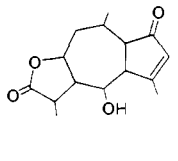
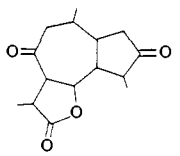
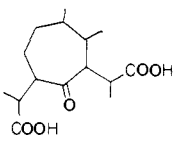


XI



XII



XIII

The cyclopentenone moiety established previously[2] can be placed on the guaiazulene template in two different fashions, leading to III or XI. Quantitative evaluation of the nuclear magnetic resonance spectra of I, II, III and IV to be discussed in detail later, indicate that helenalin is represented by I (*e.g.*, the calculated ratio of C=C—C—H to CH,CH_2 to CH_3 in XI is 4:4:6, in III 2:3:9; found: 2.2:3.2:8.6).

Similarly it was possible to differentiate between the two isomeric ketolactones VII and XII by this method. The calcd. ratio of HC—C=O to CH,-CH_2 to CH_3 in XII is 7:3:9; calcd. for VII is 6:4:9; found: 5.8:3.9:9.5.

Support for the resulting expression VII for tetrahydrohelenalone was found in the base catalyzed cleavage of VII to a dicarboxylic acid, $C_{15}H_{22}O_5$ (λ_{max} 236 mμ, ϵ 7700) first observed by Herz.[4] The ultraviolet spectrum of this compound is very similar to that of Butenandt acid.[5] We would like to propose the following scheme to rationalize this unusual reaction: VII → α,β-unsaturated ketoacid ⇄ trienediol ⇄ conjugated enedione ⇄ vinylogous β-diketone → XIII. The nature of the changes involved in the formation of XIII requires the presence of a 1,5-diketone which is absent in XII.

Acknowledgments.—We are indebted to Eli Lilly and Co. for financial support. Our thanks are due to Prof. J. Waugh for his help with the NMR spectra, to Prof. R. Adams for a sample of helenalin, to Dr. A. Eschenmoser for a gift of alantolactone and to Prof. W. Herz for sending us a copy of his manuscript prior to publication.

(4) W. Herz, private communication.

(5) L. F. Fieser, THIS JOURNAL, **75**, 4386 (1953).

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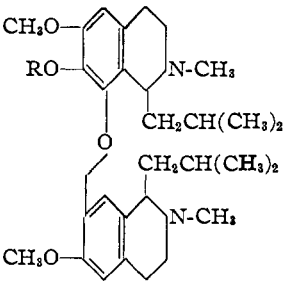
RECEIVED MAY 28, 1956

ALKALOID STUDIES. XIV.[1] THE STRUCTURE OF THE CACTUS ALKALOID PILOCEREINE

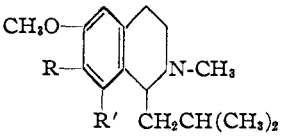
Sir:

In the first paper of this series[2] attention was called to the fact that the alkaloid pilocereine ($C_{30}H_{44}N_2O_4$),[3] isolated from several giant cacti,[2,4] appears to be quite unusual since even the most complicated cactus alkaloid of established constitution (lophophorine)[5] possesses only the empirical formula $C_{13}H_{17}NO_3$. We should now like to report the key experiments which lead to the assignment of structure I for pilocereine.

Cleavage of pilocereine methyl ether (II) with potassium in liquid ammonia[6] led to a mixture of phenolic and non-phenolic fractions readily separable by extraction with alkali. Methylation of the crude phenolic portion (III) with diazomethane in methanol–ether furnished 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IV) which was identified with a synthetic specimen[7] by infrared comparison of the bases and by mixture melting point determination of the respective picrates. The non-phenolic mixture could be resolved into its components by careful chromatography on acetic acid-deactivated alumina and yielded in order of increasing polarity 1-isobutyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (V), 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IV) and 1-isobutyl-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (VI). Identity of IV and V with synthetic material[7,8] was established by direct comparison of the respective bases and of their crystalline picrates while VI (kryptophenolic) was first methylated with diazomethane in methanol-ether for nine days to give 1-isobutyl-2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (VII), which proved to be identical with the base (infrared comparison and undepressed mixture melting point of respective picrates) recently synthesized[8] from mescaline. The isolation of all four possible cleavage products of the methyl ether II confirms unambiguously the skeletal structure of pilocereine. The kryptophenolic character[2] of the alkaloid and the difficulty encountered in methylation require that the free phenolic group be located at C-7 as shown in I. Potassium–ammonia cleavage of pilocereine (I) itself proceeded by a more complicated path since in addition to III[9] and V there were also encountered rearrangement products. These experiments and the results of



I, R = H
II, R = CH_3



III, R = OH; R′ = H
IV, R = CH_3O; R′ = H
V, R = R′ = H
VI, R = CH_3O; R′ = OH
VII, R = R′ = CH_3O
VIII, R = C_2H_5O; R′ = H

(1) Paper XIII, O. O. Orazi, R. A. Corral, J. S. E. Holker and C. Djerassi, *J. Org. Chem.*, **21**, Sept. (1955).

(2) C. Djerassi, N. Frick and L. E. Geller, THIS JOURNAL, **75**, 3632 (1953).

(3) G. Heyl (*Arch. Pharm.*, **239**, 451 (1901)), who first isolated this alkaloid in an amorphous form, assigned to it the $C_{30}H_{44}N_2O_4$ formula while our analytical data of the crystalline base and its derivatives were more compatible (ref. 2) with $C_{30}H_{42}N_2O_4$. The presently described structure elucidation requires the H_{44} formulation.

(4) C. Djerassi, C. R. Smith, S. P. Marfey, R. N. McDonald, A. J. Lemin, S. K. Figdor and H. Estrada, THIS JOURNAL, **76**, 3215 (1954).

(5) For a review on cactus alkaloids see L. Reti, *Progr. Chem. Org. Nat. Prod.*, **6**, 242 (1950).

(6) *Cf.* M. Tomita, *ibid.*, **9**, 175 (1952).

(7) C. Djerassi, J. J. Beereboom, S. P. Marfey and S. K. Figdor, THIS JOURNAL, **77**, 484 (1955).

(8) C. Djerassi, F. X. Markley, R. Ehrlich and R. Mirza, *J. Org. Chem.*, **21**, Sept. (1956). The synthesis of V, VI and VIII was carried out exactly as described in ref. 7 for IV by starting with the appropriate β-phenylethylamine.

(9) Ethylation with diazoethane furnished 1-isobutyl-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (VIII) which was shown to be identical with a synthetic specimen (ref. 8).

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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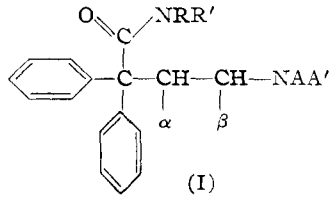
A NEW SERIES OF POTENT ANALGESICS

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.

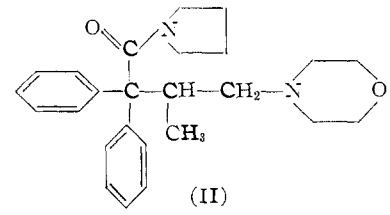
(4) Quaternary amines are devoid of analgesic activity.

(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.

CONTRIBUTION FROM THE
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