prepn of the incubation mixt of **8** gave a final soln of 1 mg/30 ml. Each mixt was incubated for 30 min in a shaker at 37°.

**Isolation Procedures.**—Each incubation mixt was extd twice with $Et_2O$. The combined ethereal layers were washed twice with $H_2O$, dried ($Na_2SO_4$), and evapd to dryness under vacuum. The residue was dissolved in MeOH (spectrograde) and was applied to analytical precoated tlc plates (GF 254 Merck, 20 × 20 cm, 0.25 mm). Sepn of **6** ($R_f$ 0.69) from the metabolites **7** and desmethyldiazepam ($R_f$ 0.45) was achieved in $CHCl_3$–$Me_2CO$–EtOH (8:1:1). In order to resolve desmethyldiazepam from **7** the $R_f$ 0.45 band was eluted with MeOH (spectrograde) and was subjected to a second tlc sepn using $C_6H_6$–EtOAc (5:1). Desmethyldiazepan ($R_f$ 0.1) and **7** ($R_f$ 0.2) were clearly sepd. Compd **7** was eluted with MeOH (spectrograde) in prepn for mass spectral analysis. Estimates of the yield of **7** by glpc analyses[14] indicated that about 50 μg was obtd from the $[^{18}O]H_2O$ incubation and 150 μg from the $[^{18}O]O_2$ incubation.

(14) W. Sadée and E. van der Kleijn, *J. Pharm. Sci.*, in press.

## Synthesis and Pharmacology of Some N-Substituted Derivatives of 1-Amino-4,6-dimethylbenzocyclobutene

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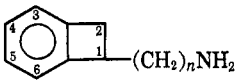
The potential medicinal applicability of benzocyclobutenes has been reported predominantly within the patent literature.[2-11] Early studies concentrated on the manipulation of 1-aminoalkylbenzocyclobutenes.




Since patents do not deal heavily in structure–activity relationships, it remained for Skorcz[2,4-6] to provide initial insight into the relative pharmacological activity of these compounds.

We describe below the synthesis and physiological action of precursors and derivatives of the heretofore unknown 1-amino-4,6-dimethylbenzocyclobutene·HCl.

**Biological Evaluation.**—Testing protocol consisted of suspending or dissolving all drugs in 0.5% methylcellulose soln followed by ip administration to white mice (17–20 g) at a dosage level of 100 mg/kg. Three animals were tested simultaneously with constant observation for 1 hr subsequent to injection and every 30 min thereafter for 2 hr. A final reading was taken at +24 hr.

In addition to testing the base moiety, its precursors, and derivatives, biological tests were preformed on other structurally similar compounds: 1-aminobenzocyclobutene·HCl (XII),[12] 1-indanamine·HCl (XIII),[13] benzylamine·HCl (XIV), and phenethylamine·HCl (XV).

Results are reported in Table I.

TABLE I
PHARMACOLOGIC RESULTS[a]

| Compd | CNS stim | CNS depression | Biphasic act. | Other |
|---|---|---|---|---|
| III | 0−+ | − | − | |
| IV | − | +++ | − | Transient action |
| V | ++ | − | − | Hypothalamic depression |
| VI | − | +++ | − | Skel musc relaxant |
| VII | − | + | − | Skel musc relaxant |
| VIII | − | + | − | Skel musc relaxant |
| IX | − | − | ++ | |
| X | − | − | ++ | |
| XI | − | − | + | Tranquilization |
| XII | − | + | − | Spinal stimulant |
| XIII | + | − | − | Hypersensitivity |
| XIV | 0 | 0 | − | |
| XV | ++ | − | − | Psychotropic |

[a] M. H. Malone and R. C. Robichand, *Lloydia*, **25**, 320 (1962).

The newly synthesized base compd V appears to be a moderately potent CNS stimulant differing in activity from its nonmethylated relative XII which exhibited central depression. Both side-chain fusion to the benzene ring and aromatic alkylation seem to effect the nature and strength of biological activity in this series. Acylation of V results in a nonspecific CNS depression on the order: *N*-Ac ≫ *N*-propionyl ≥ *N*-butyryl while arylation provides biphasic central action (stimulation–depression) with the latter predominating.

### Experimental Section[14]

**Trichloromethylmesitylene** (I).—A modification of the method of Hart and Fish[15] was employed. To a stirred slurry of 670 g (5.0 moles) of anhyd $AlCl_3$ in $CCl_4$ (3 l.) was added over a 3-hr period 300 g (2.31 moles) of commercial mesitylene. The mixt was maintained at 40° for 4 hr and, upon cooling, poured into 4 l. of cold 5% HCl. The org layer was then washed well ($H_2O$), evapd *in vacuo* to 1 l., dried ($Na_2SO_4$), and distd to provide 414 g (69%) of product: bp 119–121° (4 mm); lit.[15] 126° (5 mm).

**1,1-Dichloro-4,6-dimethylbenzocyclobutene** (II).—A scale-up of a reported procedure[16] was utilized. I (50 g, 0.21 mole) was placed under $N_2$ in a flask fitted with a condenser and maintained at 170°. After 9 hr, 71% (of theoretical) HCl had evolved. Cooling, filtration, and recrystn (pentane) of the ppt afforded 6.5 g (67%) of white cubes: mp 50–52°; lit.[16] 55–60°.

**4,6-Dimethylbenzocyclobutenone** (III).—II (26.0 g, 0.13 mole) was dissolved in 200 ml of EtOH and treated with a soln of 4.88 g (0.029 mole) of $AgNO_3$ in 750 ml of EtOH (80%) while briskly stirring. The suspension was warmed (0.5 hr), filtered, and flash-evapd and the residue was extd with petr ether. The ext was dried ($Na_2SO_4$) and evapd in a stream of dry air giving 16.0 g (85%) of solid yellow ketone: mp 40–42°; lit.[15] 45–46°.

**4,6-Dimethylbenzocyclobutenoxime** (IV).—To a cooled soln of NaAc (5.6 g, 0.041 mole) and $NH_2OH$·HCl (4.8 g, 0.069 mole) in

(1) Present address: Gillette Toiletries Company, South Boston, Mass. 02106.

(2) J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8**, 255 (1965).

(3) Ciba, Ltd., Belgian Patent 635,901, 1964; *Chem. Abstr.*, **62**, 3987*f* (1965).

(4) J. A. Skorcz and J. E. Kaminski, *J. Med. Chem.*, **8**, 732 (1965).

(5) C. Kaiser and C. L. Zirkle, U. S. Patent 3,149,159, 1964.

(6) J. A. Skorcz, J. T. Suh, C. I. Judd, M. Finkelstein, and A. C. Conway, *J. Med. Chem.*, **9**, 656 (1966).

(7) Colgate-Palmolive Co., German Patent 1,235,903, 1967; *Chem. Abstr.*, **68**, 59371 (1968).

(8) J. E. Robertson and J. A. Skorcz, U. S, Patent 3,308,157, 1967.

(9) Ciba, Ltd., Swiss Patent 454,130, 1968.

(10) J. A. Skorcz, U. S. Patent 3,359,300, 1967; *Chem. Abstr.*, **68**, 104832 (1968).

(11) J. A. Skorcz, U. S. Patent 3,408,391, 1968.

(12) L. Horner, W. Kormše, and K. Muth, *Chem. Ber.*, **91**, 430 (1958).

(13) "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1965, p 148.

(14) Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are corrected. Spectra (ir) were recorded on a Perkin-Elmer PE-21 spectrophotometer while nmr data were obtained on a Varian A-60 instrument. Elemental analyses were performed by Baron Consulting Co., Orange, Conn., and are indicated only by symbols when within ±0.4% of theoretical values.

(15) H. Hart and R. W. Fish, *J. Amer. Chem. Soc.*, **83**, 4460 (1961).

(16) H. Hart, J. A. Hartlage, R. W. Fish, and R. F. Rafos, *J. Org. Chem.*, **31**, 2244 (1966).

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.

**Acknowledgments.**—The authors are indebted to the Connecticut Research Foundation and National Institutes of Health (5-F1-GM-36,004) for their financial support. We also thank Dr. Albin Kocialski for arranging *in vivo* testing.

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

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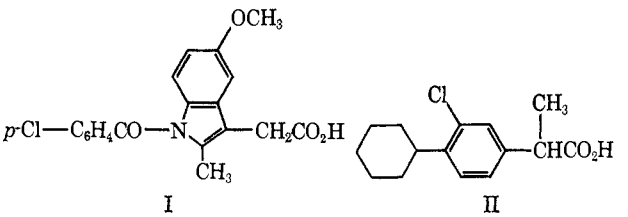
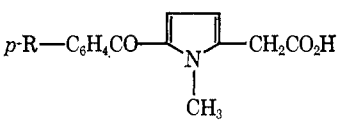
In a discussion of structure–activity relationships of indomethacin (I) and its analogs, T. Y. Shen proposed a "receptor site" for antiinflammatory activity for these compounds[1] having an interaction with three portions of the indomethacin molecule. He felt that the carboxyl function could bind to 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.