various Hofmann degradations will be described in our detailed article.

Pilocereine (I) is not only a unique cactus alkaloid bearing some structural resemblance to certain bisbenzylisoquinoline bases,[6] but it also appears to be the first naturally occurring alkaloid with an isobutyl fragment (suggestive of a leucine or equivalent precursor in the plant) fused to carbon. We hope to dwell on the biogenetic implications of this observation in a future paper.

We are greatly indebted to the American Heart Association for support in the initial phases of this work and to the National Heart Institute of the U.S. Public Health Service for a research grant (H-2040).

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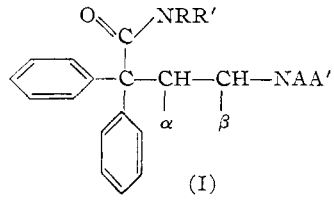
RECEIVED JUNE 25, 1956

A NEW SERIES OF POTENT ANALGESICS

Sir:

Continuing our research program on substituted phenylpropylamines,[1] we have synthesized and screened for pharmacological activity, a series of over 100 new basic amides of structure I (CONRR′ = secondary or tertiary amide group; α and β = H or CH_3; NAA′ = tertiary amine group).



(I)

Some of these compounds are highly active analgesics in mice, rats, cats, guinea pigs, dogs and man.

The relation between chemical structure and analgesic activity within this series can be described as follows: (1) NRR′: highest activity was found among N-pyrrolidine- and N,N′-dimethylamides. (2) α and β: branching the side chain with a methyl-group in α-position, considerably increases analgesic activity; the β-CH_3 isomers are much less active. (3) NAA′: the most active compounds are N-substituted morpholines. Some piperidines, pyrrolidines and dimethylamines were also found to cause marked analgesia.

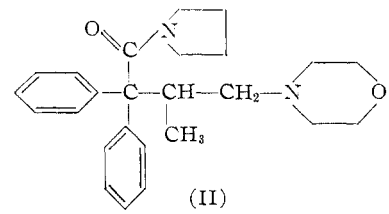
(4) Quaternary amines are devoid of analgesic activity.

(5) In the α-CH_3 series, one of the optical isomers of each enantiomorphic pair is twice as active as the racemic mixture; the other optical isomer is devoid of significant analgesic activity. The spatial configuration of the analgesically active optical isomers is probably identical and related to that of D-(−)-alanine.[2]

(6) Reduction or complete loss in activity occurs when one or both phenyl groups are substituted or replaced, or when the ethyl side chain is lengthened or shortened.

These basic amides (I) are formed when a secondary or tertiary amine is allowed to react in suitable conditions with the corresponding acid chloride.[1d, 1f, 3,4]

The tertiary amides of type I may also be prepared by condensation of an N,N′-disubstituted diphenylacetamide with a tertiary aminoalkyl chloride, using a condensing agent such as sodamide.[1d,1f,4,5] Mixtures of α-CH_3- and β-CH_3-isomers of type I are formed when tertiary aminoisopropylchlorides are used in this reaction.



(II)

Serial number R 610 (II: *dl*-2,2-diphenyl-3-methyl-4-morpholinobutyryl-pyrrolidine) appears to be one of the promising candidates for further study (m.p. 170–172°; *Anal.* Calcd. for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14; found: C, 76.31; H, 8.23; N, 7.21).

The *d*-isomer of II, serial number R 875, is twice as active as the racemic mixture (m.p. 180–184°; $[\alpha]^{20}D + 25.5 \pm 0.5°$ in benzene; $c = 5.0$). As an analgesic, R 875 is 60 to 100 times more active than meperidine, 10 to 40 times more active than morphine, 5 to 20 times more active than methadon and about four times more active than diacetylmorphine (heroin) in various experimental conditions.

In animals R 875 has a higher oral activity and a better therapeutic ratio than any other analgesic compound tested.

Preliminary double-blind experiments with the racemic modification of II in patients indicate an analgesic potency of about three times that of morphine; no side effects were observed after subcutaneous injections of up to 12 mg. R 610. The physicochemical and pharmacological properties of these compounds will be published elsewhere.

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RECEIVED JUNE 19, 1956

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