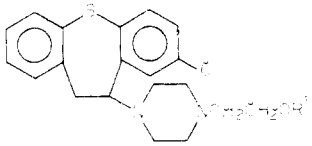
112.76°, and $\gamma = 99.66°$ (these are unpublished data obtained by Mrs. Barbara Toeplitz of this Institute).

(6) The two procedures employed for the evaluation of these compounds are described in the Experimental Section.

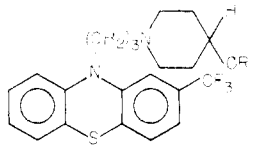
(7) J. O. Jilek, A. Dlabac, and M. Protiva, at the Conference on the Chemistry of Psychotropic Agents held at Usti nad Labem, May 13–17, 1974, reported that the 1-adamantanoate, 4, of the highly potent neuroleptic, 3, was totally devoid of activity when evaluated against apomorphine-induced emesis in the dog or catalepsy in the rat. These tests are widely employed in other laboratories, especially in Europe, to evaluate long-acting neuroleptics [see, for example, L. Joulou, G. Bourat, R. Ducrot, J. Fournel, and C. Garret, *Acta Psychiat. Scand., Suppl.*, **241**, 9 (1973)], and data from these tests compare well with data obtained on inhibition of conditioned avoidance behavior. Thus, the lack of activity with 4 reinforces the concept that the efficacy of 1h and **2b** is unique. Although R. T. Rapara, R. J. Kraay, and K. Gerzon, *J. Med. Chem.*, 8. 580 (1965), have shown that the highly symmetrical cage-like adamantane molecule confers lipophilic character, steric hindrance, and, in its esters, a unique stability toward hydrolysis, these attributes, in toto, do not necessarily lead to an active compound.



3, R^1 = H

4, R^1 =

Another example to demonstrate that long-chain fatty acid esters of an active antipsychotic agent may not lead to an active, long-acting ester, and may, in fact, lead to an inactive compound, has been observed with **5**. In the conditioned avoidance procedure, **5** [French Patent 1 305 353; *Chem. Abstr.*, **58**, 9092 (1963)] was found to have 0.5–1.0 times the potency of **1a**, the most potent phenothiazine available, on a milligram basis, in medicine. When, however, **5** was converted to the laurate and myristate esters, **6** and **7**, respectively, both compounds were inactive in the conditioned avoidance procedure. Note that **1f** and **1g** (Table I), the laurate and myristate of **1a**, were both potent and long-acting derivatives.



5, R = H
6, R = n-$C_{11}H_{23}CO$
7, R = n-$C_{13}H_{27}CO$

It is also worth noting that very recently, B. T. Ho, L. F. Englert, and M. L. McKenna, *J. Med. Chem.*, **19**, 850 (1976), have reported that the 1-adamantylcarbamate of **1a** was less effective than was 1a in several laboratory tests designed to uncover amphetamine antagonism.

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Substituent Constants for Correlation Analysis

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Constants for π and σ have been measured for a miscellaneous group of aromatic substituents of interest to medicinal chemists. Swain and Lupton's $\mathcal{F}$ and $\mathcal{R}$ values have been calculated from the σ constants. Values for molar refractivity are also given for each of the substituents.

The use of substituent constants in the field of physical organic chemistry has had an enormous impact on the study of organic reaction mechanisms.[1-3] The use of such constants has enabled us to delineate the role of substituents on organic and biochemical processes in terms of polar, resonance, steric,[4] hydrophobic,[5] and polarizability[6] vectors. There is a dichotomy between the fields of physical organic chemistry and biomedicinal chemistry in that interest in the former field centers on more and more precise definitions of electronic[7] and steric[8] constants in order to enable one to formulate sharper relationships in relatively well-defined homogeneous organic reactions. On the other hand, biomedicinal chemists need a great variety of substituent constants on a range and type of substituent far beyond the current interests of physical organic chemists. Moreover, the noise in the dependent variables with which the biomedicinal chemist is forced to work is so large that the quality of the substituent constants is not as critical as is the need for having the largest possible number of substituents parameterized. For this reason we have been collecting Hammett–Taft constants as well as hydrophobic constants[6] from whatever source available. Table I contains constants on a miscellaneous set of substituents with which we became involved in correlation analysis and is an extension of our earlier compilation.[6] All of the π constants were determined in our laboratory from the benzene solute system, i.e., by partitioning $X\text{-}C_6H_5$ between octanol and water. Some of the σ constants were determined in our laboratory; others, as indicated, have been taken from the literature.

Experimental Section

A number of the compounds used in determining π and σ have not been previously reported. Their preparation and properties are considered below. The purity of all compounds was checked by thin-layer chromatography as well as elemental analysis. The carbon–hydrogen analyses all agreed with the theoretical analyses within 0.4. The analyses were made by C. F. Geiger of Ontario, Calif.

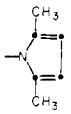
The hydrazone derivatives of benzoic acid were all prepared by reaction of the appropriate hydrazine with 3- or 4-carboxybenzaldehyde.

3-Carboxybenzaldehyde carbazone was purified by precipitation from alkaline solution and extraction with hot absolute ethanol: mp 230–231 °C.

4-Carboxybenzaldehyde carbazone was purified as in the 3 isomer: mp 284 °C.

3-Carboxybenzaldehyde thiosemicarbazone was recrystallized from methanol: mp 284 °C.

Table I. "Aromatic" Substituent Constants

No.	Substituent	π[a]	σ_m	σ_p	$\mathcal{F}$[b]	$\mathcal{R}$[b]	MR[c]	Mol wt	Wiswesser	Ref[d] σ_m	Ref[d] σ_p
1			0.49	0.38	0.52	−0.10	31.86	94.1	* AT5NJ B1 E1	1	1
2	c-$C_5H_{10}N$–	0.65		0.45			27.46	84.1	* AT6NTJ		1
3	OCF_2CF_2H		0.34	0.25	0.36	−0.08	11.63	117.0	*0XFFYFF	2	2
4	OCH_2CONH_2	−1.37					15.87	74.1	*01VZ		
5	$OCH_2CON(Me)_2$	−1.36					24.86	104.1	*01VN1&1		
6	$OCH_2CON(CH_2CH_2)_2O$	−1.39					34.22	144.2	*01V- AT6N DOTJ		
7	$OCH_2CONHC_6H_5$	0.60					41.47	150.2	*01VMR		
8	$OCH_2CON(Me)C_6H_5$	0.12					45.82	164.2	*01VN1&R		
9	$SO_2N(Me)_2$	−0.78					21.57	108.1	*SWN1&1		
10	OCH_2CO-c-NC_5H_{10}	−0.32					37.11	142.2	*01V- AT6NTJ		
11	2-C_5H_4N	0.50	0.33	0.17	0.38	−0.18	23.03	78.1	* BT6NJ	1	1
12	OSO_2CF_3		0.56	0.53	0.56	0.01	16.36	149.1	*0SWXFFF	3	3
13	$C(CF_3)_3$		0.35	0.52	0.28	0.27	17.65	219	*XXFFFXFFFXFFF	4	4
14	$NHC(=S)NHCH_2CH_3$	−0.71	0.30	0.07	0.38	−0.28	31.48	103.2	*MYUS&M2	5	5
15	$CH=NNHCONH_2$	−0.85					21.45	86.1	*1UNMVZ		
16	$CH=NNHCOC_6H_5$	0.43	0.39	0.51	0.33	0.20	42.37	147.2	*1UNMVR	1	1
17	$CH=NNHCSNH_2$	−0.27	0.45	0.40	0.46	−0.02	29.92	102.1	*1UNMYZUS	1	1
18	$CH=NNHSO_2Me$	−0.93					25.90	121.1	*1UNMSW1		
19	$CH=NN(CH_2)_5$	0.91					35.19	111.2	*1UN- AT6NTJ		
20	$CH=NNHCONHNH_2$	−1.32	0.22	0.16	0.23	−0.05	24.86	101.1	*1UNMVMZ	1	1
21	$NHCOCH_2Cl$	−0.50	0.17	−0.03	0.23	−0.24	19.77	92.5	*MV1G	6	6
22		−0.25					19.85	67.1	* BT5M CNJ		
23		0.95	0.47	0.37	0.50	−0.09	22.57	66.1	* AT5NJ	1	1
24	c-$N(CH_2CH_2)_2O$	−0.77					24.57	86.1	* AT6N DOTJ		
25	$NHCH_2C_6H_5$	1.00					34.73	106.1	*M1R		
26	$N=NN(Me)COMe$	0.54					25.48	100.1	*NUNN1&V1		
27	$OCH_2C_6H_5$	1.66		−0.42			32.19	107.1	*01R		7
28	$COCH_2CH_3$			0.48			15.83	57.1	*V2		7
29	$COCH(CH_3)_2$			0.47			20.48	71.1	*VY		7
30	$COC(CH_3)_3$			0.32			25.13	85.1	*VX		
31	$CSNH_2$	−0.64					17.68	61.1	*YZUS		
32	$CONHNH_2$	−1.92					13.11	59.1	*VMZ		
33	$CH=NOCH_3$	0.40	0.37	0.30	0.39	−0.06	14.93	58.1	*1UN01	1	1
34	c-C_3H_5	1.14	−0.07	−0.21	−0.03	−0.19	13.53	41.1	* AL3TJ	8	8
35	$CH_2OC_6H_5$	1.66	0.03	0.04	0.02	0.02	32.19	107.1	*10R	9	9
36	$CH=C(CN)_2$	0.05	0.66	0.84	0.58	0.30	21.53	77.1	*1UYCN&CN	1	1
37	$-C(NH_2)=NH_2^+Cl^-$	−3.72[e]						79.5	*YZUM &GH		
38	CH_2OCH_3	−0.78	0.02	0.03	0.01	0.02	12.06	45.1	*101	9	9
39	$C\equiv CC_6H_5$	2.65	0.14	0.16	0.12	0.05	33.88	101.1	*1UU1R	9	9
40	$NHC(=O)CH(Me)_2$	−0.18	0.11	−0.10	0.18	−0.26	24.22	86.1	*MVY	6	6
41	$OC(=O)C_6H_5$	1.46	0.21	0.13	0.23	−0.08	32.33	121.1	*0VR	6	6
42	$COOC_6H_5$	1.46	0.37	0.44	0.33	0.13	32.33	121.1	*V0R	10	10
43	$C(OH)(CF_3)_2$	1.28	0.29	0.30	0.28	0.05	15.18	167.0	*XQXFFFXFFF	11	11
44	$P(=O)(OMe)_2$	−1.18	0.42	0.53	0.37	0.19	21.87	109.0	*P0&01&01	12	12
45	$CH=CHC_6H_5$ trans	2.68	0.03	−0.07	0.06	−0.12	34.17	103.1	*1U1R -T	13	13
46	n-C_4H_9	2.13	−0.08	−0.16	−0.06	−0.11	19.59	57.1	*4	14	15
47	3-$NHC(=O)$-C_5H_4N	−0.40					32.31	121.1	*MV- CT6NJ		
48	NHCN	−0.26	0.21	0.06	0.26	−0.18	10.14	41.0	*MCN	16	16

[a] Calculated as $\pi = \log P_{X\text{-}C_6H_5} - \log P_{benzene}$ with $\log P_{benzene} = 2.13$. [b] Swain and Lupton's $\mathcal{F}$ and $\mathcal{R}$ constants have been calculated according to our corrected equation. [c] MR values have been calculated as before. [d] (1) This work; (2) W. A. Sheppard, *J. Am. Chem. Soc.*, **85**, 1314 (1963); (3) L. M. Yagupol'skii and V. P. Nazaretyan, *Zh. Org. Khim. (Engl. Ed.)*, **7**, 1016 (1971); (4) L. M. Yagupol'skii, N. V. Kondratenko, N. I. Delyagina, B. L. Dyatkin, and I. L. Knunyants, *ibid.*, **9**, 669 (1973); (5) T. Nishiguchi and Y. Iwakura, *J. Org. Chem.*, **35**, 1591 (1970); (6) O. Exner and J. Lakomý, *Collect. Czech. Chem. Commun.*, **35**, 1371 (1970); (7) K. Bowden and M. J. Shaw, *J. Chem. Soc. B*, 161 (1971); (8) J. Smejkal, J. Jonas, and J. Farkaš, *Collect. Czech. Chem. Commun.*, **29**, 2950 (1964); (9) O. Exner, *ibid.*, 31, 65 (1966); (10) O. Exner and K. Bocek, *ibid.*, **38**, 50 (1973); (11) W. A. Sheppard, *J. Am. Chem. Soc.*, **87**, 2410 (1965); (12) E. N. Tsvetkov, D. I. Lobanov, L. A. Izosenkova, and M. I. Kabachink, *J. Gen. Chem. USSR (Engl. Transl.)*, 39, 2126 (1969); (13) J. K. Kochi and G. S. Hammond, *J. Am. Chem. Soc.*, **75**, 3452 (1953); (14) M. Charton, *J. Org. Chem.*, **30**, 552 (1965); (15) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); (16) J. C. Kauer and W. A. Sheppard, *J. Org. Chem.*, **32**, 3580 (1967). [e] Determined using 0.1 N HCl as the aqueous phase.

4-Carboxybenzaldehyde thiosemicarbazone was recrystallized from glacial acetic acid: mp 330 °C.

3-Carboxybenzaldehyde phenylhydrazone was recrystallized from ethanol: mp 174–175 °C. The melting point for this compound has been reported as 112–115[9] and 164 °C.[10]

4-Carboxybenzaldehyde phenylhydrazone was recrystallized from ethanol–water: mp 236 °C.

3-Carboxybenzaldehyde benzoylhydrazone was recrystallized from glacial acetic acid: mp 261–262 °C.

4-Carboxybenzaldehyde benzoylhydrazone was recrys-

tallized from glacial acetic acid: mp 305 °C.

3-Carboxybenzaldehyde *O*-methyloxime was recrystallized from ethanol: mp 149–150 °C.

4-Carboxybenzaldehyde *O*-methyloxime was recrystallized from ethanol–water: mp 177–178 °C.

3-Carboxybenzylidenemalonitrile. 3-Carboxybenzaldehyde (0.1 M) and malonitrile (0.1 M) were dissolved in 150 ml of 95% ethanol. A few drops of triethylamine were added and, on standing for several hours, a white solid separated which was recrystallized from ethanol: mp 228–229 °C.

4-Carboxybenzylidenemalonitrile was prepared and purified in the same way as the 3 isomer: mp 179–180 °C.

3-Carboxyphenylpyrrole. 3-Aminobenzoic acid (0.04 M) and 4-picoline (0.08 M) were dissolved in a small amount of hot DMF. With stirring, 0.04 M mucic acid was added slowly after which the mixture was refluxed for 3 h. After standing at room temperature overnight, the picoline was removed on a rotary evaporator and the resulting syrup dissolved in ethyl acetate and extracted with 5% sodium hydroxide. The alkaline extract was acidified to pH 5.0 and the white precipitate removed by filtration, dissolved in chloroform, applied to a silica gel column, and eluted with chloroform. The fractions which showed a single TLC spot were combined and the chloroform was removed by rotary evaporation: mp 268–270 °C.

4-Carboxyphenylpyrrole was prepared and purified in the same way as the 3 isomer: mp 288–290 °C.

3-(2,5-Dimethylpyrrolyl)benzoic Acid. 3-Aminobenzoic acid (0.02 M) and acetonylacetone (0.02 M) were dissolved in 30 ml of 95% ethanol and 2.4 ml of glacial acetic acid. The solution was refluxed with stirring for 4 h. The crystals which separated on cooling were recrystallized from ethanol: mp 144 °C.

4-(2,5-Dimethylpyrrolyl)benzoic acid was prepared and purified in the same way as the 3 isomer: mp 177–179 °C.

3-(2-Pyridyl)benzoic Acid. 3-Methyl-1,2′-pyridylcyclohexanol was prepared according to Abramovitch and Saha.[11] It was dehydrated in glacial acetic acid with sulfuric acid, according to their directions. The acetic acid was removed under vacuum and the residue poured into water. After making the aqueous phase alkaline, the product was extracted with ether which was dried over $MgSO_4$ and evaporated, and the residue was dehydrogenated by refluxing overnight in dry decalin with 5% palladium on charcoal (200 mg of compound/50 mg of 5% Pd/carbon). Abramovitch and Saha did not mention[11] the necessity of this step which we found to be necessary. The carbon was filtered from the hot solution and the filtrate extracted with 5% HCl. Neutralization yielded 3-(2-pyridyl)toluene which was not purified but oxidized with aqueous $KMnO_4$ to yield the desired acid: mp 213 °C after recrystallization from ethanol.

4-(2-Pyridyl)benzoic acid was prepared and purified in the same way as the 3 isomer: mp 235–237 °C.

pK_a Determinations. In determining the pK_a values of the various benzoic acids, the guidelines of Albert and Serjeant[12] were followed. A Corning digital 112 research model pH meter was used to determine the hydrogen ion concentration in the potentiometric titrations which were carried out in a 200-ml jacketed beaker. The beaker was fitted with a specially designed Plexiglas cover with holes fitted to Corning glass calomel electrodes, a Corning automatic temperature compensator, a nitrogen inlet tube, and buret tip. Since the determinations were made in 50% ethanol–water (by volume), the electrodes were allowed to soak in this solution for several days before use. The pH meter was standardized against NBS potassium hydrogen phthalate buffer (pH 4) and potassium dihydrogen phosphate–disodium hydrogen phosphate (pH 7) buffer. The temperature was maintained at 25 ± 0.01 °C.

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Synthesis and Structure–Activity Relationship Studies of Cytotoxic Epoxide Derivatives of 7-Oxabicyclo[2.2.1]heptane

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Dimethyl *exo*-5,6-oxido-7-oxabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate (1) and the 1-methyl homologue 2 were shown to exhibit significant cytotoxicity in the 9KB tissue culture assay. Several analogues of 1 were prepared and it was found that removal of the epoxide, or the oxygen bridge, or the 2,3 double bond from 1 resulted in loss of significant cytotoxic activity. One compound which lacked the epoxide moiety, dimethyl 1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (5), also exhibited marginal cytotoxic activity.

A number of naturally occurring and synthetic epoxy compounds have been shown to possess significant antitumor and/or cytotoxic activity. Within this category one finds the complex triepoxides, triptolide[1] and tripdiolide,[1] and diepoxides such as crotepoxide,[2] fumagillin,[3] mikanolide,[4] 1,2,3,4-diepoxybutane,[5] and "Mannitol-Myleran".[6] In addition, a variety of polyfunctional natural products which possess an epoxide moiety as one potentially reactive site in the molecule has been shown to possess significant antitumor and/or cytotoxic activity.[7-12]

During the course of our continuing effort to prepare simple polyfunctional analogues of naturally occurring tumor inhibitors, we synthesized dimethyl *exo*-5,6-oxido-7-oxabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate (1). The significant reproducible cytotoxic activity of 1 in the 9KB tissue culture assay prompted us to undertake a more