hr, then the hot solution was filtered. The filtrate was reduced to half its volume under reduced pressure, and on cooling a solid separated which was recrystallized (Me_2CO) to yield 0.55 g (29%) of light yellow cubes, mp 152–153°. *Anal.* ($C_{20}H_{24}N_2O_5$) C, H, N.

N-Amino-O,O′-diacetylnormorphine (4). To 1.9 g (0.005 mole) of N-nitroso-O,O′-diacetylnormorphine (**3**)[8] in 9 ml of glacial AcOH at 35° was added 9.5 g (0.145 g-atom) of Zn dust at such a rate that the temperature remained at 45–50°. H_2O (9.5 ml) was then added and the reaction mixture was maintained at 50° for 15 min. The mixture was filtered and the solid on the filter was washed with H_2O which was added to the filtrate. The solution was saturated with $NaHCO_3$ and extracted with $CHCl_3$, and the solvent was removed from the extract under reduced pressure at 40°. Recrystallization of the solid residue (EtOH) produced 0.85 g (46%) of white crystals: mp 171–172°; ir (KBr) 1738, 1764 cm^{-1} (C=O). *Anal.* ($C_{20}H_{22}N_2O_5$) C, H, N.

N-Aminonormorphine Hydrochloride (1). A solution of 0.2 g (0.0005 mole) of **4** in 10 ml of 10% HCl was maintained at 70–75° for 24 hr. The solvent was removed under reduced pressure, and the solid residue was recrystallized (absolute EtOH) to yield 0.12 g (70%) of light yellow crystals, mp 257–258° dec. *Anal.* ($C_{16}H_{19}ClN_2O_3$) C, H, Cl, N.

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Receptor Binding of the Analgetic Aryl Moiety. I. α-Prodine Analogs

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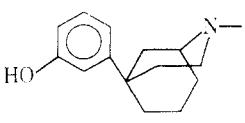
The study of strong analgetics has been the subject of several reviews.[1–5] Compounds of diverse chemical structure have been highly active in the laboratory and in the clinic. However, the mode of interaction of these analgetic drugs with their receptors is not very well understood.

In 1956, Beckett[6] postulated that the analgetic activity of a drug can be correlated with its absolute stereochemistry, and introduced a theoretical analgetic receptor site which has an anionic site, a cavity, and a flat portion allowing for van der Waal's forces binding the aromatic ring of the analgetic drug. Beckett's hypothesis fails to explain the analgetic activity of some compounds. For example, **1**[7] is as potent as



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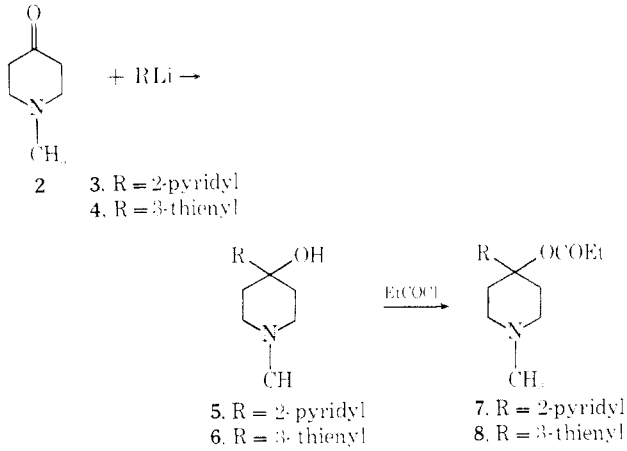
morphine, yet the aromatic group is fixed in the equatorial position while Beckett's hypothesis demands the aromatic group to be in the axial position.

Because of this and other exceptions,[8] Portoghese[9] recently postulated a new concept to explain the analgetic activity of conformationally unrelated analgetic drugs. The binding of the aromatic ring in analgetic molecules had been attributed to van der Waal's forces.[9] Since such forces are highly distance specific, Portoghese[9] assumed that hydrophobic attractive rather than van der Waal's forces are operative. However, it appears that the type of interaction between the aromatic group of the analgetic molecules and the postulated receptor has yet to be studied experimentally.

We would like to report the synthesis of two new compounds designed to study the type of interaction between the aromatic group of the analgetic molecules and the receptor site.

Synthetic Methods.—Analogs of the prodine analgetics were synthesized according to Scheme I. The

SCHEME I



Li salts of pyridine and thiophene were prepared by treatment of the corresponding bromo compounds with *n*-BuLi. Addition of these Li salts to **2** afforded the corresponding alcohols which were esterified by treatment with propionyl chloride.

Experimental Section[10]

1-Methyl-4-(2-pyridyl)-4-hydroxypiperidine (5).—To 0.1 mole of pyridyllithium in 150 ml of dry Et_2O was added dropwise at −70° with stirring under N_2 a solution of 0.1 mole of **2** in 100 ml of dry Et_2O over 10 min. The temperature was then allowed to rise to 0° and was maintained for 45 min. The reaction mixture was decomposed by pouring it onto ice–HCl (1:1). The Et_2O layer was separated and washed with dilute HCl and the acid solution was returned to the reaction mixture. This was made basic with cold 10% NaOH and extracted with Et_2O which was then dried (Na_2SO_4). Removal of Et_2O gave 10.5 g of **5** which distilled at 96° (0.1 mm). This fraction solidified on standing, mp 70–72°. For microanalysis **5** was converted to the corresponding methiodide salt by treating a small amount of **5** with excess MeI in MeOH at room temperature. The quaternary salt was recrystallized from MeOH–Et_2O, mp 250–251°. *Anal.* ($C_{12}H_{19}N_2OI \cdot H_2O$) C, H, N.

1-Methyl-4-(2-pyridyl)-4-propionoxypiperidine (7).—To 3.6 g of **5** in 50 ml of dry PhMe was added dropwise with stirring at room temperature a solution of 5.3 g of propionyl chloride in 20 ml of dry PhMe. The mixture was refluxed for 8 hr and allowed to stand overnight at room temperature. Removal of solvent *in vacuo* gave a white solid which was made alkaline with 5% $NaHCO_3$, extracted with Et_2O, and dried (Na_2SO_4). Removal of Et_2O *in vacuo* gave 4.6 g of **7**. For microanalysis, **7** was con-

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(4) H. B. Murphee, *Clin. Pharmacol. Therap.*, **3**, 473 (1962).
(5) L. P. Melletti and L. A. Woods, *Progr. Drug Res.*, **5**, 155 (1963).
(6) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).
(7) N. B. Eddy, *Chem. Ind.* (London), 1462 (1959).
(8) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).
(9) A. H. Beckett, *Progr. Drug Res.*, **1**, 455 (1959).
(10) Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. All analytical samples have nmr and ir spectra in agreement with the assigned structures.

verted to the methiodide salt as above, mp 195–196°. *Anal.* ($C_{15}H_{23}N_2O_2I$) C, H.

1-Methyl-4-(3-thienyl)-4-hydroxypiperidine (**6**) was prepared in 90% yield according to the method described for **5** using 0.14 mole of freshly prepared 3-thienyllithium and 0.14 mole of **2**. For microanalysis **6** was converted to the corresponding benzyl bromide salt in THF. The solid material was washed several times with absolute EtOH, mp 244–246°. *Anal.* ($C_{17}H_{22}BrNOS$) C, H, N.

1-Methyl-4-(3-thienyl)-4-propionoxypiperidine (**8**) was obtained by treatment of **6** with 3 equiv of propionyl chloride. For microanalysis **8** was converted to the corresponding benzyl bromide salt. *Anal.* ($C_{20}H_{26}BrNO_2S$) C, H, N.

Biological Data.—Using the mouse hot plate method, **7** had an ED_{50} of 16.0 mg/kg. The onset peak and duration are respectively 3.4, 26.1, and 151.2 min. Compound **8** had an ED_{50} of 3.9 mg/kg as compared with 1.3 for morphine and 7.5 for codeine. These results suggest that forces other than hydrophobic or van der Waal's are operative.

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The Biochemorphology of Cyclobutanecarboximides

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We have shown several imides of cyclobutanecarboxylic acid to have sedative and hypnotic properties.[1] The effects appear to be structure related since cyclobutanecarboxamide, a variety of small ring imides, and several imides of cyclobutane-1,1-dicarboxylic acid[2] are essentially inactive. To better ascertain the biochemorphology of the cyclobutanecarboximides we have synthesized and evaluated the imides in Table I. They were produced using either the reaction of cyclobutanecarboxamide with excess acetylating agent or amide acylation with cyclobutanecarbonyl chloride in pyridine. The compounds comprise related series. Their biological activity has been correlated with molecular structure, water solubility, and partition coefficients. They have been evaluated for general CNS depressant properties, barbiturate potentiation, myorelaxant, antitremorine, and anticonvulsant potency.

Experimental Section

Chemical Methods.—Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated by elemental symbols only, analytical results obtained for those elements were within ±0.4% of theoretical values.

N-Formylcyclobutanecarboxamide. Method A.—A solution of 0.4 g (0.009 mole) of formamide, and 10 ml of neutral alumina treated and KOH-dried pyridine was cooled in an ice bath. Cyclobutanecarbonyl chloride, 1 g (0.009 mole), was added with stirring. An exothermic reaction ensued. When it subsided the mixture was heated on a steam bath for 1 hr and poured into 100 g of crushed ice. The soluble product was separated by bringing the solution to pH 3 with 1 *N* HCl and extracting with two 50-ml fractions of $CHCl_3$. Evaporation of the solvent after Na_2SO_4 drying gave N-formylcyclobutanecarboxamide which was crystallized from pentane to yield 0.5 g (40%) of product, mp 90°. *Anal.* ($C_6H_9NO_2$) N.

N-Caproylcyclobutanecarboxamide. Method B.—Cyclobutanecarboxamide (0.89 g, 0.009 mole) was dissolved in 8 ml of pyridine treated as above, by heating on a steam bath for 15 min. To this 1.6 g (0.009 mole) of caproyl chloride was added with stirring and cooling. After the vigorous reaction ceased, the mixture was heated for 1 hr on a steam bath and poured over 100 g of crushed ice. The product was filtered, dried, and crystallized from pentane to yield 1.02 g (50%) of imide, mp 65°. *Anal.* ($C_{13}H_{23}NO_2$) N.

Solubility.—An excess of imide was shaken for 2 hr at 25° with 20 ml of distilled H_2O at 200 oscillations/min. The suspensions were filtered and the filtrates were analyzed for imide by uv spectrophotometry using the λ_{max} at 260 mμ.

Partition Coefficients.—The system 1-octanol–glass-distilled H_2O was used. The H_2O phase was presaturated with 1-octanol. The 1-octanol was washed with 6 *N* H_2SO_4, 6 *N* NaOH, and glass-distilled H_2O until the aqueous phase was neutral. The imide (40 mg) was dissolved in 20 ml of 1-octanol, and the solution was mixed with 200 ml of glass-distilled H_2O at 25° and shaken for 1.5 hr as above. The phases were separated and the H_2O layer was centrifuged for 1.5 hr at 2500 rpm. Uv spectroscopy, as above, was used to determine the imide in the H_2O phase; imide content of the 1-octanol layer was determined by difference. Data are expressed as ratios of 1-octanol content/H_2O content.

Pharmacological Methods.—In all of the following, mice were used once. They were previously untreated with any drug and permitted to feed *ad libidum*.

Bioassay for Sedative and Hypnotic Properties.—The depressant activity of the compounds was determined by observing their effects on the spontaneous activity and righting reflex of virgin female, Swiss–Webster mice weighing 18–22 g. When the righting reflex was lost a sleeping time determination was made. On oral administration, the compounds were given either as a solution or suspension in 0.2–0.4 ml of 1% gum tragacanth using a blunted and bent 18-gauge hypodermic needle feeding tube. On intraperitoneal administration the compounds were given as solutions or suspensions in 0.25% methylcellulose sterile vehicle. The volume of administered solution was 0.2–0.4 ml. In all experiments the control animals received vehicle. For each dose four control and four test mice were used.

Barbiturate Potentiation.—Mice, as above, weighing 18–30 g were used and the test substances were administered orally and intraperitoneally as above. Pentobarbital sodium (50 mg/kg) was administered 30 min after the test drug. All solutions were adjusted so that 0.2–0.4 ml was used. For each test and each control experiment five mice were used. One-way analysis of variance tests were run to determine the significance of differences between test group mean sleeping times and their respective controls. For all experiments with probabilities <0.01, the data were further analyzed using Duncans multiple range test. Generally, all animals lost the righting reflex within 10 min after pentobarbital injection. The animals were placed on their backs until spontaneous righting occurred. They were again placed on their backs until righting was effected within 5 sec at which time the animals were judged to have regained the righting reflex. The measure of potentiation used was the ratio (drug + barbiturate$_{\text{sleep time}}$)/(barbiturate$_{\text{sleep time}}$ + drug$_{\text{sleep time}}$).

Myorelaxant Activity.—Male Swiss–Webster mice weighing 20–22 g were used. The test compounds were given orally as above. Strychnine sulfate (2 mg/kg) in 0.25% methylcellulose sterile vehicle was administered intraperitoneally 30 min after the test substance. The strychnine dosage was 100% lethal in controls which died within 10–12 min. The ability of a drug to protect against strychnine-induced convulsions was assessed by survival of animals after 30 min and 24 hr. Survival for 30 min was judged as partial protection; survival for 24 hr was judged as complete protection.

Antitremorine Activity.—Male Swiss–Webster mice weighing 18–24 g were used. The test compounds were administered orally as above and at a dose of 1000 mg/kg. Tremorine (20 mg/kg) in 0.25% methylcellulose sterile vehicle was given intraperitoneally 30 min after the test substance. In controls this dose produced centrally mediated tremors plus signs of parasympathetic stimulation including salivation, lachrymation, diarrhea, and urination. Subjective grading was used to establish the degree of protection

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