75% EtOH (120 ml) was added with stirring 9.4 g (0.069 mole) of III in EtOH. The ice bath was removed after 2 hr followed by continued stirring (20 hr) and refluxing (2 hr). The EtOH was then flash-evapd, and the residue was pentane-extd, dried (Na_2SO_4), and evapd in a dry air stream to provide 5.1 g (49%) of white needles, mp 132–133° (cyclohexane–Et_2O). *Anal.* ($C_{10}H_{11}NO$) C, H, N.

1-Amino-4,6-dimethylbenzocyclobutene·HCl (V).—A mixt of 1.0 g (0.0062 mole) of IV and 0.5 g of 5% Pd/C was suspended in 75 ml of glacial AcOH to which was added 1.0 ml of concd H_2SO_4. Hydrogenation for 3.5 hr at 3.5 kg/cm² was followed by treatment with 6 *N* NaOH (4.0 ml), removal of the pptd Na_2SO_4, and evapn *in vacuo* of the filtrate. The residue was made basic with 50% KOH soln (cold), and the free amine was taken up in CH_2Cl_2, dried (Na_2SO_4), and satd with dry HCl. Suction filtration and recrystn (EtOH) yielded 0.385 g (35%) of white needles, mp 221–222°. *Anal.* ($C_{10}H_{14}ClN$) C, H, N. Absorption bands (ir, nmr) were as expected.

***N*-Acetyl-1-amino-4,6-dimethylbenzocyclobutene (VI).**—A soln of 0.480 g (0.0026 mole) of V (as free amine) and 0.43 ml (0.0031 mole) of Et_3N in CH_2Cl_2 (cold) was treated dropwise with 0.35 ml (0.005 mole) of AcCl in CH_2Cl_2. After addn was complete, the soln was refluxed for 2 hr and stirred for an addnl 4 hr at 25°. The resulting mixt was washed (2 *N* HCl; then 2 *N* Na_2CO_3, H_2O), dried (Na_2SO_4), and filtered, and the filtrate was evaporated *in vacuo*. Recrystn (CCl_4–CH_2Cl_2, 25:1) provided 0.60 g (97%) of fine white needles, mp 178–180°. *Anal.* ($C_{12}H_{15}NO$) C, H, N. The spectrum (ir) was as expected.

***N*-Propionyl-1-amino-4,6-dimethylbenzocyclobutene (VII).**—Procedure was as in VI. Reactants were: 1.2 g (0.0056 mole) of V (as free amine), 0.82 ml (0.0094 mole) of EtCOCl, and 1.44 ml (0.0082 mole) of Et_3N. Work-up yielded 0.77 g (58%) of white needles, mp 171.5–173.5°. *Anal.* ($C_{13}H_{19}NO$) C, H, N.

***N*-Butyryl-1-amino-4,6-dimethylbenzocyclobutene (VIII).**—Used were: 1.2 g (0.0056 mole) of V (as free amine), 0.865 ml (0.0083 mole) of *n*-PrCOCl, and 0.33 ml (0.095 mole) of Et_3N. Recrystn (CCl_4) gave 1.2 g (67%) of white needles, mp 147–149°. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

***N*-Benzoyl-1-amino-4,6-dimethylbenzocyclobutene (IX).**—Employed were: 1.2 g (0.0056) of V (as free amine), 0.98 ml (0.0083 mole) of BzBr, and 2.32 ml (0.017 mole) of Et_3N. The desired amide (1.4 g, 85%) was recrystd (CCl_4) as white needles, mp 175–178°. *Anal.* ($C_{17}H_{17}NO$) C, H, N.

***N*-Phenacetyl-1-amino-4,6-dimethylbenzocyclobutene (X).**—Ingredients included were: 1.2 g (0.0056 mole) of V (as free amine), 1.1 ml (0.0083 mole) of $PhCH_2COCl$, and 1.95 ml (0.014 mole) of Et_3N. Recrystn (CCl_4) yielded 1.35 g (79%) of white needles, mp 181–183°. *Anal.* ($C_{18}H_{19}NO$) C, H, N.

Ethyl *N*-(4,6-Dimethylbenzocyclobutyl) carbamate (XI).—A soln of 1.5 g (0.007 mole) of V and 2.25 ml (0.016 mole) of Et_3N in dry $CHCl_3$ was cooled and treated dropwise with a $CHCl_3$ soln of ClCOOEt (0.78 ml, 0.0082 mole) while stirring. When addn was complete, stirring was continued for 10 hr at 25°. The mixt was then washed (H_2O), dried (Na_2SO_4), and evapd *in vacuo*. Recrystn (hexane) provided 1.065 g (63%) of carbamate, mp 116–118°. *Anal.* ($C_{12}H_{15}NO_2$) C, H, N. Spectrum (ir) was as expected.

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5-Benzoyl-1-methylpyrrole-2-acetic Acids as Antiinflammatory Agents

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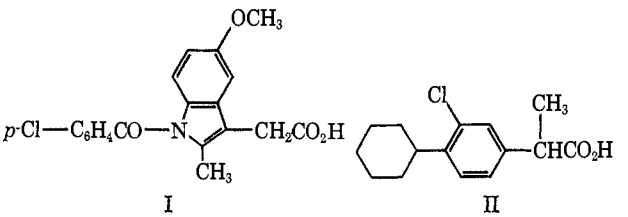
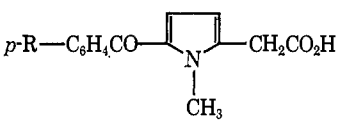
In a discussion of structure–activity relationships of indomethacin (I) and its analogs, T. Y. Shen proposed a "receptor site" for antiinflammatory activity for these compounds[1] having an interaction with three portions of the indomethacin molecule. He felt that the carboxyl function could bind to a "cationic site," that the indole ring system fit a "flat aromatic surface," and that the *p*-chlorophenyl ring fit into a "lipophilic trough." The benzoyl carbonyl and the MeO group on the indole ring could also contribute to binding.

Upon the disclosure[2] from Shen's laboratory of the potent antiinflammatory activity of 3-chloro-4-cyclohexyl-α-methylphenylacetic acid (II), we attempted a further analysis of the structural features necessary for activity in the aryl acetic acid. Although the phenyl ring of II should occupy the same portion of the receptor site as the indole system of indomethacin, it is smaller in size. We, therefore, decided to prepare compounds in which the indole ring of indomethacin is replaced by a simple 5-membered ring.

Among the compounds chosen were the 5-benzoyl-1-methylpyrrole-2-acetic acids (III) of which the *p*-chlorobenzoyl (IIIa) and *p*-toluoyl (IIIb) compounds are representative.



I II



IIIa, R = Cl
b, R = CH_3

Pharmacology.—Compounds of type III possess marked antiinflammatory activity. A comparison of their potencies to those of standard nonsteroidal antiinflammatory drugs in two acute rat paw edema tests is shown in Table I.

TABLE I

RELATIVE POTENCY OF INDOMETHACIN, PHENYLBUTAZONE, AND COMPOUNDS IIIa AND IIIb IN THE KAOLIN- AND CARRAGEENIN-INDUCED RAT PAW EDEMA TESTS

Compd	Relative potency (95% confidence limits)
I. Kaolin-Induced Edema Test	
Indomethacin	1.00
IIIa	0.47 (0.25–0.71)
IIIb	0.27 (0.17–0.50)
Phenylbutazone	0.09 (0.05–0.21)
II. Carrageenin-Induced Edema Test	
Indomethacin	1.00
IIIa	0.39 (0.29–0.52)
IIIb	0.38 (0.24–0.58)
Phenylbutazone	0.02 (0.01–0.03)

Antiinflammatory activity was also demonstrated in the cotton pellet granuloma test and the adjuvant-

(1) T. Y. Shen, *Int. Symp. Non-Steroidal Anti-Inflammatory Drugs, Proc.*, **1964**, 18 (1965).

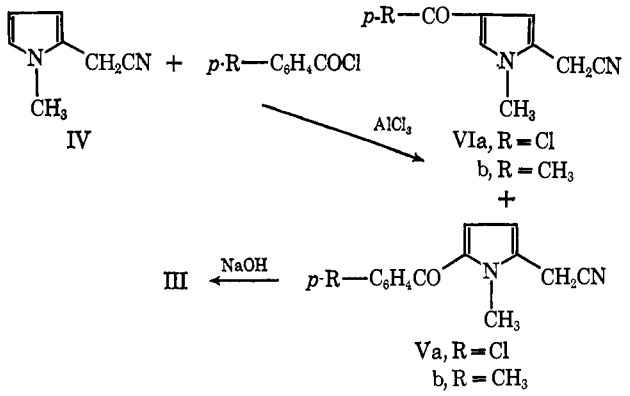
(2) T. Y. Shen, C. P. Dorn, W. V. Ruyle, B. E. Witzel, C. H. Shunk, A. R. Matzuk, H. Schwam, R. L. Bugianesi, L. Bock, H. M. Lewis, G. Arth, and A. A. Patchett, 2nd Middle Atlantic Regional Meeting of the American Chemical Society, New York, N. Y., Feb 1967, p 46.

induced arthritis assay. Compound IIIb was estimated to be 5.79 (2.43–10.08) times as potent as phenylbutazone and 0.14 (0.08–0.25) times as potent as indomethacin in the cotton pellet granuloma test.

In addition, significant analgetic activity, as measured by the acetylcholine bromide induced writhing test,[3] and antipyretic activity[4] were observed.

Chemistry.—Compounds of type III can be prepared *via* Friedel–Crafts aroylation of 1-methylpyrrole-2-acetonitrile (IV)[5] with the appropriate aroyl halide in the presence of $AlCl_3$. Both the 5-aroyl (V) and the 4-aroyl (VI) derivatives are formed in this reaction. The desired 5-aroyl derivatives (V) can be isolated by fractional crystn and/or adsorption chromatography on Al_2O_3. The structures of V and VI can be demonstrated from their nmr spectra. The spectra of the 1,2,5-substituted compounds V show a 3.8–4.0 Hz coupling of the pyrrole protons indicative of coupling across the 3 and 4 positions. The 1,2,4-substituted compounds show a 1.5–1.8 Hz 3,5 coupling.

Saponification of the nitriles V affords the corresponding acids III.



Experimental Section

All melting points were detd using a Thomas-Hoover capillary mp apparatus and are uncorrected. The nmr spectra were obtained using a Varian A60 instrument (Me_4Si). Elemental analyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark. Where analyses are indicated by the symbols of the elements, the anal. results obtained for those elements are within ±0.4% of the theoretical values.

Chemistry. Friedel–Crafts Reactions.—A soln of 13.3 g (0.1 mole) of anhyd $AlCl_3$ and 0.1 mole of the appropriate acid chloride (*p*-ClBzCl or *p*-CH_3BzCl) in 50 ml of $ClCH_2CH_2Cl$ was added over 30 min to a soln of 1-methylpyrrole-2-acetonitrile in 50 ml of $ClCH_2CH_2Cl$. The mixt was stirred for 15 min and heated under reflux for 5 min. The soln was poured into ice–HCl. The residue remaining in the reaction flask was triturated with $CHCl_3$–HCl. The combined org soln was washed with H_2O, *N*,*N*-dimethyl-1,3-propanediamine soln,[6] HCl, and brine. It was dried ($MgSO_4$) and the solvent was evapd *in vacuo*. The residue was chromatographed on acid-washed Al_2O_3. Elution with C_6H_6, evapn of the eluate, and recrystn of the residue from MeOH afforded the 5-aroyl-1-methylpyrrole-2-acetonitrile: Va, 5.4 g (21%), mp 128–130°, *anal.* ($C_{14}H_{11}ClN_2O$) C, H, N; Vb, 6.0 g (25%), mp 103–105°, *anal.* ($C_{15}H_{14}N_2O$) C, H, N.

Further elution of the above chromatographic column with 10% $CHCl_3$ in C_6H_6, evapn of the eluate, and recrystn of the residue from MeOH gave the 4-aroyl-1-methylpyrrole-2-acetonitrile: VIa, 1.9 g (7.4%), mp 93–95°, *anal.* ($C_{14}H_{11}ClN_2O$) C, H, N; VIb, 1.59 g (6.7%), mp 117–119°, *anal.* ($C_{15}H_{14}N_2O$) C, H, N, O.

Saponifications.—A soln of 1 equiv of the appropriate 5-aroyl-1-methylpyrrole-2-acetonitrile (Va or Vb) in 2 equiv of 1 *N* NaOH and twice that vol of EtOH was heated under reflux overnight. The EtOH was evapd *in vacuo* and the residue was acidified with HCl. The pptd solid was extd into Et_2O and the Et_2O was evapd to give the 5-aroyl-1-methylpyrrole-2-acetic acid: IIIa, 81% yield (from Et_2O–hexane), mp 188–191° dec, *anal.* ($C_{14}H_{12}ClNO_3$) C, H, N; IIIb, 69% yield, (from CH_3CN), mp 155–157° dec, *anal.* ($C_{15}H_{15}NO_3$) C, H, N.

Pharmacology.—Compounds of type III and phenylbutazone were administered as solns of their sodium salts. EtOH was added to facilitate the dissolution of phenylbutazone. Indomethacin was administered as an aq suspension contg 0.1% Tween.

Antiinflammatory activity was assessed by measuring the inhibition of edema induced by 0.1-ml intraplantar injections (1% carrageenin or 10% kaolin) in the hind paw of male Holtzman rats (170–180 body weight). Paw vol were detd by the mercury displacement method of Van Arman as described by Winter, *et al.*,[7] with modifications[8] to provide digital readout on paper tape. All statistical analyses of data were processed by computer.

A min of 3 doses for each test or ref compd was administered orally to groups of 10 rats per dose, 1.0 hr prior to the intraplantar injections. Edema was measured 3 hr later in the carrageenin test and 6 hr later in the kaolin test. Analysis of variance was performed and group means were compared by Dunnett's procedure at the 5% protection level. Any treatment mean significantly less than the control mean was indicative of significant antiinflammatory activity.

Rat paw edema vol of treated animals was compared to that of animals receiving saline, indomethacin, or phenylbutazone by computer estn of relative potency (95% confidence limits) using Finney's parallel line assay.[9] Results are presented in Table I.

Inhibition of cotton pellet granuloma was studied using the procedure of Meier, *et al.*,[10] with minor modifications. Only the granuloma formed in the cotton pellets was retained and dried for analysis of response. The granuloma forming a capsule was not included in the studies.

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(3) H. O. J. Collier, L. C. Deneen, C. A. Johnson, and C. Schneider, *Brit. J. Pharmacol. Chemother.*, **38**, 295 (1968).

(4) U. M. Teotino, L. P. Friz, A. Gandini, and D. Della Bella, *J. Med. Chem.*, **6**, 248 (1963).

(5) W. Herz and J. L. Rogers, *J. Amer. Chem. Soc.*, **73**, 492 (1951).

(6) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 274.

(7) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(8) Modifications of the method are to be described in detail elsewhere.

(9) D. J. Finney, "Statistical Method in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952, pp 99–117.

(10) R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950).

Phosphorus–Nitrogen Compounds. 12. Phosphamidase Studies. 2. *N*-Alkylphosphoramidic Acids[1,2]

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Although a few *N*-arylphosphoramidic acids, most notably *N*-(4-chlorophenyl)phosphoramidic acid (CPA), have been studied with phosphamidase prepara-

(1) (a) Presented at the combined SE–SW Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970; (b) supported by Grant E-297 from the Robert A. Welch Foundation, Houston, Texas.

(2) For paper 11 see L. A. Cates, *J. Med. Chem.*, **13**, 301 (1970).