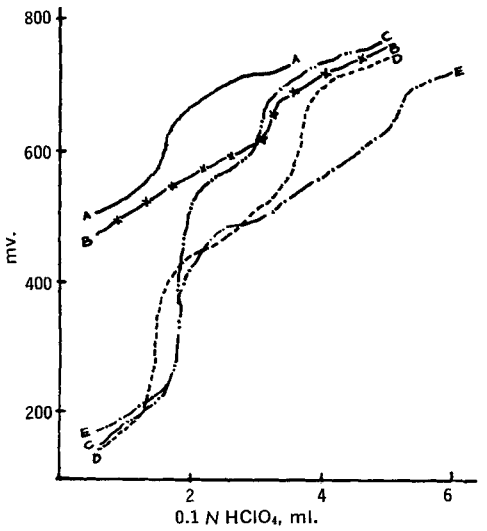

Fig. 2—Titration curves of glycine and its sodium salt individually as well as in combination with theophylline against 0.1 N acetous perchloric acid. Key: A, glycine, 15 mg.; B, glycine, 15 mg. and theophylline, 30 mg.; C, sodium glycinate, 17 mg.; D, sodium glycinate, 17 mg. and theophylline, 40 mg. (with salicylaldehyde treatment); E, sodium glycinate, 17 mg. and theophylline, 40 mg. (without salicylaldehyde treatment).

and sodium glycinate were analyzed by the modified method (Table I). The procedure was applied to determine the theophylline content of theophylline sodium glycinate NF and its tablets. The difference between the first and second end points corresponds to the amount of theophylline present. The results agree closely with those obtained by NF method (Table II).

The usual additives of the tablets except magnesium stearate do not seem to interfere with the determination of theophylline.

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Keyphrases

Theophylline combinations—nonaqueous titrations
Nonaqueous titration—acetous perchloric acid
Potentiometric analysis

Synthesis of Adamantyl Analogs of Analgesics

By A. NELSON VOLDENG, C. ALLEN BRADLEY, ROBERT D. KEE, EDDIE L. KING, and FRED L. MELDER

The synthesis of adamantyl esters related to heroin, meperidine, and aspirin is reported. Preliminary comparisons in mice indicate the adamantyl ester (V) is more potent and longer acting than meperidine hydrochloride.

THE INCORPORATION of the adamantyl moiety into drugs has been reported to increase the duration of action, and sometimes potency, of the parent compound. For example, 1-(1-adamantyl)-3-(*p*-tolylsulfonyl) urea, the adamantyl analog of tolbutamide, was found to be a very potent and long-acting oral hypoglycemic agent possessing activity two to fifteen times that of tolbutamide (1). The 17β-adamantoate ester of 19-nortestosterone is reported to be much longer acting with little androgenic activity as compared to other esters of the same steroid (2). This increase in duration of action was explained as being due to a decreased rate of enzymatic hydrolysis of the ester, thus making the 17β-hydroxyl group unavailable for biological oxidation to an inactive anabolic agent(2, 3).

In the penicillin series, resistance to penicillinase has been found by experiment to be associated with a side chain derived from a sterically hindered acid. Doyle and Nayler believe that restriction of rotation about the single bond linking the side chain to the amide carbonyl group constrains the molecule to adopt a conformation which is not readily accommodated at the active site of the enzyme (4). Substitution of the usual side chain with various adamantane carboxamide groups provides potent antibiotics that are penicillinase resistant and in some cases are active against Gram-negative bacteria (5–8).

Because of these profound pharmacological effects within different classes of drugs, the authors chose to prepare adamantyl analogs of known analgesics. The proposed compounds were expected to be much

Received January 24, 1968, from the School of Pharmacy, University of Arkansas Medical Center, Little Rock, AR 72205
Accepted for publication March 8, 1968.
This investigation was supported by grant NB 06759 from the National Institutes of Health, Bethesda, Md.

TABLE I—COMPARISON OF REACTION TIME (IN SEC.) OF MEPERIDINE AND ITS ADAMANTYL ANALOG (V) IN MICE[a]

Drug	Mean Reaction Time Recorded after Injection i.p., sec.[b] 0	30	60	90	120	150	180	210
Meperidine hydrochloride, 50 mg./Kg.	0.97 ± .11	1.21 ± .13	0.97 ± .11	0.87 ± .12	0.79 ± .18	0.83 ± .07	0.78 ± .05	0.78 ± .03
Adamantyl analog (V), 50 mg./Kg.	0.96 ± .14	1.2 ± .10	1.31 ± .16	1.17 ± .10	1.06 ± .10	1.00 ± .10	0.92 ± .06	0.85 ± .05
Adamantyl analog (V), 87 mg./Kg.[c]	0.91 ± .17	1.37 ± .22	1.18 ± .13	1.14 ± .13	1.10 ± .10	1.04 ± .07	0.94 ± .07	0.85 ± .05

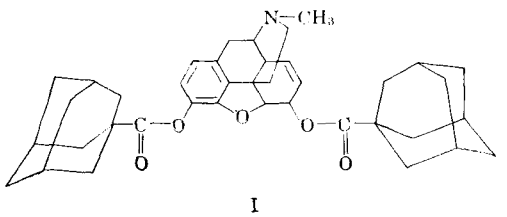
[a] Method: see *Reference 13*, 16 mice per dose, water bath temperature 56°. [b] Mean reaction time ±95% confidence limit. [c] Equimolar to 50 mg. meperidine hydrochloride.

longer acting since the ester function would not be hydrolyzed as rapidly *in vivo*. In addition, these analogs should still retain some activity since the moiety being replaced is not essential for the analgesic action.

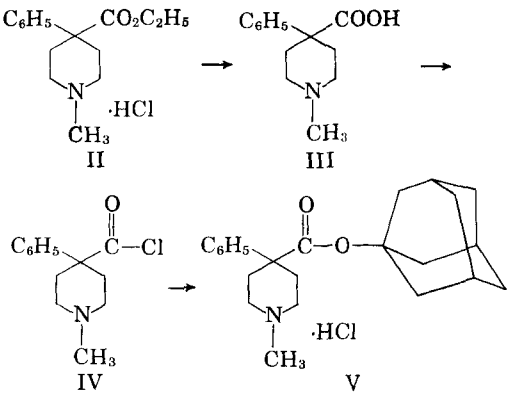
Certain esters related to dihydroheroin also possess analgesic activity (9). Both the 3,6-diglycyl and 3,6-di-(*o*-acetyl-L-tyrosyl) esters have the same toxicity as dihydromorphine but their analgesic actions are greater. Substitution of a propionyl or a carbomethoxy group for the 4-carboethoxy radical of meperidine does not materially alter activity (10). Other substitutions including larger ester functions such as phenyl or butyl at this point decrease the analgesic effect. Chlorthenoxazine, 2-(2-chloroethyl)-2,3-dihydro-1,3-benzoxazin-4-one, is an example of a cyclic derivative of aspirin (acetylsalicylic acid) and salicylamide. It is reported to be more potent and a longer-acting analgesic than either of the parent molecules (11).

The adamantyl analog of heroin, 3,6-diadamantoylmorphine (I), was prepared in 70% yield by reacting morphine with adamantoic anhydride (12). Attempts to simplify the procedure and improve the yield of I were not successful. Only starting materials could be obtained when morphine was heated with adamantoyl chloride (12) in the presence of pyridine, or when stirred with trifluoroacetic anhydride and adamantoic acid. The nitrate, sulfate, phosphate, and hydrochloride salts of the diester (I) were prepared but are not soluble in water. Since the compounds could not be pharmacologically evaluated by injection of a solution, the diester (I) was purified for analysis and testing as the free base.

Meperidine (II) was hydrolyzed to the acid (III) and esterified by reaction of the acid chloride (IV) with 1-adamantyl alcohol. Using the method of Ben-Bassat (13) comparison of the analgesic activity demonstrated the adamantyl analog to be more potent and longer acting than meperidine. The results are shown in Table I.

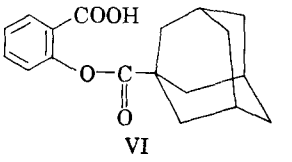


I



II III IV V

The adamantyl analog of aspirin, adamantoylsalicylic acid (VI), was prepared by reaction of salicylic acid with adamantoyl chloride (12) in the presence of pyridine.



VI

Attempts to prepare the adamantyl ester related to *d*-propoxyphene have been unsuccessful. The incorporation of the adamantyl moiety into appropriate positions of different classes of drugs and their pharmacological evaluation is presently being pursued in these laboratories.

EXPERIMENTAL[1]

3,6-Diadamantoylmorphine (I)—Anhydrous morphine was prepared by dissolving morphine sulfate in water and adding 10% sodium bicarbonate until precipitation was complete. The alkaloid was filtered, rinsed with water, and dried *in vacuo* for 24 hr. Anhydrous morphine (2.0 Gm., 0.007 mole) was added to a solution of 7.2 Gm., 0.020 mole, of adamantoic anhydride (12) in 15 ml. anhydrous toluene and the mixture heated for 24 hr. under reflux in an oil bath maintained at 130°. The solution was allowed to cool and the toluene removed *in*

[1] Melting points were determined on a Thomas-Hoover capillary melting point apparatus or a Fisher-Johns hot stage and are corrected. Infrared spectra were obtained using a Beckman IR10 spectrophotometer with KBr pellets. Elemental analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England. Adamantoic acid and 1-adamantanol were purchased from Aldrich Chemical Company.

vacuo. The oily residue was dissolved in anhydrous ether and a solution of hydrogen chloride in ether was added until precipitation was complete. The hydrochloride salt was filtered, added to a 10% sodium hydroxide solution (20 ml.), and extracted twice with 100-ml. portions of ether. The ether solutions were combined, washed with 20 ml. of water, dried over anhydrous magnesium sulfate, filtered, and the solvent removed *in vacuo*. A small amount of absolute methanol (5 ml.) was added to the oily residue, affording crystals of I (2.9 Gm., 70%) which were filtered, m.p. 239–241°. Recrystallization from ethyl acetate furnished an analytical sample, m.p. 240–241°. The infrared spectrum showed the characteristic ester C=O peaks at 1720 and 1750 cm.$^{-1}$ (14). The infrared spectrum of heroin, 3,6-diacetylmorphine (15) also showed two ester C=O peaks (1735 and 1755 cm.$^{-1}$).

Anal.—Calcd. for $C_{39}H_{47}NO_5$: C, 76.81; H, 7.76; N, 2.29. Found: C, 76.47; H, 7.65; N, 2.26.

1-Methyl-4-phenylisonipecotic Acid (III)—A solution of meperidine hydrochloride (II, 5.0 Gm., 0.018 mole) in 40 ml. of methanol was added to a solution of potassium hydroxide (5.0 Gm.) in 50 ml. of water and heated to reflux for 2 hr. The solution was allowed to cool and the methanol removed *in vacuo*. The alkaline solution was extracted with 30 ml. ether and adjusted to pH 6 with dilute hydrochloric acid. The white powder was filtered, rinsed with 50 ml. water, and dried for 24 hr. *in vacuo*, affording a quantitative yield of III, m.p. 310° dec. [lit. (16) m.p. 309–310°].

Adamantyl N-Methyl-4-phenylisonipecotate Hydrochloride (V)—A mixture of the acid III (2.7 Gm., 0.013 mole) and 5 ml. thionyl chloride was heated to reflux in an oil bath for 30 min., then 10 ml. of anhydrous benzene was added and heating continued for 30 min. After cooling, the acid chloride IV was filtered under suction and washed twice with 20 ml. anhydrous benzene as rapidly as possible. The white powder was quickly added to a solution of 1-adamantanol (3.0 Gm., 0.020 mole) in 20 ml. anhydrous benzene and the mixture was heated to reflux. A solution of anhydrous pyridine (1.2 ml., 0.015 mole) in 10 ml. of anhydrous benzene was slowly added and heating was continued for 4 hr. The flask was allowed to cool and the solvent removed *in vacuo*. To the white residue was added 80 ml. of water and the mixture was warmed to dissolve most of the material. After filtration under reduced pressure the insoluble material was stirred with 50 ml. of warm water. The mixture was filtered yielding 1.2 Gm. of unreacted 1-adamantanol. The aqueous solutions were combined, cooled in an ice bath, and 10% sodium carbonate was added until the extract was alkaline (pH 11). The mixture was placed in the refrigerator overnight and filtered affording 3.8 Gm. of the crude ester, V. Recrystallization from alcohol–water gave a white product which was dried *in vacuo* and dissolved in 30 ml. of anhydrous ether. A saturated solution of hydrogen chloride in anhydrous ether was slowly added with stirring and the white powder was filtered. Recrystallization from absolute alcohol gave an analytical sample of V (3.0 Gm., 60%), m.p. 267°. The infrared spectrum showed the characteristic ester C=O at 1725 cm.$^{-1}$ (14).

Anal.—Calcd. for $C_{23}H_{32}ClNO_2$: C, 70.84; H, 8.27; N, 3.59; Found: C, 70.74; H, 8.27; N, 4.31.

Adamantoyl Salicylic Acid (VI)—To a solution of 1.6 ml. of anhydrous pyridine and 2.7 Gm. of salicylic acid (0.020 mole) in 20 ml. of anhydrous benzene was added a solution of 3.9 Gm., 0.020 mole of adamantoyl chloride (12) in 20 ml. of anhydrous benzene. The mixture was heated to reflux for 3 hr. and allowed to stand at room temperature overnight. After filtration the solvent was removed *in vacuo*. The oily residue became crystalline upon standing at room temperature for 1 hr., affording 7 Gm. of crude VI, m.p. 145–147°. Recrystallization from alcohol–water gave an analytical sample of VI (4 Gm., 67%), m.p. 166–167°. The infrared spectrum showed the characteristic ester C=O at 1750 cm.$^{-1}$ and the broad acid C=O at 1690 cm.$^{-1}$ (14).

Anal.—Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71; Found: C, 71.91; H, 6.73.

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Keyphrases

Adamantyl analogs—synthesis
Analgesics—adamantyl analogs
IR spectrophotometry—structure
Meperidine adamantyl analog—analgesic activity