide and strychnine convulsions, lethality, and electroshock convulsions] have been described previously.[7-9] Other test procedures used for this series of compds are described below. ED_{50} values were calcd by the method of Spearman and Karber.[10]

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

(8) J. B. Hester, A. D. Rudzik, H. H. Keasling, and W. Veldkamp, *ibid.*, **13**, 23 (1970).

(9) H. H. Keasling, E. L. Schumann, and W. Veldkamp, *ibid.*, **8**, 548 (1965).

(10) D. J. Finney, "Statistical Methods in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952.

TABLE III

PHARMACOLOGICAL DATA[a]

			Antagonism						Potentiation		Antagonism
			Nicotine		Thiosemi-	Strych-	Electro-	Pentylene-		Pento-	Foot-
No.	LRR	Tr	TE	D	carbazide	nine	shock	tetrazole	EtOH	barbital	shock
1[b]	50	7	0.28	0.28	0.7	8	50	0.8	0.9	5.0	1.8
2	>100	0.6	0.02	0.02	0.16	0.3	25	0.2	0.16	0.45	0.13
3	>200	4	0.2	0.23	0.56	9.0	>6	1.0	5.0	6.0	
4	>25	6	0.36	0.36	1.8	8.0	>25	3.1	7	7.0	
5	>200	112	20	20	79	>100	>100	63	79	>100	
6	>200	142	25	25	126	225	200	>50	126	>100	
7	>200	63	3.5	4	2.8	18	>200	8.0	36	71	>16
8	>25	2.8	0.08	0.1	1.0	23	>25	0.6	0.7	7.0	0.26
9	>25	25	0.32	0.32	0.8	>25	>25	1.1	13	56	8.4
10	5.6	0.6	0.08	0.08	0.28	0.63	>0.8	0.2	0.32	0.32	
11	>50	0.6	0.13	0.13	0.35	1.1	3.6	0.25	0.25	0.18	0.32
12	16	2.8	0.7	0.7	2.2	2.8	7.9	1.6	2.0	2.8	1.5
13	>200	0.4	0.009	0.009	0.01	0.18	20	0.03	0.13	0.45	0.19
14	>25	0.6	0.013	0.014	0.028	0.23	50	0.03	0.63	2.0	0.30
15	50	0.07	0.003	0.005	0.09	0.56	28	0.023	0.008	0.09	0.031
16	>25	0.1	0.018	0.02	0.01	0.22	16	0.022	0.13	0.56	0.39
17	>100	>100	0.18	0.16	0.9	>100	>100	0.55	>100	79	21.0

[a] See Experimental Section for explanation of the symbols. Values are ED_{50}'s expressed in mg/kg. [b] A sample of diazepam was obtd from Hoffmann-LaRoche, Inc.

Antagonism of Pentylenetetrazole-Induced Clonic Convulsions.—An aq soln of pentylenetetrazole (85 mg/kg) was administered sc to groups of 6 mice, 30 min after the test compd. The mice were then observed for a period of 20 min for symptoms of clonic convulsions. The number of animals in each group which were protected against the pentylenetetrazole-induced clonic convulsions was used as a quantal response parameter for calculating the effective dose (ED_{50}) of the test compd.

Antagonism of Foot-Shock-Induced Aggression.—In this procedure the fighting response was produced in male albino mice. Pairs of mice were placed on a grid and covered by a petri dish (5 cm high and 10 cm in diameter). Foot shock was then administered intermittently through the grid for a 3-min period or until the mice fought spontaneously or dominance was established by one of the mice. The dominant mouse was used within 48 hr for drug studies. Multiple dose levels of test compd at 0.3 log intervals were administered ip to groups of 8 dominant or spontaneously fighting mice. Thirty min later pairs of drug-treated mice were placed on the grid and exposed to intermittent foot shock for 30 sec. The number of pairs of mice that fought at each dose level was recorded and the ED_{50}, the dose which prevented fighting in 50% of the animals, was calcd.

Results and Discussion

The pharmacologic results obtained for the 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines are presented in Table III and are compared with the results obtained for diazepam (**1**) in the same test systems. The data reflect the activity of the compds after ip administration; however, they were generally as active when administered orally.

In our initial studies of the structure–activity relationships in this series, we sought to determine the steric requirements of the C-1 substituent. We thus varied the substituent at C-1 from H to *n*-Pr and found that a Me group imparted optimum activity to the system (compare **2** with **3**, **4**, and 8); incorporation of a Ph (**5**), benzyl (**6**), or carboethoxy (**7**) group at C-1 eliminated the activity in most tests. With this established, it was next of interest to determine if substituents at C-8 and at the ortho positions of the C-6 Ph would influence the activity of our system in a manner similar to that previously found in the 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one studies.[11] In the latter series it was found that electronegative substituents (halogen, CF_3, and NO_2) at C-7 were essential for high activity and that the activity increased as the electronegativity of the substituent increased; the analogs with H or electropositive substituents at C-7 had a very low order of activity. In the 6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine series an electronegative substituent at C-8 was also necessary for optimum activity (compare **2** with **9**), but the type of electronegative substituent at this position did not seem to have a marked influence on the overall potency of the system (compare, for example, the pentylenetetrazole, thiosemicarbazide, and Tr results for **2**, **10**, and **11**). Qualitative differences were apparent, however. For example, the CF_3 analog **10** was outstanding in its ability to eliminate the loss of righting reflex (LRR) at low doses; the nitro derivative **11** was a relatively good antagonist of electroshock-induced tonic-extensor convulsions (ES). Methylthio substitution at C-8 gave a compd (**12**) that was qualitatively different than either the unsubstituted analog **9** or the chloro substituted derivative **2**. Thus **12** was more effective than **2** in LRR and ES while being much less active in most other tests. On the other hand, **12** was more active than **9** in most tests but was about equipotent or slightly less active than **9** for antagonizing the effects of nicotine, thiosemicarbazide, and pentylenetetrazole.

As was the case in the diazepam series,[11] substitution of Cl or F at the ortho position of the C-6 Ph moiety gave compds with dramatically enhanced activity in many tests (compare **13** and **14** with **2** and **15** with **11**). The 6-(*o*-chlorophenyl)-8-nitro derivative (**15**) was the most active compound in the series, being effective in many tests at doses of less than 10 μg/kg. Substitution of a second ortho halogen substituent on the C-6 Ph did not further potentiate the activity (compare **16** with **13**).

As we have already demonstrated, the activity of 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**9**) could be enhanced by a factor of 10–100 by the

(11) 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.

incorporation of appropriate substituents. This compd (**9**) is itself, however, highly effective for antagonizing the effects of nicotine, thiosemicarbazide, and pentylenetetrazole in mice, being only slightly less active than diazepam (**1**) in this regard. On the other hand, **9** was less active than diazepam in the ES and Tr tests and for potentiating the effects of EtOH and pentobarbital. This selective activity was enhanced in the 6-(*o*-chlorophenyl) derivative **17**. This compd was as good or better than diazepam for antagonizing the effects of nicotine, thiosemicarbazide, and pentylenetetrazole in mice, but had little or no activity in any other test.

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

Molecular Orbital Calculations on Coumarins and the Induction of Drug-Metabolizing Enzymes

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A structure–activity relationship study has been carried out for the capability of coumarin and 9 of its derivatives to induce drug-metabolizing enzymes in the rat liver. Extended Hückel molecular orbital calculations have been performed to generate various electronic parametric descriptions of the series. Multiple regression analyses, as described by Hansch, simultaneously involving the experimentally determined partition coefficient as well as either the energy of the highest occupied molecular orbital or the first electronic transition energy and the net charge on the carbonyl or α-pyran moiety of the lactone ring of the coumarinic structure, yielded significant multiple correlations ($p < 0.01$) accounting for, resp, over 86 and 91% of the variation in induced enzyme activity. A mechanism of action involving a charge-transfer and/or H-bonded complex formation with at least partial localization of the activity related site to the carbonyl and/or α-pyran moiety of the lactone ring seems to be implicated.

The induction of hepatic drug-metabolizing enzymes by closely related coumarin derivatives has been found to vary widely.[1] Attempts to demonstrate any correlation between the inducing capability of these compounds and their lipid solubility, absorption, or metabolism have been unsuccessful.[1,2] However, electrochemical properties of drugs may be responsible for, or contribute to their pharmacological action.[3-7] Therefore, it has been suggested that this may elucidate the differences in the hepatic action of various coumarins.[1]

A mathematical model relating biological activity to chemical constitution developed by Hansch and coworkers[8] has been applied to numerous biological systems.[8-13] This model can be represented by eq 1

$$\log BA = -a\pi^2 + b\pi + c \log K_{CR} + d \qquad (1)$$

where BA = biological activity, $\pi = \log (P_x/P_h)$, P_x and P_h are partition coefficients of the derivative and parent compound, resp, K_{CR} = rate or equilibrium constant of the critical reaction, and a, b, c, d are constants for a given activity and system.

The model accounts for the arrival of the biologically active compound to its site of action by random walk (π and π^2 terms). The component involving the critical reaction is free energy dependent and may be expressed in terms of a linear combination of the parameters[12-14] that contribute to the total free energy change of the reaction.

These contributions have been tested empirically[12] and they could be of various types: hydrophobic, electronic, steric, H bonding, charge-transfer complexing, or others. Good correlations of the form described by eq 1 have been found using a large variety of quantitative parameters descriptive of one or other of the above factors including some quantum mechanically calcd ones.[13] Accordingly, molecular orbital calculations have been performed on coumarin and 9 of its derivatives, hoping that such an approach might help to elucidate the variation in their activity.

Experimental Section

Molecular Orbital Calculations.—Molecular orbital calcns of the extended Hückel type were performed on the IBM 7094-II computer using a program previously described by Hoffman.[15]

Input to the program consisted of Cartesian coordinates of the atoms, Slater exponents, and Coulomb integrals, H_{ii} for the 2s and 2p orbitals of C and O and the 1s orbital of H. The overlap matrix, **S**, for 1 s and 3 p orbitals for each C and O atom and an s orbital on each H atom was computed explicitly. The

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