saline in order to rule out antihistaminic activity of the test compound. Percent inhibition was determined from the difference between mean spot diameters in test drug-treated and control animals.

Inhibition of Anaphylactic Histamine Release from Rat Peritoneal Mast Cells. Male Harlan–Sprague–Dawley rats (200–300 g) were decapitated and injected ip with 10 mL of Hank's balanced salt solution (HBSS) containing 0.1% human albumin and 5 mM potassium phosphate. The peritoneum was massaged for 1 min and the lavage fluid aspirated and centrifuged at 350 g. The supernatant was discarded and the cell pellets were suspended in 2 mL of rat antisera (prepared as in the PCA test) containing 0.1 mg of heparin. The cells were centrifuged after sensitization by incubation at 37 °C for 2 h with shaking. The resulting cell pellets were resuspended and diluted to the final working volume in buffered HBSS. Aliquots (1.5 mL) of the sensitized cell suspension were challenged with 0.5 mL of EA (80 mg/mL). Drugs were tested at several different concentrations by adding them simultaneously with the antigen challenge, employing four trials at each drug concentration. After antigen and drug additions, the cells were incubated for 10 min and histamine was assayed fluorimetrically. Percent inhibition was determined by comparison with histamine release in the absence of drug.

Inhibition of Rat Lung Phosphodiesterases. Inhibition of rat whole lung cAMP and cGMP phosphodiesterases was determined on rat, whole lung homogenate using the method of Thompson and Appleman.[24] The phosphodiesterase assays were carried out using two substrate concentrations (2×10^{-6} and 1×10^{-6} M) of cAMP and cGMP and using four drug substrate concentrations bracketing the K_i values. The drug concentrations were chosen on the basis of a preliminary experiment. The drugs were allowed to incubate with the enzymes for 30 min at 30 °C prior to the addition of the substrate. The results were plotted according to the method of Dixon.[25]

Spontaneous Motor Activity in Rats. Male Charles River/Sprague–Dawley rats were dosed orally with test compounds and placed in annular activity cages as previously described.[26] One hour later their activity scores were compared with those of simultaneously tested control animals, employing groups of 20 rats per drug dose. A compound was considered a stimulant or depressant if the log motor activity scores were 0.3 above or below that of the control (AED ± 0.3).

Acknowledgment. The authors gratefully acknowledge the interest and assistance of Dr. Dan Lednicer in the completion of this effort. We also acknowledge Charles M. Combs who provided analytical data and spectral interpretation.

(24) W. J. Thompson and M. M. Appleman, *Biochemistry*, **10**, 311 (1971).
(25) M. Dixon and E. C. Webb, in "Enzymes", Academic Press, New York, 1964, p 329.
(26) J. W. Kissel, *Science*, **139**, 1224 (1963).

Antimalarials. 12. Preparation of Carbon Isosteres of Selected 4-Pyridinemethanols as Suppressive Antimalarials

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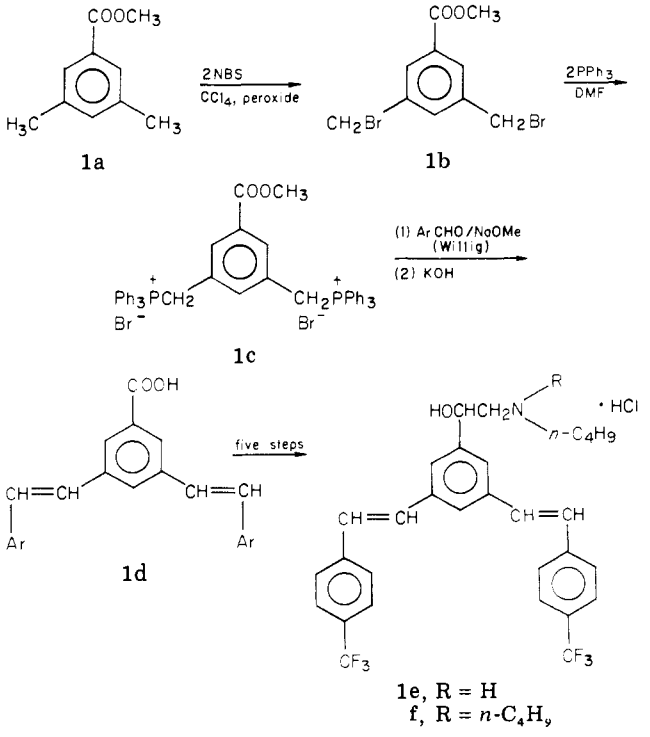
Ash Stevens Inc., Detroit, Michigan 48202. *Received May 27, 1980*

Four carbon isosteres related to the highly active 4-pyridylcarbinolamines were prepared and evaluated for suppressive antimalarial activity against *Plasmodium berghei* in mice. Three of the four examples possessed significant activity but were approximately one dose level less active than the corresponding pyridines.

We have previously reported the preparation of 2,6-bis(aryl)-4-pyridinemethanols[1] and 2,6-bis(styryl)-4-pyridinemethanols[2] which demonstrated a high level of suppressive antimalarial activity against *Plasmodium berghei* in mice. The four compounds reported herein were prepared in order to assess the effect of replacing the pyridine nitrogen atom with a carbon atom. Similar studies have previously been performed on the highly active 2-aryl-4-quinolinemethanols and corresponding carbon isosteres.[3]

Chemistry. Two examples were prepared in the 3,5-bis[4-(trifluoromethyl)styryl]phenylcarbinolamine series and the synthetic sequence is shown in Scheme I. Commericially available 3,5-dimethylbenzoic acid was converted to the methyl ester **1a**, which upon bromination with *N*-bromosuccinimide according to the procedure of Wenner[4] afforded methyl 3,5-bis(bromoethyl)benzoate (**1b**). Treatment of **1b** with triphenylphosphine[5a,b] afforded the bisphosphonium salt **1c**. Treatment of **1c** with 4-(trifluoromethyl)benzaldehyde under Wittig conditions followed by ester hydrolysis afforded 3,5-bis(styryl)benzoic acid (**1d**). Conversion of acid **1d** to the desired phenylcarbinolamines (**1e** and **1f**) involved the standard Lutz

Scheme I



(1) Markovac, A.; LaMontagne, M. P.; Blumbergs, P.; Ash, A. B.; Stevens, C. L. *J. Med. Chem.* **1972**, *15*, 918.
(2) LaMontagne, M. P. *J. Med. Chem.* **1973**, *16*, 68.
(3) Gillespie, J. S.; Acharya, S. P.; Shamblee, D. A.; Davis, R. E. *J. Med. Chem.* **1975**, *18*, 1223.
(4) Wenner, W. *J. Org. Chem.* **1952**, *17*, 523.
(5) (a) Campbell, T. W.; McDonald, R. N. *J. Org. Chem.* **1959**, *24*, 1246. (b) Maercker, A. *Org. React.* **1965**, *14*, 270.

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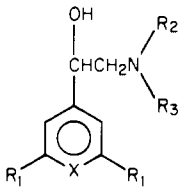
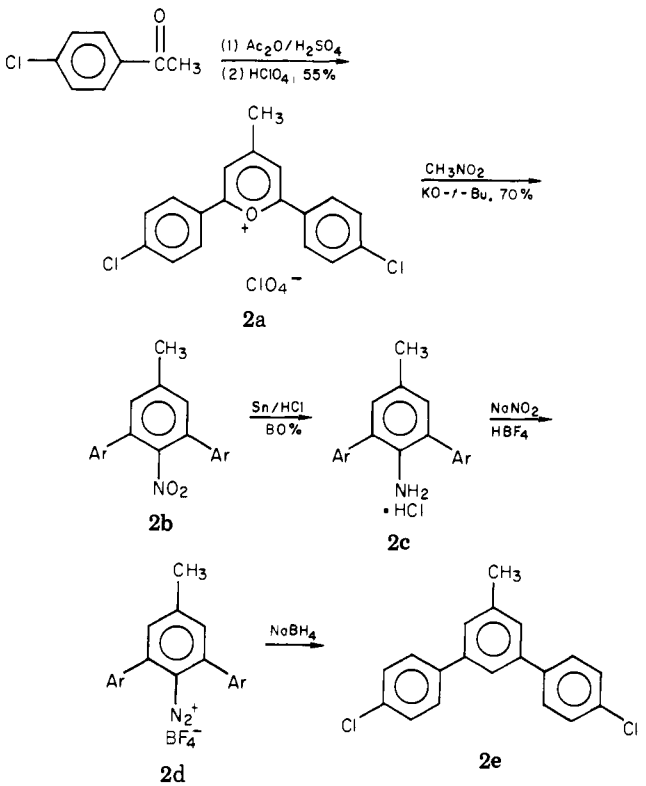
Table I. Antimalarial Activity Data[a]



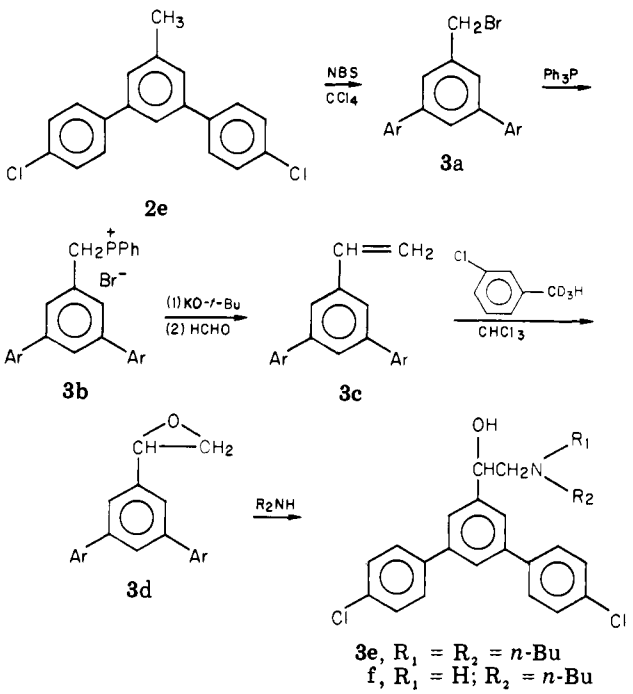
					Δ MST, days, or no. of cures, C^a					
no.	X	R_1	R_2	R_3	dose, mg/kg: 20	40	80	160	320	640
1e	C	-CH=CHC$_6$H$_4$CF$_3$-*p*	H	*n*-C$_4$H$_9$			inact			
	N[b]	-CH=CHC$_6$H$_4$CF$_3$-*p*	H	*n*-C$_4$H$_9$			inact			
1f	C	-CH=CHC$_6$H$_4$CF$_3$-*p*	*n*-C$_4$H$_9$	*n*-C$_4$H$_9$	0.5	0.5	8.1 (A)	5C	5C	
	N[b]	-CH=CHC$_6$H$_4$CF$_3$-*p*	*n*-C$_4$H$_9$	*n*-C$_4$H$_9$	0.2	2.9	2C	5C	5C	5C
3e	C	-C$_6$H$_4$Cl-*p*	*n*-C$_4$H$_9$	*n*-C$_4$H$_9$	0.3	0.5	4.1	9.7 (A)	13.9 (A)	5C
	N[c]	-C$_6$H$_4$Cl-*p*	*n*-C$_4$H$_9$	*n*-C$_4$H$_9$	2.3	15.7 (A)	3C	3C	4C	5C
3f	C	-C$_6$H$_4$Cl-*p*	H	*n*-C$_4$H$_9$	0.5	1.3	3C	5C	5C	
	N[c]	-C$_6$H$_4$Cl-*p*	H	*n*-C$_4$H$_9$	10.8 (A)	1C	2C	3C	5C	5C

[a] Activity vs. *P. berghei* in five mice, determined by Rane Laboratories, University of Miami, as described by Osdene and co-workers.[8] Mean survival time (MST) of infected controls was 6.1 days. Increase in survival time (Δ MST) of mice treated with a single dose of compound administered subcutaneously 72 h after infection is considered evidence of antimalarial activity if the increase is at least 100% Number of cures (*C*) is the number of mice surviving out of five at 60 days post-infection. A = active. [b] See ref 2. [c] See ref 1.

Scheme II



Scheme III



side-chain procedure.[6] Examples (**3e** and **3f**) are 3,5-bis(4-chlorophenyl)phenylcarbinolamines. The requisite 3,5-bis(aryl)toluene intermediate **2e** was prepared as shown in Scheme II. Pyrylium salt **2a** was prepared via the condensation of 4-chloroacetophenone with acetic anhydride in the presence of sulfuric acid, followed by treatment with perchloric acid. Reaction of the pyrylium perchlorate with nitromethane, according to the procedure of Dimroth,[7] afforded the nitrotoluene derivative **2b** in 70% yield.

Reduction of the nitrotoluene **2b** with tin and hydrochloric acid afforded the aminotoluene hydrochloride **2c**, which upon deamination via the diazonium fluoroborate **2d** with sodium borohydride gave the 3,5-bis(aryl)toluene **2e**. The introduction of the amino alcohol side chain onto bis(aryl)toluene **2e** is shown in Scheme III. This represents a new approach relative to previously described procedures.[1,6] The 3,5-bis(aryl)toluene was brominated with *N*-bromosuccinimide[5] to yield the crude bromotoluene **3a**, which was converted directly without purification to the phosphonium salt **3b**. The latter was converted in situ to the phosphorane with base, followed by treatment with formaldehyde, to yield the 3,5-bis(aryl)styrene **3c**. The styrene was successfully converted to the epoxide **3d**, which

(6) Lutz, R. E.; Bailey, P. S.; Clark, M. T.; Codington, J. F.; Deinet, A. J.; Freek, J. A.; Harnest, G. H.; Leake, N. H.; Martin, T. A.; Rowlett, R. J., Jr.; Salsbury, J. M.; Shearer, N. H., Jr.; Smith, J. D.; Wilson, J. W. III *J. Am. Chem. Soc.* **1946**, *68*, 1813.

(7) Dimroth, F. *Angew. Chem.* **1960**, *72*, 331.

was isolated but not purified. Treatment of the epoxide with mono- and di-*n*-butylamine afforded target carbinolamines 3e and 3f.

Biological Activity Data. Target compounds 1e, 1f, 3e, and 3f were screened for suppressive antimalarial activity against *Plasmodium berghei* in mice.[8] The data are shown in Table I along with the data for the corresponding 4-pyridylcarbinolamines. Compound 1e was inactive in this screen, as was the corresponding pyridyl analogue. In the remaining three cases the carbon isosteres, although they possessed significant activity, were approximately one dosage level less active than the corresponding nitrogen analogue. The data would indicate, therefore, that a heterocyclic ring is not necessary for antimalarial activity, although it does definitely enhance such activity. A similar but more drastic effect was also observed in the 4-quinolylcarbinolamine series.[3]

Experimental Section

All melting points and boiling points are uncorrected. The melting points were taken on a Thomas-Hoover capillary apparatus. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, Ind. The IR spectra were recorded on a Perkin-Elmer 237B spectrophotometer, and the NMR spectra were recorded on a Varian T60-A spectrometer.

Methyl 3,5-Dimethylbenzoate (1a). A solution of 3,5-dimethylbenzoic acid (50 g) in CH_3OH (500 mL) containing H_2SO_4 was refluxed for 10 h. The solution was partly evaporated, poured over ice, and extracted with Et_2O. The extract was washed with aqueous Na_2CO_3, dried ($MgSO_4$), and evaporated. The residue was suspended in petroleum ether and refrigerated. The resulting precipitate was collected to yield the title ester (45 g, 82%), mp 35–36 °C. Anal. ($C_{10}H_{12}O_2$) C, H.

Methyl 3,5-Bis(bromomethyl)benzoate (1b). A solution of methyl 3,5-dimethylbenzoate (16.8 g), *N*-bromosuccinimide (35.6 g), and benzoyl peroxide (500 mg) in CCl_4 (150 mL) was refluxed for 3 h. After the solution cooled, the precipitate (succinimide) was separated and washed with CCl_4. The filtrate was washed with H_2O, dried ($MgSO_4$), and evaporated. The thick residue was suspended in petroleum ether and refrigerated. The product crystallized to yield the title compound (27 g, 85%), mp 65–69 °C, which was used as such in the following reaction.

Methyl 3,5-Bis(methyltriphenylphosphonio)benzoate Dibromide (1c). The above dibromide (3.2 g) and triphenylphosphine (6 g) in DMF (20 mL) was refluxed for 16 h. After the mixture cooled, the crystalline salt was separated and washed with DMF and with Et_2O to yield the title ester (6.8 g, 80%), mp 300 °C dec. Anal. ($C_{46}H_{40}Br_2P_2O_2$) Br, P.

Methyl 3,5-Bis[4-(trifluoromethyl)styryl]benzoate. To a stirred suspension of the above bisphosphonium dibromide (4.2 g) and 4-(trifluoromethyl)benzaldehyde (1.9 g) in absolute EtOH (80 mL) was added dropwise a solution of $NaOCH_3$ (from 300 mg of Na and 20 mL of MeOH). The solution was stirred at room temperature overnight and refluxed for 2 h. Part of the EtOH was evaporated (ca. 40 mL) and replaced with Et_2O. The semisolid precipitate was recrystallized from EtOH to give the title ester (1.4 g, 59%), mp 70–72 °C. Anal. ($C_{16}H_{18}F_6O_2$) C, H.

3,5-Bis[4-(trifluoromethyl)styryl]benzoic Acid (1d). The above ester (2.4 g) was refluxed with 5% KOH in EtOH (50 mL) for 1 h. The EtOH was partly evaporated. The solution was diluted with H_2O and acidified with 10% HCl. After refrigeration of the solution, the precipitate was recrystallized from EtOH to give the title acid (2 g, 81%), mp 220–222 °C. Anal. ($C_{25}H_{16}F_6O_2 \cdot 0.5H_2O$) C, H.

α-[(*n*-Butylamino)methyl]-3,5-bis[4-(trifluoromethyl)styryl]phenylcarbinol Hydrochloride (1e). The above benzoic acid was converted to the ethylene oxide via standard procedures.[1,6] The epoxide (900 mg), EtOH (50 mL), and *n*-butylamine (10 mL) were refluxed for 8 h. The solution was evaporated and the residue was dissolved in Et_2O, washed with H_2O, and dried (K_2CO_3). The solvent was evaporated, and the free base was dissolved in Me_2CO and treated with dry HCl. The solution was evaporated and the resulting salt was recrystallized from Me_2CO and petroleum ether to yield the title compound (590 mg, 50%), mp 161–163 °C. Anal. ($C_{30}H_{30}ClF_6NO$) C, H, N.

α-[(Di-*n*-butylamino)methyl]-3,5-bis[4-(trifluoromethyl)styryl]phenylcarbinol Hydrochloride (1f). The precursor epoxide (900 mg), EtOH (50 mL), and di-*n*-butylamine (10 mL) were refluxed for 8 h and worked up as described for 1e. The hydrochloride salt was crystallized from acetone–petroleum ether to yield the title compound (580 mg, 45%), mp 147–149 °C. Anal. ($C_{34}H_{38}ClF_6NO$) C, H, N.

2,6-Bis(4-chlorophenyl)-4-methylpyrylium Perchlorate (2a). Sulfuric acid (9.0 mL) was added slowly and with stirring to well-cooled Ac_2O (30 mL). The temperature was raised to 75–80 °C (internal) and held 3 h. 4-Chloroacetophenone (9.2 g) was added in one portion. The mixture was held at 50–60 °C for 3 h and overnight at room temperature. The mixture was diluted with an equal volume of EtOH (50 mL) and refrigerated. The yellow precipitate was separated and washed with EtOH and with Et_2O. The solid was suspended in 10% $HClO_4$ (100 mL) and stirred for 1 h. The lemon-yellow precipitate was filtered and washed with cold EtOH and with Et_2O. After drying there was obtained the title pyrilium salt (6.8 g, 55%), mp ~280 °C dec.

3,5-Bis(4-chlorophenyl)-4-nitrotoluene (2b). A solution of potassium *tert*-butoxide (4 g) in *t*-BuOH (30 mL) was added dropwise to a stirred suspension of the above pyrilium salt (4.11 g) in CH_3NO_2 (20 mL) and *t*-BuOH (40 mL). The dark red mixture was refluxed for 45 min and filtered hot, saving the precipitate. The filtrate was chilled to afford the crude title compound, which was washed with cold EtOH and dried. The original precipitate was digested with hot C_6H_6 (100 mL) and filtered. The filtrate was evaporated, and the residue was suspended in EtOH (50 mL), filtered, and dried. The combined crude product (3 g) was crystallized from C_6H_6–EtOH to give the title compound as colorless crystals (2.5 g, 70%), mp 166–168 °C. Anal. ($C_{19}H_{13}Cl_2NO_2$) C, H, N, Cl.

3,5-Bis(4-chlorophenyl)-4-aminotoluene Hydrochloride (2c). A mixture of **2b** (3.5 g), tin metal (10 g), concentrated HCl (60 mL), and HOAc (60 mL) was refluxed with stirring until all the starting material dissolved. The unreacted tin was separated and the resulting clear solution was refrigerated. The crude title salt was separated, washed with cold H_2O, suspended in Et_2O to dissolve starting material, and filtered to give the title salt (2.9 g, 80%), mp 181–183 °C. Anal. ($C_{19}H_{15}Cl_3N$) N.

3,5-Bis(4-chlorophenyl)toluene (2e). To a chilled suspension of the above amine salt (3.6 g), H_2O (100 mL), and 40% HBF_4 (20 mL) was added slowly a solution of $NaNO_2$ (700 mg) in H_2O (15 mL). The internal temperature was held at 5–10 °C. The suspension was stirred at 10 °C for 2 h. The yellow diazonium fluoroborate salt was filtered and washed successively with cold 5% HBF_4, a small amount of cold MeOH, and with Et_2O. The crude salt was suspended in MeOH (60 mL), cooled at 0 °C, and solid $NaBH_4$ (2 g) was added in small portions to maintain the temperature at 0–5 °C. The suspension was stirred for 2 h, poured into ice–5% HCl, and filtered. The crude solid was recrystallized from C_6H_6–EtOH to give the title compound (2 g, 66%), mp 173–175 °C. Anal. ($C_{19}H_{14}Cl_2$) C, H, Cl.

3,5-Bis(4-chlorophenyl)benzyl Bromide (3a). A suspension of **2e** (3.1 g), *N*-bromosuccinimide (1.74 g), and CCl_4 (100 mL) was refluxed with stirring for 8 h. After the mixture cooled, succinimide was separated and washed with warm CCl_4. The filtrate was washed with H_2O and dried ($MgSO_4$), and the solvent was evaporated. The solid residue was predominantly the title benzyl bromide (3.3 g, 90%), which was used directly in the next step.

Triphenyl-3,5-bis(4-chlorophenyl)benzylphosphonium Bromide (3b). A solution of the above benzyl bromide (3.8 g) and triphenylphosphine (3.7 g) in xylene (100 mL) was refluxed for 18 h. After the solution cooled, the phosphonium salt was separated and washed with Et_2O. The yield was 3.85 g (59%), mp 265–268 °C. Recrystallization from $CHCl_3$ gave an analytical sample, mp 266–268 °C. Anal. ($C_{37}H_{28}Cl_2BrP$) Br, P.

3,5-Bis(4-chlorophenyl)styrene (3c). A solution of potassium *tert*-butoxide (3 g) in EtOH (30 mL) was added dropwise to a stirred suspension of the above phosphonium salt (3.25 g) and formaldehyde (1.5 g) in absolute EtOH (30 mL). The suspension

(8) Osdene, T. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.

was stirred at room temperature for 2 h and evaporated to dryness. The residue was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was crystallized from EtOH to give the title styrene (1.3 g, 80%), mp 125–127 °C. Anal. ($C_{20}H_{14}Cl_2$) C, H.

3,5-Bis(4-chlorophenyl)styrene Oxide (3d). A solution of the above styrene (1.7 g) and *m*-chloroperbenzoic acid (1 g) in $CHCl_3$ (50 mL) was kept at 40 °C for 4 h and held at room temperature overnight. The solution was washed with $NaHCO_3$, dried (K_2CO_3), and evaporated to yield the crude epoxide (1.7 g) containing about 10% of starting material as shown by TLC (silica; dichloromethane–petroleum ether, 1:1). The crude product was used directly in the next step.

α-[(Di-*n*-butylamino)methyl]-3,5-bis(4-chlorophenyl)-phenylcarbinol Hydrochloride (3e). The above crude epoxide (1.1 g) and di-*n*-butylamine (3 mL) in EtOH (10 mL) were refluxed 3 h. The solution was evaporated to dryness and the mixture was dissolved in 10% HCl–MeOH. The solution was evaporated to dryness again and the residue was suspended in Et_2O. The colorless precipitate was filtered, washed with H_2O, and recrystallized from acetone–petroleum ether to give the target compound (800 mg, 51%), mp 231–233 °C. Anal. ($C_{28}H_{34}Cl_3NO$) C, H, Cl, N.

α-[(*n*-Butylamino)methyl]-3,5-bis(4-chlorophenyl)-phenylcarbinol Hydrochloride (3f). A solution of **3d** (700 mg) and *n*-butylamine (3 mL) in EtOH (20 mL) was refluxed for 4 h. The mixture was processed as for **3e** to give the target compound (450 mg, 48%), mp 248–250 °C. Anal. ($C_{24}H_{26}Cl_3NO$) C, H, Cl, N.

Acknowledgment. This work was supported by the U.S. Army Medical Research and Development Command under Contract DADA17-69-C-9065. This is contribution no. 1562 from the Army Research Program on Antiparasitic Drugs. The advice and timely suggestions of Dr. R. E. Strube of the Walter Reed Army Institute of Research are gratefully acknowledged.

Confidence Interval Estimators for Parameters Associated with Quantitative Structure–Activity Relationships

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Use of the "jackknife" as a statistical tool for construction of both point and confidence interval estimators for parameters which are functions of regression coefficients and/or iteratively estimated parameters is described. Examples are presented demonstrating its utility in constructing estimators for log P_0 and π_0 using the parabolic and bilinear quantitative structure–activity relationship (QSAR) models relating nonlinear dependence of activity on hydrophobicity and for log $[1/K_{i(app)}]$ assuming competitive enzyme inhibition.

Medicinal chemists are increasingly attempting to come into line with Lord Kelvin's famous dictum: "If you cannot measure, your knowledge is meager and unsatisfactory". Quantifying results accurately in medicinal chemistry is considerably more difficult than in the field of physics. The biological data obtained from animal experiments, or even in vitro experiments with purified enzymes, contain considerable noise; therefore, simply expressing results in numerical terms is not enough. One must have some idea of how reliable the numbers are that one obtains. This is particularly important in the area of QSAR. In the formulation of these mathematical models, one wants to know where shortcomings in the model are most likely to reside. It is necessary, therefore, to be aware not only of error (experimental variance) in the observed biological data but also of the error asssociated with predicted values derived from the mathematical model using these data.

Two parameters of importance in QSAR work are log P_0 (or π_0) for nonlinear dependence of activity on hydrophobicity and log $1/C$ = log $[1/K_{i(app)}]$ [or log $(1/K_i)$] for enzyme inhibition. This report discusses a technique for placing confidence limits on these parameters.

The analysis of experimental data in the biological sciences frequently entails the use of linear regression analysis:

$$Y = \alpha_0 + \alpha_1 X_1 + \alpha_2 X_2 + \ldots + \alpha_m X_m + \text{error}$$

In many instances the researcher then finds it necessary to calculate an estimate for a parameter θ, which is a function of the coefficients of the regression equation:

$$\theta = f(\alpha_0, \alpha_1, \ldots, \alpha_m)$$

The complexity of such a relationship often makes it difficult, if not impossible, to directly provide a confidence interval associated with the calculated parameter. In addition, analysis of other experimental data involves nonlinear regression techniques which may require iterative solutions for estimates $\{B_j\}$ of parameter(s) $\{\beta_j\}$, as well as estimates $\{A_i\}$ of regression coefficients $\{\alpha_i\}$. Such regression analyses provide approximate confidence intervals for the regression coefficients $\{\alpha_i\}$ directly, assuming that the iteratively derived $\{B_j\}$ values are the true $\{\beta_j\}$. (This assumption could create problems in the confidence interval statements on the $\{\alpha_i\}$ due to inaccuracies in the estimation of the $\{\beta_j\}$. The standard statistical procedure in the literature[1-3] is to assume that the iteratively derived $\{B_j\}$ values are the true $\{\beta_j\}$ and then to calculate the confidence intervals for the $\{\alpha_i\}$ based on the least-squares linear regression using a Student's t value with $(n - K)$ degrees of freedom, where K = the total number of $\{\alpha_i\}$ and $\{\beta_j\}$.) However, such regression analyses do not provide simple confidence intervals for the iteratively derived $\{B_j\}$. Derivation of confidence intervals for a parameter θ, which is a function of both the α_i and β_j values [i.e., $\theta = g(\{\alpha_i\},\{\beta_j\})$], is therefore also difficult.

(1) Kubinyi, H. *J. Med. Chem.* **1977**, *20*, 625.
(2) Kubinyi, H. *Arzneim.-Forsch.* **1976**, *26*, 1991.
(3) Kubinyi, H.; Kehrhahn, O.-H. *Arzneim.-Forsch.* **1978**, *28*, 598.

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