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Experimental Antiulcer Drugs. 2. 2-Substituted 2,4,5,6-Tetrahydro-1,3,4,6,6-pentamethylcyclopenta[*c*]pyrrole-4-carboxamides[1]

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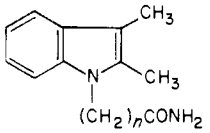
Condensation of a 1-substituted 2,5-dimethylpyrrole **6** with 2 mol of 2-amino-2-methylpropionitrile in hot acetic acid yielded a 2-substituted 2,4,5,6-tetrahydro-1,3,4,5,6,6-pentamethylcyclopenta[*c*]pyrrole-4-carbonitrile (**4**). Hydrolysis of the nitriles to the amides gave a group of compounds which were active as antisecretory agents in the pyloric-ligated rat. Outstanding in this respect was the 2-phenyl derivative **5b**, the most active compound in the series. It did not possess anticholinergic properties. In contrast to the indoles and pyrroles reported earlier, **5b** demonstrated marked activity in blocking gastric acid secretion in the histamine-stimulated dog.

In the first paper of this series[2] we reported the gastric antisecretory activity of 2,3-dimethylindole-1-alkanamides (**1**) and 2,3,4,5-tetramethylpyrrole-1-acetamide (**2**) in the pyloric-ligated rat and the lack of gastric antisecretory activity of this class of compounds in the histamine-stimulated dog. A candidate antiulcer drug should have demonstrated activity in at least two species[3] and thus we continued our efforts to solve the problem of the lack of carryover of activity from the rat to the dog in this class of compounds.

The fact that the length of the alkanamide chain could be varied (n = 1, 2, or 3 in **1**) without an appreciable change



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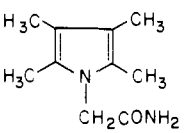
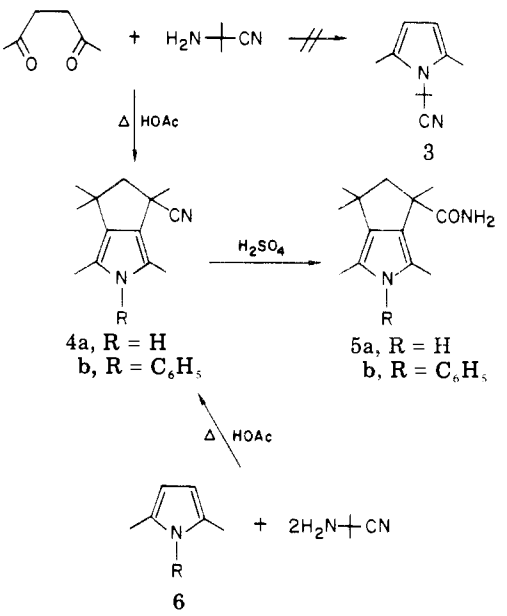


2

in the antisecretory activity suggested that the activity of these compounds was mediated by 2,3-dimethylindole, a theoretical metabolite of all the indole-1-alkanamides. N-Dealkylation is a common metabolic transformation[4] and probably results from enzymatic hydroxylation at the carbon atom adjacent to the nitrogen atom, followed by spontaneous cleavage of the resulting carbinolamine. 2,3-Dimethylindole was found to be active in the rat but appeared to be considerably less active than the parent amides and was only modestly active in the dog. We therefore turned our attention to the construction of indole and pyrrole derivatives with a metabolically stable alkanamide side chain.

An obvious candidate structure is one in which hydroxylation is blocked by replacement of the presumably metabolically labile hydrogen atoms by methyl groups. With the objective of preparing an example of this structural type in the pyrrole series, we attempted the condensation of 2,5-hexanedione with 2-amino-2-methylpropionitrile in hot acetic acid in the hope of obtaining **3** (Scheme I). The reaction took an unexpected course and resulted instead in the formation of the cyclopentapyrrolecarbonitrile **4a**. The same product resulted

Scheme I



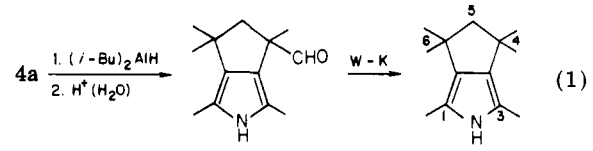
upon condensation of 2,5-dimethylpyrrole (**6**, R = H) with 2-amino-2-methylpropionitrile. Although the corresponding carboxamide **5a** was not active in the rat, the *N*-phenyl derivative **5b** proved to be highly active in this species (Table I). Furthermore, compound **5b** was effective in blocking histamine-induced gastric acid secretion in the dog in contrast to **1** and **2** which are inactive in this model. We were encouraged, therefore, to investigate the chemistry and structure–activity relationships in the cyclopentapyrrole-4-carboxamide series.

Chemistry. The structure of the cyclopentapyrrole **4a** was supported by its spectral data, in particular the NMR spectrum. Confirmation of the structural assignment was provided by conversion to the aldehyde **7** (eq 1), followed by Wolff–Kishner reduction to the hexamethylcyclopentapyrrole **8** whose NMR spectrum showed the presence of the four equivalent methyl groups at C-4 and C-6. A pathway to the cyclopentapyrroles may be written if it is

Table I. Gastric Antisecretory Activity in the Pyloric-Ligated Rat

Compd	R (5)	pH[a]	Mp, °C	Formula[b]	Recrystn solvent	Yield, %
		1.1				
5a	H	1.4	230–233	$C_{13}H_{20}N_2O$	EtOAc	43
5b	C_6H_5	6.2	141–143	$C_{19}H_{24}N_2O$	n-C_7H_{16}-Et_2O	93
10	2-ClC_6H_4	1.1	181–183	$C_{19}H_{23}ClN_2O$	MeOH	25
11	3-ClC_6H_4	1.1	139–142	$C_{19}H_{23}ClNO_2$	MeCN	49
12	4-ClC_6H_4	1.2	165.5–167.5	$C_{19}H_{23}ClN_2O$	MeCN	57
13	2-$CH_3C_6H_4$	1.0	159–161	$C_{20}H_{26}N_2O$[c]	MeOH	30
14	3-$CH_3C_6H_4$	1.2	149.5–151.5	$C_{20}H_{26}N_2O$	MeOH	48
15	4-$CH_3C_6H_4$	1.1	198–202	$C_{20}H_{26}N_2O$	MeCN	58
16	4-FC_6H_4	1.4	150–151	$C_{19}H_{23}FN_2O$	MeCN	65
17	$C_6H_5CH_2$	1.0	170–171	$C_{20}H_{26}N_2O$	EtOAc	88
18	CH_3	4.2	184.5–187.5	$C_{14}H_{22}N_2O$	EtOAc	85
19	CH_3CH_2	4.8	162–164	$C_{15}H_{24}N_2O$	EtOAc	44
20	$CH_3(CH_2)_2$	5.3	164.5–166.5	$C_{16}H_{26}N_2O$	i-PrOH	92
21	$CH_3(CH_2)_3$	2.5	135–137	$C_{17}H_{28}N_2O$[d]	Cyclohexane	40
22	$(CH_3)_2CH$	1.8	156–158	$C_{16}H_{26}N_2O$	Cyclohexane	41
23	c-C_3H_5	3.7	188–192	$C_{16}H_{24}N_2O$	n-C_7H_{16}	78
24	c-C_4H_7	2.2	149–152	$C_{17}H_{25}N_2O$[e]	n-C_5H_{12}	55
25	c-C_5H_9	1.3	152–155	$C_{18}H_{28}N_2O$	n-C_5H_{12}	76
26	c-C_3H_5-CH_2	5.1	150–153	$C_{17}H_{26}N_2O$	EtOH-H_2O	47
Cimetidine[f]		2.1				

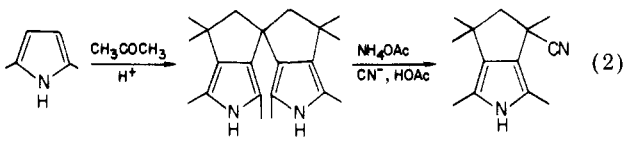
[a] pH of gastric contents after administration of the drug at 100 mg/kg po 1 h prior to the 5-h pyloric-ligation period. [b] Elemental analyses were within 0.4% of the calculated values unless otherwise noted. [c] C: calcd, 77.38; found, 76.05. [d] C: calcd, 73.87; found, 73.24. [e] C: calcd, 74.68; found, 74.16. [f] Reference 6.



7 8 (1)

assumed that 2-amino-2-methylpropionitrile functions as a source of acetoneimine and acetoneenamine in hot acetic acid by loss of cyanide ion which, itself, participates in the final step of the sequence. Acetone, ammonium acetate, and cyanide could be substituted for 2-amino-2-methylpropionitrile but the yields of cyclopentapyrrole were lower and increased amounts of tarry by-products were formed.

Formation of a cyclopentapyrrole under these conditions is reminiscent of Treibs' observation[5] of the acid-catalyzed condensation of excess acetone with 2,5-dimethylpyrrole to give the spiro[cyclopentapyrrole] **9** (eq 2).



9 4a (2)

Indeed, we have shown that **9** is converted to the cyclopentapyrrole **4a** in the presence of ammonium acetate and cyanide in hot acetic acid and have also demonstrated the appearance and eventual disappearance of spiro[cyclopentapyrroles] (e.g., **9**) during condensations which ultimately led to the cyclopentapyrroles **4** in good yield. Substitution of mesityl oxide for acetone resulted in the formation of only trace amounts of **4a**, a result which contrasts with Treibs' report[5] that mesityl oxide may replace acetone in the synthesis of the spiro[cyclopentapyrroles]. We cannot rule out the possibility that some derivative of mesityl oxide may be an intermediate in the formation of **4** but we believe that the main course of the reaction involves the stepwise attachment of acetone units to the pyrrole nucleus.

All the 2-substituted cyclopentapyrrole-4-carboxamides listed in Table I were prepared by the following three-step sequence: (1) condensation of an amine with 2,5-hexanedione to give an N-substituted 2,5-dimethylpyrrole **6**, (2) formation of the cyclopentapyrrole **4** by condensation of **6** with 2 mol of 2-amino-2-methylpropionitrile in hot acetic acid, and (3) hydrolysis of **6** in 91% sulfuric acid at 0–5 °C to the carboxamides **5**.

Discussion

In Table I are summarized the results of the evaluation of a selected group of cyclopentapyrroles at 100 mg/kg po in the pyloric-ligated rat. pH's of less than 2 are considered to indicate that the compound tested is inactive in this series. Interestingly, the H_2-receptor blocker cimetidine[6] does not have an appreciable effect on pH in the 5-h pyloric-ligated rat at the dose tested in comparison with the most active cyclopentapyrroles.

The most active compound in the series is the 2-phenyl derivative **5b**. Administration of **5b** at the screening dose resulted in a pH greater than 6. Substitution of a methyl or chlorine atom at any one of the three open positions of the benzene ring resulted in the complete loss of antisecretory activity in this test system (**10–15**). Although a number of active compounds resulted when the R group at position 2 was changed to a small aliphatic substituent (**18–21, 23, 24, 26**), none of them was as active as **5b** in the rat.

In contrast to the indole- and pyrrole-1-alkanamides, the cyclopentapyrrole-4-carboxamides inhibited histamine-induced gastric acid secretion in the dog and were only modestly emetic in the dog. The carryover of activity from the rat to the dog may be related to the presence of a metabolically stable alkanamide group attached to a pyrrole nucleus. The results of the evaluation of compound **5b** in the pyloric-ligated rat and in the histamine-stimulated dog are shown in Tables II and III. In both assay systems the drug effected a dose-related decrease in the volume and total acidity of gastric secretion and a dose-related increase in the pH of the secretions.

The following results suggest that **5b** does not possess significant anticholinergic properties: (1) it did not induce mydriasis in mice; (2) there was no effect on the carbamylcholine-induced depression of heart rate of the guinea pig auricle in vitro; and (3) there was no effect on the carbamylcholine-induced constriction of guinea trachea in vitro.[7]

Table II. Effect of 5b in the 5-h Pyloric-Ligated Rat[a]

		Gastric secretions			
				Total acid output	
Dose,[b] mg/kg po	No. of rats	pH ± SE	Vol, mL/100 g ± SE	mequiv/L per rat ± SE	% inhibn
0	39	1.07 ± 0.01	4.05 ± 0.21	117 ± 2	0
12.5	5	1.34 ± 0.12[c]	2.66 ± 0.12[d]	69 ± 4[d]	41
25	15	1.83 ± 0.21[d]	2.16 ± 0.21[d]	56 ± 7[d]	52
50	15	3.28 ± 0.45[d]	1.66 ± 0.18[d]	29 ± 7[d]	75
100	15	6.40 ± 0.25[d]	1.19 ± 0.14[d]	0[d]	100

[a] Mean data from several experiments. [b] Administered as a single dose 2 h prior to pyloric ligation. [c] Significantly different from control mean, $p \leq 0.05$. [d] Significantly different from control mean, $p \leq 0.01$.

Table III. Effect of 5b on Histamine-Induced Gastric Secretions in the Dog

	Gastric secretions[a]			
			Total acid output	
Dose,[b] mg/kg po	pH	Vol, mL/15 min	mequiv/L per dog	% inhibn
0	1.0	14.7	2.13	0
1.6	1.2	11.9	1.09	49
3.1	1.8	3.8	0.35	84
6.2	3.9	2.0	0.10	95
12.5	4.7	4.8	0.25	88
25	6.7	2.4	0.14	93

[a] Average of five determinations taken at 15-min intervals 16 min after injection of 0.04 mg/kg of histamine dihydrochloride calculated as the base. Six to eight dogs were used at each dose level. [b] Drug was administered 18 and 2 h prior to injection of histamine.

Compound **5b** was evaluated in vitro for its effect on the histamine response of guinea pig atria and found to be at best weakly active when compared to the H_2-receptor antagonist metiamide.[7,8]

The results of our investigations of the chemistry and structure–activity relationships of the cyclopentapyrroles will be reported in future papers in this series.

Experimental Section

NMR spectra supplemented by MS and IR spectra were used to aid in the characterization of all new compounds. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. The structures of the intermediate 2-substituted 2,5-dimethylpyrroles 6 and cyclopentapyrroles 4 were checked by examination of their NMR spectra and, without further characterization, converted to the corresponding carboxamides listed in Table I. The pyrroles 6 were prepared by condensation of 2,5-hexanedione with the appropriate amine in benzene or toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid under a Dean–Stark water separator.

2,4,5,6-Tetrahydro-1,3,4,6,6-pentamethylcyclopenta[*c*]pyrrole-4-carbonitrile (4a). A solution of 9.5 g (0.1 mol) of 2,5-dimethylpyrrole, 18.6 g (0.22 mol) of 2-amino-2-methylpropionitrile, 16 mL of trifluoroacetic acid, and 75 mL of AcOH was refluxed for 1 h. The reaction mixture was poured into ice–water and the brown solid collected and dissolved in ether. Concentration of the dried (Na_2SO_4) solution left 13 g (64%) of crude product. Recrystallization from CH_3CN and subsequent sublimation at 130 °C (0.02 mm) furnished the analytical sample: mp 150.5–152.5 °C (sealed evacuated capillary); UV max (95% EtOH) 220 nm (ε 6392); IR (KBr) 3340 and 2230 cm^{-1}; NMR ($CDCl_3$) 1.31 (3 H, s), 1.37 (3 H, s), 1.63 (3 H, s), 2.20 (3 H, s), 2.21 (2 H, d, J = 13 Hz), 2.25 (3 H, s), 2.7 (2 H, d, J = 13 Hz), 7.5–7.9 (1 H, br); mass spectrum m/e 202 (M^+), 187, 160. Anal. ($C_{13}H_{18}N_2$) C, H, N.

2,4,5,6-Tetrahydro-1,3,4,6,6-pentamethylcyclopenta[*c*]pyrrole-4-carboxaldehyde (7). A suspension of 83 g (0.41 mol) of nitrile 4a in 400 mL of absolute toluene was cooled to <5 °C with an ice–MeOH mixture under argon. Diisobutylaluminum hydride in toluene (24.1% by weight, 250 g, 0.424 mol, Texas Alkyls) was added over 15 min with stirring and continued cooling. The clear solution was allowed to come to ambient temperature and stirred for 4 h. The mixture was cooled to 0 °C and at 0–5 °C were added, dropwise with stirring, 140 mL of MeOH, 600 mL of 40% AcOH, and finally 400 mL of 20% AcOH. The eventually clear, pale brown solution was stirred at room temperature overnight. The organic layer was separated and the aqueous phase extracted repeatedly with Et_2O. The combined organic fractions were washed (H_2O, saturated $NaHCO_3$, and brine), dried ($MgSO_4$), and evaporated to dryness under vacuum to afford 84 g (100%) of the aldehyde 7, mp 116–119 °C. This material was free of nitrile (IR, $CHCl_3$) and sufficiently pure (TLC) for further reactions. It is unstable under nitrogen at 0–5 °C. A sample was recrystallized from C_6H_{12}: mp 116–119 °C; IR ($CHCl_3$) 3450 and 1710 cm^{-1}; NMR ($CDCl_3$) 1.31 (3 H, s), 1.37 (3 H, s), 1.40 (3 H, s), 2.00 (1 H, d, J = 14 Hz), 2.08 (3 H, s), 2.17 (3 H, s), 2.58 (1 H, d, J = 14 Hz), 7.5–7.9 (1 H, br), 9.58 (1 H, s).

2,4,5,6-Tetrahydro-1,3,4,4,6,6-hexamethylcyclopenta[*c*]pyrrole (8). The aldehyde 7 (20.5 g, 0.1 mol) was reduced by the Huang-Minlon modification of the Wolff–Kishner procedure using 19 g (0.29 mol) of KOH, 16.5 mL (0.28 mol) of 85% hydrazine hydrate, and 165 mL of triethylene glycol. A major portion of the product (13.5 g) sublimed into the condenser at the initial reflux temperature (130 °C). The crude product (18.5 g) was purified by sublimation at 80 °C (0.01 mm) to give 14.8 g (76%) of 7: mp 144–146 °C (sealed evacuated capillary); UV max (95% EtOH) 210 nm (ε 3890); NMR ($CDCl_3$) δ 1.31 (12 H, s), 2.10 (2 H, s), 2.17 (6 H, s), 7.20 (1 H, br). Anal. ($C_{13}H_{21}N$) C, H, N.

2,4,5,6-Tetrahydro-1,3,4,6,6-pentamethyl-2-phenylcyclopenta[*c*]pyrrole-4-carbonitrile (4b). To a stirred solution of 1-phenyl-2,5-dimethylpyrrole (200 g, 1.17 mol) and 2-amino-2-methylpropionitrile (220 g, 2.62 mol) in 800 mL of AcOH was added over 10 min 173 mL of trifluoroacetic acid. The temperature rose to 60 °C. The mixture was refluxed for 3.5 h. After cooling 500 mL of $CHCl_3$ was added and the solution poured into 1.5 L of cold H_2O. The organic layer was separated and washed (H_2O, dilute NH_4OH). The dried ($MgSO_4$) filtrate was evaporated under vacuum to give a dark oil which yielded, after one crystallization from 500 mL of *i*-PrOH and one trituration with 300 mL of *i*-PrOH, 165 g (50.5%) of tan product, mp 115–117 °C. A second crop of 45 g (13.8%) melted at 114–115 °C. Recrystallization from MeOH gave the analytical sample: mp 115–117.5 °C; UV max (95% EtOH) 233.5 nm (ε 9150); IR (KBr) 2210 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (3 H, s), 1.43 (3 H, s), 1.70 (3 H, s), 1.93 (3 H, s), 2.03 (3 H, s), 2.28 (1 H, d, J = 7 Hz), 7.0–7.7 (5 H, m). Anal. ($C_{19}H_{22}N_2$) C, H, N.

2,4,5,6-Tetrahydro-1,3,4,6,6-pentamethyl-2-phenylcyclopenta[*c*]pyrrole-4-carboxamide (5b). The nitrile 4b (400 g, 1.44 mol) was added in portions over 45 min to a stirred solution of H_2SO_4 (1.24 L, 2.28 mol) in H_2O (124 mL, 6.9 mol) at <5 °C. The reaction mixture was stirred at 25 °C for 8 h. The solution was poured into 16 L of a stirred ice–H_2O mixture and extracted with Et_2O (2 × 8 L). The combined Et_2O extracts were washed with H_2O (10 L), 10% NaOH (2 × 8 L), and H_2O until the wash became neutral. The dried (K_2CO_3) solution was treated with charcoal and concentrated to dryness under vacuum. The residue was slurried in 3 L of heptane, filtered, and washed with cold heptane to furnish 385 g (90.5%) of white product, mp 141–143 °C. The analytical sample was dried at 60 °C (20 mm) overnight:

mp 142–143.5 °C; UV max (95% EtOH) 243.5 nm (ε 13 820); IR (KBr) 1672 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.37 (3 H, s), 1.57 (3 H, s), 1.97 (3 H, s), 2.00 (3 H, s), 2.23 (1 H, d, J = 13 Hz), 2.73 (1 H, d, J = 13 Hz), 6.0–6.6 (2 H, br), 7.0–7.8 (5 H, m).

Biological Methods. The following test procedures have been described previously:[2] the 5-h pyloric-ligated rat test, the method for measuring inhibition of histamine-induced gastric acid secretion in the dog, the mouse mydriasis test for anticholinergic activity, and the procedure for assessment of H_2-receptor inhibitory activity in vitro.

The effect of **5b** on the response of guinea pig auricles to carbamylcholine was measured in vitro in a Krebs–Henseleit solution at 35 °C. The compound was dissolved in Me_2SO–H_2O and then added to the bath solution. The tissue was exposed to the drug for 5 min. At concentrations of 10^{-6} and 10^{-5} M the compound did not affect the dose-related carbamylcholine-induced decrease in spontaneous heart rate. At higher concentrations the drug precipitated from the bath solution.

In a similar manner the effect of **5b** on the response of guinea pig trachea to carbamylcholine was measured. At a concentration of 10^{-5} M the drug did not affect the dose-related carbamylcholine-induced constriction of the trachea.

References and Notes

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Hydrogen-Bonding Parameter and Its Significance in Quantitative Structure–Activity Studies

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When the relative hydrogen-bonding effect of drugs on phases involved in the binding at the site of biological action differs from that in the 1-octanol–H_2O partitioning phases used as the reference to estimate the hydrophobicity, a parameter (or parameters) which represents the "extra" hydrogen-bonding effect on the biological activity is required in the Hansch-type correlations. As a first approximation, the effect is analyzed in terms of the ratio of hydrogen-bonding association constants and the ratio of molarities of hydrogen-bonding species constituting the biological and organic phases. Sometimes, the association constants in both phases are so similar that they are not important in determining the extra hydrogen-bonding effect. The net result is that the effect is expressible by an indicator variable term the slope of which corresponds to the molarity ratio. The variable only applies to substituents having appreciable association capability in correlating a certain biological action exhibited by a series of congeners.

Quantitative analysis of structure–activity relationships of the Hansch-type assumes that the variation in a certain biological activity expressed as Δ log BR of a series of congeners can be analyzed in terms of variations in their free-energy-related physicochemical parameters, such as π or log P for hydrophobic, σ, σ*, or Δ log K_A for electronic, and E_s, E_s^c, or MV for steric and others.[1]

Although hydrogen bonding has long been recognized as being very important in biological reactions including drug actions, examples where the particular use of hydrogen-bonding parameters as an independent variable is necessary have scarcely been found so far. One of the reasons for such scarcity may stand on the fact that the hydrogen-bonding effect at a certain functional group in congeners is correlated with the electronic effect of substituents. Examples are found in analyses for the Hill reaction inhibition of herbicidal N-substituted phenylamides[2] and the bacteriostatic activity of kojic acid analogues[3] where hydrogen-bonding effects of such functional groupings as –NHCO– and –COC(OH)= on cellular components are anticipated. In fact, the free-energy-related hydrogen bond donating parameter, h_D, defined by Higuchi and co-workers[4] for a series of substituted phenols can be expressed by eq 1. A similar observation was made by Clotman and co-workers for the association equilibrium of substituted phenols with triethylamine.[5] Likewise, the hydrogen-accepting parameter, pK_{HB}, of substituted benzaldehydes has been expressed as eq 2 by Taft and associates.[6] σ^+ correlates better than σ since the site of association is partially electron deficient.

$$h_D = 1.562\ (\pm 0.169)\ \sigma + 0.096\ (\pm 0.064) \quad (1)$$
$$n = 22;\ r = 0.974;\ s = 0.115$$

$$pK_{HB} = -0.456\ (\pm 0.101)\ \sigma^+ + 0.782\ (\pm 0.092) \quad (2)$$
$$n = 5;\ r = 0.993;\ s = 0.061$$

Another line of reasoning may be that the parameter used for the hydrophobicity, log P or π, mostly estimated from the 1-octanol–H_2O partition coefficient, inherently includes the effect of hydrogen bonding. According to Hansch and co-workers, the nonspecific type of protein binding of miscellaneous molecules such as aromatic hydrocarbons, phenols, anilines, and aliphatic alcohols with bovine serum albumin (BSA)[7] and bovine hemoglobin (BHG)[8] is related only to their hydrophobicity defined by the octanol–H_2O partition coefficient. The binding equilibrium constant, log K (K is the reciprocal of the concentration of compound producing a 1:1 complex with protein), is linearly related to log P (octanol–H_2O) without any additional parameter, regardless of the number of hydrogen bonding sites of varying degrees of strength in the molecule as shown in eq 3 and 4. The effect of the relative hydrogen bonding on the octanol–H_2O partitioning is closely similar to that involved in the protein binding. Thus, the net difference in the hydrogen-bonding effect between the partitioning process and drug actions, whose