Anticonvulsant Activity of Substituted Benzoylpyridines

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Abstract □ A series of substituted benzoylpyridines was prepared and evaluated for their ability to prevent convulsions induced by electroshock. Results of regression analysis indicate that electron-releasing substituents enhance anticonvulsant activity in this series. A log P_0 of 2.66 was found, which is near the average value of 2 found for 16 series of hypnotics.

Keyphrases □ Benzoylpyridines, substituted—synthesized as potential anticonvulsants, structure-activity relationships □ Anticonvulsants, potential—synthesis of series of substituted benzoylpyridines, structure-activity correlations □ Structure-activity relationships—series of substituted benzoylpyridines, synthesized as potential anticonvulsants □ Partition coefficients—series of substituted benzoylpyridines, synthesized as potential anticonvulsants

The ability of 4-benzoylpyridine (I) to protect mice from convulsions induced by electroshock prompted the synthesis and study of a series of benzoylpyridines in which the phenyl group was replaced by a variety of alkyl groups (1). While these compounds still possessed anticonvulsant activity, they were less potent than 4-benzoylpyridine (1). In the hope of obtaining more potent compounds, a series of substituted benzoylpyridines was prepared and examined for anticonvulsant activity. The physical constants and analytical data for the compounds from the Grignard reaction are reported in Table I. 4-Nitrobenzoylpyridine was prepared following the procedure of Bryans (2). To gain additional information for structure-activity relationships, the results of the biological evaluation were subjected to regression analysis. For this purpose, the previously reported compound, 4-benzoylpyridine, was included in the analysis (1).

EXPERIMENTAL[1]

Melting points were determined in capillary tubes and are uncorrected. The structures of the compounds were confirmed by their IR and proton magnetic resonance (PMR) spectra. 1-Octanol–water partition coefficients were determined according to published procedures (3) and are the averages of at least three determinations. For some of the compounds, it was necessary that log P be estimated. This was done by taking advantage of the additive-constitutive nature of log P (3). The π values used in the estimations were from the phenoxyacetic acid system (4), with the exception of that for the 4-*tert*-butyl group which was taken from the benzene system (4). The anticonvulsant activities were determined according to Turner (5) and are reported as pC, where C is the concentration (in moles per kilogram) required to protect 50% of the mice from electroshock. Regression analyses were carried out using a nonweighted multiple linear regression program and a computer[2].

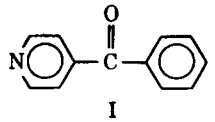
Substituted Benzoylpyridines—To a stirred suspension of 0.10 mole magnesium turnings was added dropwise, with stirring, a solution of 0.10 mole of substituted bromobenzene in 50 ml. of anhydrous ether. It was sometimes necessary to add a crystal of iodine to initiate the reaction. After the addition was completed, the resulting mixture was heated at reflux temperature for 1.5 hr. and then cooled to room temperature. A solution of 5.2 g. (0.05 mole) of 4-cyanopyridine in 100 ml. of anhydrous ether was added dropwise with constant stirring over 1 hr. The reaction mixture was heated at reflux temperature for 24 hr. and then treated with 200 ml. of 10% hydrochloric acid. The aqueous layer was separated, and the ether layer was washed three times with 50-ml. portions of 25% hydrochloric acid.

These washings were added to the aqueous layer, and the combined aqueous phase was made alkaline (pH 8) with 40% sodium hydroxide solution. This alkaline mixture was cooled to room temperature and extracted six times with ether. The ether extracts were combined and dried (sodium sulfate). The amino-ketone was obtained by evaporation of the ether; if solid, it was purified by recrystallization or, if liquid, it was purified by distillation (Table I).

4-Isonicotinylbenzenesulfonamide—To 107.2 g. (0.92 mole) of chlorosulfonic acid, cooled to 10–15°, was added 26.7 g. (0.16 mole) of 4-benzylpyridine in small portions with constant stirring. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was then heated to 70° for 30 min. It was cooled to room temperature and then poured slowly, with stirring, into 600 g. ice in 100 ml. water. The mixture was kept at 0° for 3 hr., during which time a white precipitate formed. This precipitate was filtered, dried, and used without further purification.

The crude product (34.8 g., 0.13 mole) was treated with 75 ml. of ammonium hydroxide solution (28%). After the vigorous exothermic reaction had subsided, the orange mixture was heated over a steam bath for 45 min. At the end of this time, the mixture was cooled to room temperature and 6 *N* hydrochloric acid was added dropwise with constant stirring. At pH ~5, a precipitate formed. The flask was placed in an ice bath, and more hydrochloric acid was added with constant stirring until a pH of 4 was obtained. The mixture was kept at 0° for 2 hr., and the solid precipitate was removed by filtration. Following recrystallization from water–isopropyl alcohol (1:1), 23.2 g. (72%) of a slightly tan solid, m.p. 148–151°, was obtained.

This sulfonamide (4.7 g., 0.019 mole) was treated with potassium permanganate (8.0 g., 0.05 mole) in 200 ml. of water. The reactants were thoroughly mixed and then heated at reflux temperature for 1.5 hr. At this time, an additional 8 g. (0.05 mole) of potassium permanganate was added and heating was continued for 30 min. A final 2-g. (0.012-mole) portion of potassium permanganate was added, and the mixture was heated at reflux temperature for a final 60 min. The mixture was then cooled to room temperature, decolorized with 3–4 drops of alcohol, and filtered. The brown filter cake was digested with 300 ml. of ethanol on a steam bath, cooled to room temperature, and filtered. The alcoholic filtrate was then concentrated under vacuum. A gray crystalline product formed and was recrystallized from ethanol, giving 1.6 g. (32.1%) of white needles, m.p. 185–187°. The initial aqueous filtrate was made neutral with 6 *N* hydrochloric acid and was concentrated to 50 ml. This slightly yellow solution was then placed in an ice bath, and further quantities of 6 *N* hydrochloric acid were added until a precipitate began to appear at pH ~5. The beaker was scratched with a glass rod and placed in the freezer for 60 min. At this time



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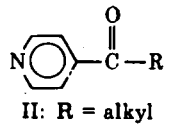
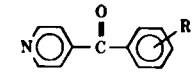


II: R = alkyl

[1] Analyses for carbon, hydrogen, and chlorine were performed by Micro-Tech Laboratories, Skokie, Ill. Analyses for nitrogen were performed with a Coleman automatic nitrogen analyzer.

[2] IBM 370/155.

Table I—4-(Substituted benzoyl) Pyridines



R	Boiling Point or Melting Point	Yield, %	Crystallization Solvent[a]	Formula	Analysis, % Calc.	Found
4-F	81–84°	67	A	$C_{12}H_8FNO$	C 71.64	71.69
					H 3.98	4.09
					N 6.97	7.00
3-CF_3	116–117°[b]	40	A	$C_{13}H_8ClF_3NO$	C 54.26	54.58
					H 3.13	3.41
					N 4.87	4.69
2-OH	76–77°	44	B	$C_{12}H_9NO_2$	C 72.36	72.41
					H 4.52	4.41
					N 7.04	7.02
2-OCH_3·HCl	215–218°[b]	60	A	$C_{13}H_{12}ClNO_2$	C 62.53	62.46
					H 4.81	4.87
					Cl 14.23	14.35
					N 5.61	5.70
4-OCH_3	118–120°[c]	64	A	$C_{13}H_{11}NO_2$	C 73.24	73.36
					H 5.16	5.21
					N 6.57	6.81
4-CH_3	93–95°	51	A	$C_{13}H_{11}NO$	C 79.19	79.05
					H 5.58	5.58
					N 7.11	7.25
2-CH_3	113–115°(0.07)	65		$C_{13}H_{11}NO$	C 79.19	78.92
					H 5.58	5.87
					N 7.11	7.24
2,5-$(CH_3)_2$·HCl	176–178°[b]	54	A	$C_{14}H_{14}ClNO$	C 67.88	67.62
					H 5.66	5.75
					Cl 14.34	14.19
					N 5.66	5.66
4-$(CH_3)_3$-C	62–64°	44	A	$C_{16}H_{17}NO$	C 80.33	80.32
					H 7.11	7.25
					N 5.86	5.97

[a] A = ethanol, and B = 2-propanol. [b] Isolated as the hydrochloride. [c] H. Marxer, *Helv. Chem. Acta*, **52**, 262(1969), reported a melting point of 118–122°.

the mixture was filtered and the solid was air dried for 3 hr. and then recrystallized from ethanol to yield an additional 1.5 g. (total yield 61.7%) of white needles, m.p. 184–187.5°.

Anal.—Calc. for $C_{12}H_{10}N_2O_3S$: C, 54.96; H, 3.82; N, 10.69. Found: C, 54.60; H, 3.51; N, 10.42.

RESULTS AND DISCUSSION

Attempts to correlate the anticonvulsant activity of the substituted benzoylpyridines with various physicochemical parameters are summarized in Eqs. 1–3:

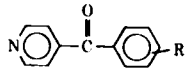
$$pC = 2.84(\pm0.49) + 0.15(\pm0.20)\log P$$
$$n = 13\ s = 0.26\ r = 0.46 \quad \text{(Eq. 1)}$$

$$pC = 2.17(\pm0.79) + 0.80(\pm0.68)\log P - 0.14(\pm0.14)(\log P)^2$$
$$n = 13\ s = 0.22\ r = 0.69 \quad \text{(Eq. 2)}$$

$$pC = 2.37(\pm0.64) - 0.35(\pm0.28)\sigma + 0.77(\pm0.54)\log P - 0.14(\pm0.11)(\log P)^2$$
$$n = 13\ s = 0.18\ r = 0.84\ \log P_0 = 2.66(2.16 \text{ to } 4.22) \quad \text{(Eq. 3)}$$

In these equations, n is the number of compounds used to derive each equation, s is the standard deviation of the regression, and r is the correlation coefficient. The reduction in variance that results from addition of the Hammett σ constant to Eq. 2 is significant at the 95% level of confidence; $F_{1,9} = 7.932$, $F_{1,9,\alpha 0.05} = 5.117$. Although the correlation of Eq. 3 is not exceedingly sharp, the "unexplained" variance is small (0.27) and is probably due mainly to experimental error. The values in parentheses are 95% confidence intervals on the coefficients that they follow. For the derivatives of this study, there is no interrelationship between the independent variables (r^2 for correlation of log P with σ is 0.102). The negative coefficient with the σ term indicates that electron-releasing substituents enhance anticonvulsant activity in the series. The series contains only three compounds with negative σ groups. More derivatives with electron-donating groups, as measured by σ, and lipophilic groups, as measured by π, balanced so as to give a log P near the log P_0 of 2.66 found for this series, should be made. An example is the 4-isopropoxy compound with $\sigma = -0.45$ and log P estimated to be 2.74. Its activity, calculated from Eq. 3, is 3.60. The most interesting parameter determined from this analysis is the log $P_0 = 2.66$. This is very near the average value of 2.00 found for optimum lipophilicity for 16 sets of hypnotics (6). It has also been found that log $P_0 = 2.30$ gives optimum concentration of benzeneboronic acids in

Table II—Anticonvulsant Activity of 4-(Substituted benzoyl) Pyridines



	R	log P	σ[a]	pC Obs.	pC Calc. (Eq. 1)	(ΔpC)
1	4-F	2.13[b]	0.06	3.51	3.34	0.17
2	3-CF_3	3.05[c]	0.47	3.43	3.22	0.21
3	2-OCH_3	1.85[d]	0.12	3.41	3.26	0.15
4	2-CH_3	2.82[e]	0.29	3.41	3.29	0.12
5	H	1.98[d]	0.00	3.39	3.33	0.06
6	4-OCH_3	1.94[d]	−0.27	3.27	3.42	0.15
7	2,5-$(CH_3)_2$	3.33[f]	0.22	3.25	3.25	0.00
8	4-Cl	2.61[d]	0.23	3.24	3.32	0.08
9	4-CH_3	2.51[d]	−0.17	3.19	3.45	0.26
10	4-$(CH_3)_3C$	3.96[g]	−0.20	3.17	3.22	0.05
11	4-NO_2	1.75[d]	0.78	3.07	3.00	0.07
12	2-OH	2.14[d]	1.22	2.70	2.93	0.23
13	4-SO_2NH_2	0.57[d]	0.57	2.56	2.57	0.01
14	4-OH	1.37[d]	−0.37	Inactive	3.29	—

[a] G. B. Barlin and D. D. Perrin, *Quart. Rev.*, **20**, 75(1966). [b] log P = log P $C_6H_5C(=O)C_5H_4N$ + $\pi_{4\text{-}F}$ = 1.98 + 0.15 = 2.13. [c] log P = log P $C_6H_5C(=O)C_5H_4N$ + $\pi_{3\text{-}CF_3}$ = 1.98 + 1.07 = 3.05. [d] Experimental value, this laboratory. [e] log P = log P $C_6H_5C(=O)C_5H_4N$ + $\pi_{2\text{-}CH_3}$ = 1.98 + 0.84 = 2.82. [f] log P = log P $C_6H_5C(=O)C_5H_4N$ + $\pi_{2\text{-}CH_3}$ + $\pi_{5\text{-}CH_3}$ = 1.98 + 0.84 + 0.51 = 3.33. [g] log P = log P $C_6H_5C(=O)C_5H_4N$ + $\pi_{4\text{-}C(CH_3)_3}$ = 1.98 + 1.98 = 3.96.

mouse brain (6), and optimum anesthetic potency to mice (7) of a series of 26 ethers administered in vapor phase was associated with $\log P_0 = 2.35$. Our result is consistent with these observations.

The inactivity of the 4-hydroxy derivative is difficult to explain on the basis of lipophilicity and the electronic nature of the OH group. Its predicted activity according to Eq. 3 is 3.29. Since the compound showed no activity, it must not be accessible to the CNS. This could be due to metabolism but further work would be necessary to substantiate this.

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Topical Mosquito Repellents VI: Sulfonamides and Quinoline-4-carboxylic Acid Derivatives

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Abstract □ Certain sulfonamides derived from butanesulfonic acid are repellent to female *Aedes aegypti* mosquitoes. Exploration of the structure–activity relations revealed that the boiling point is the most important factor controlling duration of activity as topical repellents. Quinoline-4-carboxylic acid derivatives were explored for their repellency, and amides were found less active than were esters, primarily due to their low volatility.

Keyphrases □ Mosquito repellents, topical—synthesis, evaluation of butane sulfonamides and quinoline-4-carboxylic acid derivatives □ Repellents, mosquito, topical—synthesis, evaluation of butane sulfonamides and quinoline-4-carboxylic acid derivatives □ Quinoline-4-carboxylic acid derivatives—synthesis, evaluated as topical mosquito repellents □ Sulfonamides, butane—synthesis, evaluated as topical mosquito repellents □ Volatility, quinoline-4-carboxylic acid derivatives—relationship to mosquito repellency

In 1967, Pervomaisky *et al.* (1) reported that certain butane sulfonamides were effective mosquito repellents. The most active of these was reported to be the hexamethyleneimino derivative. This compound and several other analogs were synthesized in the present study for evaluation as topical repellents for *Aedes aegypti* mosquitoes (Table I). The syntheses were straightforward, utilizing *n*-butanesulfonyl chloride in benzene with an excess of the amine. The products were purified by vacuum distillation.

All derivatives were evaluated topically on human subjects as previously described (2). None of the analogs of Compound 1 improved on its activity as a mosquito repellent, although Compounds 3 and 4 had similar activities. As in compounds previously studied as repellents, duration of repellency in a series is a function of the boiling point of the compounds. In this series, maximum duration seems to be achieved with boiling points of 120–130°/0.5 mm. whereas *N,N*-diethyl-*m*-toluamide, which lasts longer, boils at 100°/0.5 mm.

Another interesting lead to mosquito repellents was reported in 1968 (3, 4). These investigators found that certain cinchoninic acid esters were highly repellent. These compounds were evaluated in the present study and several amide analogs were synthesized (Table II). None of the amides exhibited any degree of repellency, probably due to the fact that volatility is reduced too much going from the esters to the amides.

Four of the sulfonamides were evaluated on cloth by the U. S. Department of Agriculture (Table III). The superiority of Compound 1 in these tests over dimethyl phthalate is interesting.

EXPERIMENTAL

n-Butyl Sulfonamides—A solution of *n*-butanesulfonyl chloride (0.03 mole) in anhydrous benzene was slowly added to a solution of the amine (0.06 mole) in anhydrous benzene with cooling and stirring. The solution was then heated to reflux for 1 hr. and, after cooling, the benzene solution was washed with water and dried with sodium sulfate. The oil remaining after evaporation of the solvent was distilled through a short Vigreux column.

Quinoline-4-carboxylic Acid Pyrrolidine Amide—Quinoline-4-carboxylic acid chloride (0.1 mole) (7) was added in small portions to a solution of 0.25 mole of pyrrolidine in anhydrous benzene. After 1 hr. at room temperature, the mixture was heated to reflux for 1 hr. and then cooled, and the benzene solution was washed with water. After drying with sodium sulfate and evaporation of the solvent, the oil was distilled *in vacuo*.

Biological Evaluation: Cloth Tests—Fifty milligrams of the test material is placed in a 2-dram vial to which 0.75 ml. of acetone or other solvent is added. When the chemical is thoroughly dissolved, a 50-cm.^{2} (5 × 10-cm.) piece of muslin bandage is rolled, placed in