into ice–water–$NH_4Cl$ and treated with a little $NH_4OH$. The ether was separated and extracted three times with excess 8–10% HCl. The combined extracts were made basic with $NH_4OH$ and the liberated base was shaken into ether. Drying and evaporation of the ether left 36.5 g. of crude 2-benzyl-1,2-dihydro-1,3-dimethyl-4-propylpyridine which was dissolved in 35 ml. of methanol and 150 ml. of 10% aqueous NaOH. To the stirred solution was added 7.7 g. of $NaBH_4$. After the initial vigorous reaction had subsided, the solution was refluxed for 1.5 hr., cooled, poured into ice–water, and extracted three times with ether. The dried ($Na_2SO_4$) ethereal extracts were evaporated to dryness, and the residue was subjected to short-path distillation at 0.5 mm. (bath temperature 135–140°); yield 30 g. It gave 31 g. (62% based on starting methiodide) of hydrochloride (from ether with dry HCl), m.p. 124–127°; needles from ethyl acetate, m.p. 134–135°, after drying at 65° (80 mm.).

*Anal.* Calcd. for $C_{17}H_{26}ClN$: C, 73.0; H, 9.3. Found: C, 73.1; H, 9.5.

The **picrate** of I (yellow needles from acetone) melted at 149–150°.

*Anal.* Calcd. for $C_{23}H_{28}N_4O_7$: C, 58.5; H, 6.0. Found: C 58.3; H, 5.7.

**Cyclization of I. A. With HBr.**—A solution of 3.6 g. of I in 35 ml. of 48% HBr was kept at a bath temperature of 135–140° for 26 hr., poured into ice–water, made alkaline with $NH_4OH$, and extracted with ether. Evaporative distillation (bath temperature 150–155°) of the residue from the dried ether extracts gave 2.7 g. of impure **α-2,9-dimethyl-5-propyl-6,7-benzomorphan (III)** which, from acetone–ether–dry HCl gave 1.4 g. (32%) of the **hydrochloride** salt, m.p. 194–195°, identical (melting point and infrared data) with that prepared from β-tetralone.[3] No β-isomer (II) could be found. When 85% $H_3PO_4$ (48 hr., bath temperature 180°) was used instead of 48% HBr, the results were essentially the same.

**B. With $AlBr_3$.**—To 20 ml. of carbon disulfide and 1.9 g. of I·HCl, 2.0 g. of $AlBr_3$ was added. The mixture was stirred for 3 hr. at room temperature. Carbon disulfide was decanted from a thick syrup which was dissolved with cold water. The solution was made basic with $NH_4OH$, and the suspension was extracted several times with ether. Drying and evaporation of the ether left an oil which was distilled as described in the previous experiment; yield 1.4 g. It was converted to the hydrochloride with acetone–HCl, and the solution was evaporated to dryness *in vacuo*. The syrup resulting was dissolved in a little warm acetone. Ether was added to incipient turbidity and after seeding with III·HCl,[2] the solution was left at room temperature depositing 0.64 g. (34%) of the hydrochloride of III during 24 hr. The filtrate and acetone–ether washings, seeded with II·HCl (β-isomer),[3] deposited 0.09 g. of crystals identical with the II·HCl (infrared and melting point data) prepared from β-tetralone.[3]

**Conversion of III to α-2,9-Dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan (IV).**—To an ice-cold mixture of 16 ml. of fuming $HNO_3$ and 10 ml. of glacial acetic acid was added dropwise during 1 hr., 0.8 g. of III in 10 ml. of acetic acid. The solution was stirred overnight at room temperature. Most of the acetic acid was evaporated at reduced pressure (bath temperature about 60°). The resulting mixture was made alkaline with 9% $NH_4OH$ and extracted three times with chloroform. The extracts were dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue in 0.5 ml. of acetone was treated with 0.5 g. of picric acid to give 1.3 g. (60%) of **α-2,9-dimethyl-2′-nitro-5-propyl-6,7-benzomorphan picrate**, m.p. 202–203°.

*Anal.* Calcd. for $C_{23}H_{27}N_5O_9$: C, 53.4; H, 5.2. Found: C, 53.5; H, 5.4.

The base (0.62 g., prepared from 1.2 g. of picrate with aqueous LiOH–ligroin) was hydrogenated in 5–10 ml. of methanol with 0.5 g. of 5% Pd–$BaSO_4$ to absorb 3 *M* equiv. of hydrogen. The residue from the filtered mixture was evaporated to dryness and dissolved in 8 ml. of 10% $H_2SO_4$, and the solution was treated during 0.5 hr. with 0.28 g. of $NaNO_2$ in 2 ml. of water. The reaction flask was then placed in an oil bath at 60°. Several drops of concentrated $H_2SO_4$ was added, and the mixture was stirred at 65–75° for 1 hr., filtered, ice cooled, made alkaline with $NH_4OH$, and extracted ($CHCl_3$). The extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was evaporatively distilled at 0.5 mm. (bath temperature 170–180°). Crystallization of the residue from a little acetone gave 0.1 g. (10% over-all from III) of IV, indistinguishable from that prepared by two alternative methods described previously.[6]

## 1-(3-Phenylpropyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline, a Pharmacologically Active Narcotine Derivative

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Opium, depending on its source, is known to contain from 3–10% of an isoquinoline alkaloid called narcotine (noscapine, I). While several other alkaloids obtained from opium have been of great value in medicine, little use has been found for narcotine despite its apparent efficacy as a nonaddictive antitussive.[1]

Influenced by the nonaddictiveness and ready availability of narcotine, we have been examining this compound as part of our program to develop improved medicinal agents, especially those affecting the central nervous system. We have prepared derivatives based on the total narcotine skeleton, as well as several compounds derived from a fragmentation product, cotarnine (II). While our work was in progress, we learned from Kaneko[2] that most of our experiments had been anticipated by his group in Japan. There is, however, one new compound of interest which they do not mention. This compound, 1-(3-phenylpropyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (III), is easily obtained in 60–70% yield by treating II with 3-phenylpropylmagnesium bromide.

In Table I are given the analgetic activity and acute toxicity of III and those of meperidine and codeine (subcutaneous administration, mouse hot plate assay).[3] Compound III is comparable to codeine in potency and it has about the same therapeutic index as meperidine or codeine.

TABLE I

PHARMACOLOGICAL COMPARISON OF III, MEPERIDINE, AND CODEINE

| Compd. | $ED_{50}$, mg./kg.[b] | $LD_{50}$, mg./kg. |
|---|---|---|
| III[a] | 9.1 | 232 |
| Meperidine[a] | 4.5 | 180 |
| Codeine[a] | 7.5 | 270 |

[a] HCl salt. [b] Based on new values for morphine, codeine, meperidine, etc., obtained with more senstive mice: A. E. Jacobson and E. L. May, submitted for publication.

In addition, preliminary antimicrobial screening[4] has

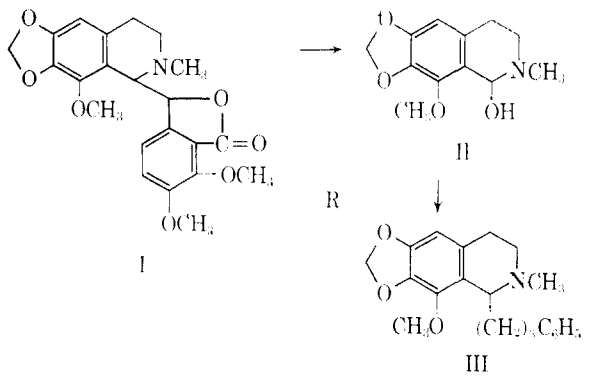
(1) H. A. Bickerman, *Med. Clin. N. Am.*, **45**, 805 (1961), and references therein.

(2) H. Kaneko, Y. Nagai, and M. Isogaki, *Yakugaku Zasshi*, **84**, 988 (1964); *ibid.*, **84**, 1094 (1964). We would like to thank Dr. Kaneko for a copy of the manuscript in advance of publication.

(3) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). We are indebted to Dr. Nathan Eddy, Mrs. Louise Atwell, and Mrs. Wendy Ness for these data. During the course of testing for analgesia, Mrs. Atwell observed that III caused considerable diuresis in the mice; morphine-like analgetics, in general, tend to produce the opposite effect.

(4) Antimicrobial screening was carried out in the Smith Kline and French Laboratories, Philadelphia, Pa. We are indebted to Dr. M. Gordon for these data.

revealed activity against several microorganisms, among them a resistant strain of *Staphylococcus aureus*.



I II III

## Experimental

**1-(3-Phenylpropyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (III) Hydrochloride.**—3-Phenylpropylmagnesium bromide (0.18 mole) was prepared from 3-phenylpropyl bromide by the Grignard procedure and added (rapidly) to a vigorously stirred suspension of cotarnine[5] (II, 0.04 mole) in ether. The mixture was stirred for about 2 hr. and poured into a mixture of $NH_4Cl$, ice, and water. The aqueous solution was separated and washed with ether. The combined organic solution was extracted with dilute HCl, cooled in ice, and made basic with concentrated $NH_4OH$. Extraction with chloroform and ether, followed by drying over $MgSO_4$, gave about 17 g. of a red oil. The oil was dissolved in ether and a hydrochloride (HCl gas) was prepared. The solid was crystallized from acetone–methanol–ether to give III·HCl, 8.9 g. (60%), m.p. 182.5–183.5 or 193°, depending on its crystalline form.

*Anal.* Calcd. for $C_{21}H_{25}ClNO_3$: C, 67.28; H, 6.72; Cl, 9.45; N, 3.73. Found: C, 67.30; H, 6.91; Cl, 9.53; N, 3.82.

The infrared spectrum of III·HCl was consistent with the given structure; $\nu_{max}^{Nujol}$ 1370 and 930 (methylenedioxy), 1270 and 1060 ($OCH_3$), 900 and 790 (isolated phenyl hydrogen), 733 and 690 (monosubstituted benzene), and 2500 cm.$^{-1}$ ($R_3N^+H$). The n.m.r. spectrum was also fully consistent with the structure III.

(5) The cotarnine was obtained as a fragmentation product of narcotine by the general procedure of T. Anderson, *Ann.*, **86**, 179 (1853), as cited in the "Chemistry of the Opium Alkaloids," L. F. Small and R. E. Lutz, Government Printing Office, Washington, D. C., 1932, p. 49. We would like to thank the Mallinckrodt Chemical Works, St. Louis, Mo., for a generous supply of noscapine.

# Structure–Activity Relationships in Antiinflammatory and Analgesic Compounds Chemically Related to α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide

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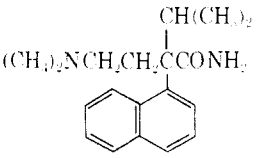
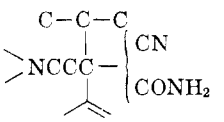
In previous papers we reported the pharmacological screening results of many naphthalene derivatives,[1] comparing them, in some cases, with corresponding benzene compounds. More specifically, 1-naphthylacetonitriles, 1-naphthylacetamides, and 1-naphthylmethyl ketones substituted in the α-position with basic radicals were studied. The most interesting result arising from these studies was the noteworthy antiinflammatory activity shown by the primary 1-naphthylacetamides, and in particular by α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide (**1**, naphthypramide),[2] a substance which is under clinical trial.



1

Some conclusions may be drawn about relationships between antiinflammatory and analgesic activities, and the structure of the above compounds and of the substances synthesized in this work. First, these activities are imparted to the compounds by the presence of a $CONH_2$ or CN group. Ketones and tertiary amides were poorly active or essentially inactive. Another important conclusion is that 1-naphthalene derivatives are, on the whole, more interesting than the corresponding benzene compounds. Substitution of the 1-naphthyl group with an isopropyl, 1-naphthylmethyl, or 2-naphthyl group leads in general to a noticeable reduction or, at most, to some retention of activity; however, the potency is never enhanced. For optimal activity, the α-methylene group in amides and nitriles must be disubstituted with an aminoethyl group along with an alkyl group. Disubstitution with two aminoethyls leads to poorly active compounds. Branching the alkyl chain is also required for the highest activity.

From these considerations the tentative conclusion may be drawn that, in the series investigated, the skeleton **2** represents the best structure for high-potency antiinflammatory and analgesic compounds.



2

## Experimental[3]

**Chemistry.**—The new compounds are listed in Table I, along with yields, physical constants, and analytical data.

**α,α-Diisopropyl-α-(2-dimethylaminoethyl)acetonitrile (I).**—Ferric nitrate [$Fe(NO_3)_3 \cdot 9H_2O$] (0.37 g.) and then sodium (13.53 g., 0.59 g.-atom) were added, in small portions and with stirring, to anhydrous liquid ammonia (265 ml.), making certain that between additions the solution's color changed from blue to gray. The mixture was then stirred for an additional 15 min.; after that α,α-diisopropylacetonitrile[4] (36.7 g., 0.293 mole) and 308 ml. (0.588 mole) of a 20.5% ethereal solution of 2-(N,N-dimethylamino)-1-chloroethane were added. The solution was then stirred for 30 hr. at the reflux temperature of liquid ammonia, using a reflux condenser cooled with Dry Ice–acetone. The ammonia was then evaporated on a water bath, and the residue was cautiously decomposed with water and extracted with ether.

(1) (a) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 731 (1964); (b) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **19**, 933 (1964); (c) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 589 (1965); (d) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 594 (1965).

(2) S. Casadio, G. Pala, E. Marazzi-Uberti, and G. Coppi, *Experientia*, **20**, 457 (1964).

(3) Boiling points are uncorrected. Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

(4) M. S. Newman, T. Fukunaga, and T. Miwa, *J. Am. Chem. Soc.*, **82**, 873 (1960).