Steric Effects of Substituents on Phenethylamine Hallucinogens. 3,4-(Methylenedioxy)amphetamine Analogues Alkylated on the Dioxole Ring

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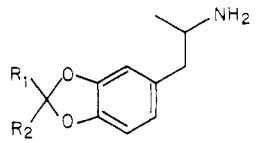
The compounds 1-(2-methyl-1,3-benzodioxol-5-yl)-2-aminopropane and 1-(2,2-dimethyl-1,3-benzodioxol-5-yl)-2-aminopropane were synthesized and evaluated for pharmacologic effects in mice. These can be viewed as analogues of the known psychotomimetic agent 3,4-(methylenedioxy)amphetamine (MDA). Their hydrochloride salts were compared with MDA for their ability to increase spontaneous motor activity and to elicit behavioral effects. The former compound was MDA-like in action, while the latter was not. The results suggest that one face of the molecule must be free of steric bulk to possess activity.

A new model was recently proposed which interrelates the structures of phenethylamine hallucinogens with the tryptamines and LSD.[1-3] Based upon the known relative planarity of the LSD molecule, it was assumed that interaction with the receptor is of an essentially planar nature. In contrast, the phenethylamine hallucinogens are very flexible and little is actually known regarding the steric or conformational properties of these types of molecules upon receptor interaction. At the para position, straight-chain alkyls but not a *tert*-butyl substituent possess activity.[4] Decreased hallucinogenic activity in certain 2,3-dimethoxy-substituted compounds has been interpreted to mean that steric crowding adjacent to the side chain cannot be tolerated. These facts could indicate a requirement for a planar interaction between the phenethylamines and the receptor. However, steric bulk may be tolerated on one face of the molecule. This is supported by the fact that compounds with a *p*-isopropoxy[5] or *p*-(isopropylthio)[6] substituent retain activity. Rotation about the Ar–O or Ar–S bond allows these groups to clear one face of the molecule, whereas with a *tert*-butyl attached directly to the ring no such steric relief is possible.

As an attempt to explore these ideas, we have synthesized and carried out a preliminary pharmacological evaluation of compounds **1** and **2**, which can be viewed to

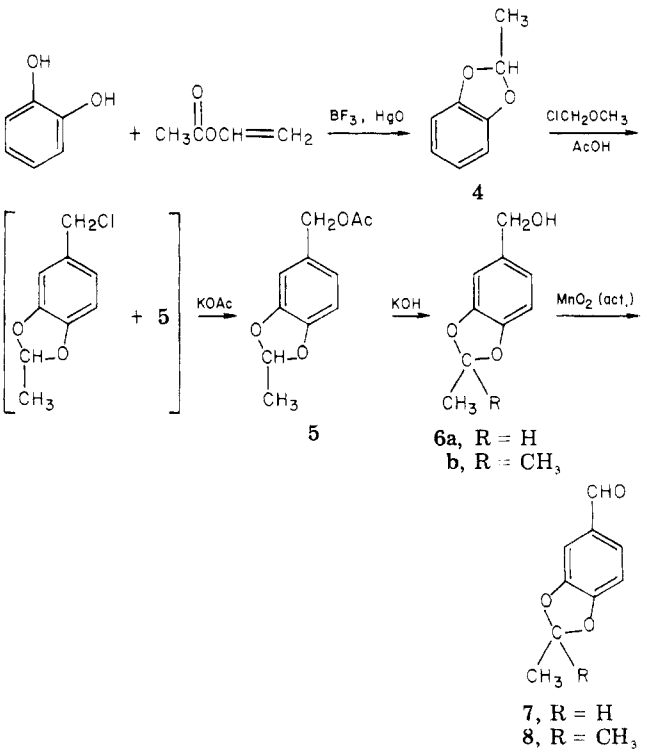


1, $R_1 = CH_3$; $R_2 = H$
2, $R_1 = R_2 = CH_3$
3, $R_1 = R_2 = H$ (MDA)

be analogues of the known psychotomimetic agent 3,4-(methylenedioxy)amphetamine (MDA) **3**. If the molecule must present at least one sterically unhindered face to the receptor, one could reason that the presence of the geminal dimethyls in **2** should hinder or prevent this interaction. In contrast, one face of the monomethyl analogue **1** remains accessible for productive interaction. Hence, one is led to speculate that **1** might show MDA-like effects, whereas **2** might not.

Chemistry. The desired 1-phenyl-2-aminopropane derivatives were readily prepared from the appropriate aldehydes **7** and **8**. However, difficulties were encountered in the preparation of these two aldehydes. Aldehyde **7** has been reported in the patent literature.[7] However, the starting material, 2-methyl-1,3-benzodioxole (**4**), is not readily available, and its reported[8] preparation by reaction between catechol and acetylene occurs under conditions which were deemed unsuitable in our laboratory. Direct

Scheme I



alkylation of catechol with 1,1-dichloroethane using methylenation conditions reported by Clark et al.,[9] Tomita et al.,[10] or by Bashall and Collins[11] failed to give acceptable yields. Attempted acetal exchange using catechol and 1,1-diethoxyethane yielded only polymeric material.

A feasible laboratory synthesis of **4** was finally developed using a modification of the method reported by Croxall et al.[12] This method involves the BF_3/HgO-catalyzed reaction between vinyl acetate and an alcohol to give the corresponding acetaldehyde acetal. Although these workers report that phenol does not give the expected diphenyl acetal, we found that the use of catechol gave reasonable yields of **4**. The synthesis of **4** and the preparation of the aldehydes **7** and **8** are detailed in Scheme I.

The overall yield for aldehyde **7** was relatively poor. Although Regnier[13] has reported that this aldehyde can be prepared by direct formylation of **4**, we were unable to effect this transformation under a variety of conditions. The Vilsmeier reaction failed to give identifiable products. Formylation attempts employing dichloromethyl methyl ether with Friedel–Crafts catalysts also failed. In the latter instance, the use of $TiCl_4$ (0 °C) caused decomposition of the starting material **4**. Although **4** was stable to treatment

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Table I. Spontaneous Activity Counts[a] per Minute in Groups[b] of Three Mice Averaged Over 90 Min

	dose, mmol/kg			
compd[c]	0.025	0.075	0.225	0.30
1	39 (4.2)[f]	25 (3.9)	94 (12)[g]	192 (19)[d,g]
2	30 (3.7)	27 (3.7)	17 (2.8)	33 (9)[d]
3 (MDA)	64 (21)	276 (30)[d,g]	105 (13)[g]	nt[e]

[a] Values in parentheses are SEM. [b] $n = 4$, except as noted. [c] Saline injected control counts = 19 (3.3). [d] $n = 3$. [e] Not tested at this dose. [f] $p < 0.01$. [g] $p < 0.001$.

with $SnCl_4$ under similar conditions, subsequent addition of Cl_2CHOCH_3 caused formation of numerous products, as detected by TLC.

We found that treatment of **4** with AcOH at moderate temperatures did not cause extensive acetolysis of the dioxole ring. We therefore carried out a chloromethylation reaction utilizing treatment with chloromethyl methyl ether in acetic acid.[14] Concentration of the reaction mixture under vacuum at room temperature caused the product to blacken and decompose. We attributed this to the presence of HCl and consequent acid-catalyzed cleavage of the dioxole ring. Since acetolysis to **5** was a side reaction, the chloromethylation reaction was neutralized with potassium acetate and heated briefly to reflux, and **5** was directly isolated. Base hydrolysis, followed by activated MnO_2 oxidation, gave the desired aldehyde **7**.

The homologous geminal dimethyl aldehyde **8** has not previously been reported. In view of the difficulties encountered in the synthesis of **7** and the greater acid sensitivity of 2,2-dimethyl-1,3-benzodioxole,[15] an alternate literature route,[16] albeit a slightly longer one, was chosen to obtain the alcohol **6b**. This route involved the treatment of 2,2-dimethyl-1,3-benzodioxole with acetic anhydride at 0 °C in the presence of catalytic BF_3. The resulting 5-acetyl derivative was oxidized with hypobromite to the corresponding acid. The acid was esterified by treatment with diazomethane and then reduced with $LiAlH_4$ to alcohol **6b**. This alcohol was oxidized to the desired aldehyde **8** with activated MnO_2. Both aldehydes, **7** and **8**, were shown to have the expected 1,3,4 substitution, as evidenced by characteristic splitting of the aromatic protons in their ^1H NMR spectra and comparison with the spectrum of piperonal.

The two aldehydes were allowed to condense with nitroethane using ammonium acetate as catalyst. The nitropropenes thus obtained were reduced with LAH and isolated as their hydrochloride salts by careful neutralization of the free base, followed by recrystallization.

Pharmacology. Compounds **1** and **2** were evaluated for their ability to elicit hyperactivity in mice and were compared with equimolar doses of MDA for possible similarities of elicited behavioral effects. Gross behavioral observations were made at each dose using three groups of three mice.

Results and Discussion

The results of the studies on spontaneous activity in mice are presented in Table I. Of compounds **1** and **2**, only **1** resembled MDA, appearing to be about one-fifth to one-tenth as potent as MDA based on increases in spontaneous activity. In the production of behavioral effects, such as exopthalmia, exploratory behavior, pilomotor erection, sniffing, salivation, and grooming, compound **1** appeared to be about one-half to three-fourths as active as MDA. In fact, salivation, excessive grooming, and exopthalmia were quite marked at the 0.225 and 0.30 mmol/kg doses of **1**. One will note from the data that MDA produces a biphasic response. The apparent decrease in spontaneous activity at the highest does of MDA is largely the result of more time spent in various stereotypic behaviors.

A dose of 0.675 mmol/kg (155 mg/kg) of **1** killed all mice within 5 min. Within 2–3 min following injection, mice became ataxic and began to show tremor. In the next 1–2 min, mice exhibited continuous asymmetric clonic convulsions with vocalization and rapidly began to die. The highest dose of **1** which was tolerated without a significant incidence of death was 0.30 mmol/kg.

Compound **2** at 0.675 mmol/kg (164 mg/kg) was also lethal in all mice tested. The chronology of intoxication followed that described above for **1**. Compound **2** appeared slightly less toxic than **1** in that no significant increase in lethality was observed at doses of 0.338 mmol/kg. At this dose, some mice did exhibit tremor and clonic convulsions within 8–10 min after injection. Mice began to recover in about 30 min and were sleeping within 1 h following injection. At a dose of 0.30 mmol/kg, mice exhibited occasional tremor or clonic convulsions during the first 20 min, but after that time most mice began to sleep. A slight but nonsignificant increase in activity shown in Table I at this dose is due to the incidence of seizures.

Although both **1** and **2** were convulsant at the highest doses used, this is the only component of action shared by the two compounds. Only **1** elicited sympathomimetic effects similar to MDA. Characteristics of **1** were its ability to elicit hyperactivity and various stereotypic behaviors. Mice never slept during the course of the experiments following administration of effective doses of **1**.

In contrast, compound **2** appeared inert until convulsant doses were reached. There was no other apparent CNS stimulant effect. No incidence of salivation, exopthalmia, or piloerection was observed. There was no increased incidence of sniffing, grooming, or exploratory behavior. Indeed, mice seemed depressed and slept apart during most of the experiments. At the highest tolerated dose of **2** (0.338 mmol/kg), following cessation of seizures, mice fell asleep. At the end of the experiment and transfer to their home cages, these mice rapidly returned to sleep and did not explore as did all other treatment groups, including saline.

Based on these observations, we tentatively classify compound **1** as MDA-like in action in mice. It increases spontaneous activity and elicits behavioral effects characteristic of MDA and other sympathomimetic agents. Depending on the behavioral measures used, its potency is approximately one-tenth to three-fourths that of MDA. Compound **2** presents a completely different profile. Mice given this agent appear sedated and sleep unless given a dose of 0.30 mmol/kg or higher. At these high doses the compound appears to be a "pure" convulsant. It elicits no other apparent symptoms of CNS activation.

In addition to the steric argument presented earlier, which we favor, two alternate explanations were considered for the observed results. (1) Addition of successive methyl groups might produce regular decrements in activity by some undefined mechanism. The lack of MDA-like activity for **2**, even at near-convulsant doses, seems to argue against this possibility. (2) Since **2** contains a more acid-labile acetonide moiety, it may be cleaved in vivo before significant concentrations can be reached in the brain. As one attempt to resolve this question, a 0.10 M solution of **2** in D_2O was prepared (pH 5.3). The ^1H NMR spectra of the solution, freshly prepared and after standing for 24 h at 37 °C, were identical, indicating no hydrolysis. Although it is possible that an enzyme-mediated hydrolysis

could occur, such metabolism would have to be specific for **2** and not occur with **1**. This seems unlikely.

Another point concerns the lipid solubility of these compounds. The optimum log *P* value (octanol–water) for psychotomimetic phenethylamine derivatives appears to be about 3.[17] This is similar to the optimum for serotonin agonist effects in a smooth-muscle preparation.[18] The log *P* for MDA is 1.64.[18] By additivity principles, addition of successive methyl groups would increase this to about 2.1 and 2.6 for **1** and **2**, respectively. If activity were to be predicted based solely on this parameter, one would expect both **1** and **2** to be considerably more active than MDA. Thus, the apparent lack of activity of **2**, especially considering the likelihood that brain levels are much higher than for MDA, seems even more dramatic.

We point out that compound **1** was tested as a mixture of diastereomers and their enantiomers, that is, as a mixture comprised of four isomers. We have so far been unsuccessful in resolving the diastereomers, although attempts are underway to do this. However, resolution of these isomers, and subsequent proof of absolute configuration for the chiral center at C(2) in the dioxole ring for the active isomer(s), does not alter our hypothesis that one face of the molecule must be free of steric interference. That much seems clear from the present work. Rather, it will allow us to determine the relative binding orientation for the aromatic substituents.

In view of the complex pharmacology of MDA,[19] which is unlike other hallucinogens,[20] it seemed inadvisable to attempt detailed pharmacological studies on the mixture of isomers in **1**. It is clear from this study that the mixture of isomers does elicit all of the characteristic behavioral effects which are produced by MDA in mice,[19] while **2** only elicits convulsions at high doses.

While there perhaps may be alternate explanations for the observed biological activities, the data are consistent with the hypothesis that one face of the molecule must be sterically unhindered to remain accessible for receptor interaction. Such an idea could account for the lack of activity in other psychotomimetic amphetamine analogues which possess bulky substituents attached to the aromatic ring.[4]

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 instrument and are reported in δ values (ppm) relative to an internal standard of tetramethylsilane. Elemental analyses were performed by the microanalysis laboratory, Chemistry Department, Purdue University, and were within ±0.4% of the calculated values.

2-Methyl-1,3-benzodioxole (4). Using a modification of the method of Croxall et al.,[12] 110 g (1.0 mol) of catechol, 255.3 g (2.8 mol) of vinyl acetate, 1 g of HgO (yellow), and 4 mL of $BF_3{\cdot}Et_2O$ were stirred together in 1 L of dry toluene under N_2 for 12 h. The reaction mixture was extracted with 3 × 200 mL of 0.5 N NaOH and dried (K_2CO_3). The solvent was removed under vacuum and the residue distilled to yield 79 g (58%) of the desired product: bp 67–68 °C (11 mmHg), lit.[8] bp 88 °C (24 mm); ^{1}H NMR ($CDCl_3$) δ 1.64 (d, 3, CH_3, J = 5 Hz), 6.28 (q, 1, CH), 6.84 (s, 4, Ar H).

5-(Acetoxymethyl)-2-methyl-1,3-benzodioxole (5). A mixture of 20 g (0.147 mol) of **4** and 75.75 g (0.84 mol) of $ClCH_2OCH_3$ was stirred in 1.4 L of AcOH at 45 °C. The reaction was allowed to proceed overnight and under N_2. The mixture was cooled and the volume was reduced to about one-half under vacuum. To the mixture was added 45 g (0.46 mol) of KOAc and this mixture was heated to reflux for 2 h. The excess AcOH was removed under vacuum. The residue was taken up into Et_2O and filtered. The filtrate was then washed with 0.5 N NaOH. Initially this produced a heavy black emulsion, which made extraction tedious and difficult. When the addition of 0.5 N NaOH no longer gave emulsion, the Et_2O phase was dried ($MgSO_4$). The solvent was removed under vacuum to give 11.8 g (38.5%) of crude **5**, which was vacuum distilled: bp 80–81 °C (0.15 mm); ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 3, CH_3, J = 5 Hz), 2.08 (s, 3, CH_3), 5.07 (s, 2, CH_2), 6.33 (q, 1, CH), 6.87 (s, 3, Ar H). Anal. ($C_{11}H_{12}O_4$) C, H.

5-(Hydroxymethyl)-2-methyl-1,3-benzodioxole (6a). To a solution of 7.7 g (0.14 mol) of KOH in 300 mL of MeOH was added 5.69 g (0.027 mol) of **5**. The reaction mixture was stirred at room temperature for 14 h. The solvent was removed under vacuum and the product partitioned between Et_2O and H_2O. The Et_2O layer was washed with H_2O and dried ($MgSO_4$). Removal of the solvent gave a quantitative yield of **6a**: bp 87–89 °C (0.1 mm); ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 3, CH_3), 2.33 (br s, 1, OH), 4.58 (s, 2, CH_2), 6.31 (q, 1, CH), 6.80 (s, 3, Ar H). Anal. ($C_9H_{10}O_3$) C, H.

5-Formyl-2-methyl-1,3-benzodioxole (7). To a solution of 6.32 g of **6a** in 150 mL of C_6H_6 was added 22.8 g of activated MnO_2. The mixture was heated to reflux under N_2 for 20 h with continuous water removal. The reaction mixture was cooled and filtered (Celite), and the filtrate was concentrated under vacuum. The residual oil (4.80 g, 77%) was vacuum distilled to give pure **7**: bp 68 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 3, CH_3), 6.44 (q, 1, CH), 6.93 (d, 1, Ar H), 7.47 (d + s, 2, Ar H), 9.93 (s, 1, CHO). Anal. ($C_9H_8O_3$) C, H.

1-(2-Methyl-1,3-benzodioxol-5-yl)-2-nitropropene (9). A mixture of 0.82 g (5 mmol) of **7**, 3.75 mL of $EtNO_2$, and 0.2 g (3 mmol) of NH_4OAc was heated to reflux under N_2 for 8 h. The excess $EtNO_2$ was removed under vacuum and the resulting brown residue was taken up into MeOH–H_2O and cooled to 0 °C to yield the desired nitro compound as light-yellow needles: mp 36 °C; yield 0.59 g (53.5%). An analytical sample was recrystallized from hexane: ^{1}H NMR ($CDCl_3$) δ 1.69 (d, 3, CH_3), 2.45 (s, 3, CH_3), 6.38 (q, 1, CH), 6.93 (d, 3, Ar H), 8.1 (s, 1, =CH). Anal. ($C_{11}H_{11}NO_4$) C, H, N.

1-(2-Methyl-1,3-benzodioxol-5-yl)-2-aminopropane Hydrochloride (1). The nitro compound **9** was reduced with LAH in Et_2O in the usual way. A dry solution of the free base in Et_2O was carefully neutralized with 5% HCl–Et_2O. The white solid thus obtained (40%) was recrystallized from acetone: mp 137–139 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 3, CH_3), 1.63 (d, 3, CH_3), 2.90 (m, 2, CH_2), 3.43 (m, 1, CH), 6.25 (q, 1, CH), 6.72 (s, 3, Ar H), 8.5 (br s, 3, NH_3^+). Anal. ($C_{11}H_{16}ClNO_2$) C, H, N.

2,2-Dimethyl-5-formyl-1,3-benzodioxole (8). Following the procedure described for the preparation of **7**, 4.5 g (0.025 mol) of 2,2-dimethyl-5-(hydroxymethyl)-1,3-benzodioxole[16] was oxidized to the aldehyde with 15 g of activated MnO_2. The crude aldehyde was vacuum distilled to yield 2.91 g (65.4%) of pure product: bp 70–71 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 6, CH_3), 6.92 (d, 1, Ar H), 7.44 (d + s, 2, ArH), 9.96 (s, 1, CHO). Anal. ($C_{10}H_{10}O_3$) C, H.

1-(2,2-Dimethyl-1,3-benzodioxol-5-yl)-2-nitropropene (10). Following the procedure described above for **9**, 0.89 g (5 mmol) of **8** was converted into 0.81 g (68.9%) of the desired nitro compound. A sample recrystallized from hexane had mp 60 °C; ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 6, CH_3), 2.52 (s, 3, CH_3), 6.97 (br s, 3, Ar H), 8.17 (s, 1, =CH). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

1-(2,2-Dimethyl-1,3-benzodioxol-5-yl)-2-aminopropane Hydrochloride (2). As described for the preparation of **1**·HCl, 0.79 g (3.4 mmol) of **10** was reduced with LAH, and the HCl salt was prepared as above. The salt was recrystallized from *i*-PrOH–Et_2O to give 0.48 g (69%): mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3, CH_3), 1.65 (s, 6, CH_3), 2.87 (m, 2, CH_2), 3.47 (m, 1, CH), 6.68 (s, 3, Ar H), 8.25 (br s, 3, NH_3^+). Anal. ($C_{12}H_{17}ClNO_2$) C, H, N.

Pharmacology. Adult male Swiss Webster mice weighing 20–30 g were housed ten to a cage and supplied with food and water ad libitum for 1 week prior to use. Animals were maintained on a 12-h light–dark cycle (0600 on; 1800 off). All testing was begun at 1400 h. The drugs (±)-MDA·HCl, (±)-**1**·HCl, and (±)-**2**·HCl were administered intraperitoneally in a volume of sterile saline equal to 0.1 mL per 10 g of body weight. Mice were divided into groups of three and placed into circular photocell activity cages (Woodard Research Corp., Herndon, VA), where they remained for the duration of the experiment. Activity counts recorded over the 90 min following injection were totaled and divided by 90 to give an "average" counts per minute value for ease of data handling. Treatments were compared to saline using

the grouped Student's t test. Behavioral observations were made during the course of these experiments.

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Structure–Activity Relationship of Aniline Mustards Acting against B-16 Melanoma in Mice[1]

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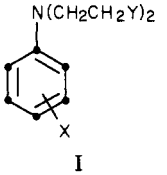
A set of 23 aniline mustards [X-$C_6H_4N(CH_2CH_2Cl)_2$] have been tested for their activity against B-16 melanoma in mice. The following quantitative structure–activity relationship (QSAR) correlates the data well: $\log 1/C = -2.06\sigma - 0.15\pi - 0.13\pi^2 + 4.13$ ($r = 0.936$). When this equation is compared with those formulated for aniline mustards acting against leukemia, it is found that $\log P_0$ (ideal lipophilicity) is higher for solid tumors. The QSAR brings out the unique activity of phenylalanine aniline mustard.

In studying the structure–activity relationships of various types of drugs acting against leukemia, we have been struck by the fact that the more effective anti-leukemia drugs appear to be unusually hydrophilic.[2] It is our belief that for solid tumors the more hydrophobic drugs in a given series should be more effective; that is, there is evidence in hand that $\log P_0$ will be higher for solid tumors than for leukemias. If our present evidence can be extended and generalized, this will be of great importance to those attempting to design better antitumor agents. The aniline mustards (I), which are widely used



I

in cancer chemotherapy, provide a good system for a study of this problem.

Equation 1 correlates the percent hydrolysis (reaction

% hydrolysis in 30 min at 66 °C in 50:50 acetone–water

$$\log \%\ \text{hyd} = -1.42\sigma + 0.45I_0 + 0.70I_{Br} + 1.21 \quad (1)$$

$$n = 42;\ r = 0.952;\ s = 0.157$$

with a nucleophile) of congeners of type I under standard conditions.[3] This equation, from the work of Ross, can be compared with eq 2 and 3 for the antitumor activity of

T/C 125 L-1210 leukemia in mice

$$\log 1/C = -0.31\pi - 0.96\sigma + 0.86I_0 + 4.07 \quad (2)$$

$$n = 19;\ r = 0.926;\ s = 0.315$$

T/C 180 P-388 leukemia in mice

$$\log 1/C = -0.34\pi - 1.39\sigma + 0.30I_0 + 4.15 \quad (3)$$

$$n = 16;\ r = 0.914;\ s = 0.311$$

other sets of aniline mustards[3] acting as antitumor agents. In eq 2 and 3, C is the molar concentration (mol/kg) producing a 25% (T/C 125) increase in life span of the mice. The indicator variable I_0 takes the value of 1 when ortho substituents are present and zero for all other cases. I_{Br} takes the value of 1 when Y of structure I is Br and zero when Y is Cl; that is, Br is the better leaving group for nucleophilic substitution. The coefficients with σ in eq 2 and 3 are in reasonable agreement with eq 1, suggesting that Ross' nucleophilic substitution model is a good one for predicting the electronic effect of substituents on the in vivo activity in chemotherapy. A most interesting feature of eq 2 and 3 is that both contain equivalent terms in π, each having a negative coefficient. Since adding a term in π^2 does not improve these two equations, this suggests that $\log P_0$ is lower than the lowest $\log P$ of any aniline mustard in these two sets (i.e., greater than −1.00 when X = $NH_3^+CHCH_2COO^-$). However, this point needs further study (see Discussion).

In the development of eq 2 and 3 and in our recent study,[3] we have used π for the neutral form of $(CH_2)_nCOOH$ even though carboxylic acids are almost

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