TABLE I

ACYLAMIDES R—C(=O)—R'

| R | R' | Formula | B.p. °C. | Mm. | $d^{25}_4$ | $n^{25}D$ | Nitrogen, % Calcd. | Found | Pungency[d] |
|---|---|---|---|---|---|---|---|---|---|
| $C_4H_9$[a] | Morpholino | $C_9H_{17}NO_2$ | 67–70 | 0.1 | 0.960 | 1.4705 | 8.18 | 8.31 | + |
| $C_5H_{11}$ | Morpholino | $C_{10}H_{19}NO_2$ | 82–86 | .1 | 1.000 | 1.4732 | 7.56 | 7.83 | ++ |
| $C_6H_{13}$ | Morpholino | $C_{11}H_{21}NO_2$ | 90–94 | .05 | 0.989 | 1.4723 | 7.63 | 7.13 | +++ |
| $C_7H_{15}$ | Morpholino | $C_{12}H_{23}NO_2$ | 87–97 | .02 | .976 | 1.4712 | 6.57 | 6.60 | ++++ |
| $C_8H_{17}$ | Morpholino | $C_{13}H_{25}NO_2$ | 105–114 | .1 | .965 | 1.4684 | 6.16 | 6.16 | +++++ |
| $C_9H_{19}$ | Morpholino | $C_{14}H_{27}NO_2$ | 148–152 | .1 | .960 | 1.4705 | 5.80 | 5.95 | +++++ |
| $C_{10}H_{21}$ | Morpholino | $C_{15}H_{29}NO_2$ | 20–21[e] | .. | .954 | 1.4710 | 5.48 | 5.55 | ++++ |
| $C_{11}H_{23}$ | Morpholino | $C_{16}H_{31}NO_2$ | 23–24.5[e] | .. | .937 | 1.4704 | 5.20 | 5.52 | +++ |
| $C_{13}H_{27}$ | Morpholino | $C_{18}H_{35}NO_2$ | 32–34[e] | .. | ... | .... | 4.71[e] | 4.76 | + |
| $C_{15}H_{31}$ | Morpholino | $C_{20}H_{39}NO_2$ | 42–44[e] | .. | ... | .... | 4.30[f] | 4.62 | + |
| $C_6H_{13}SCH_2$ | Morpholino | $C_{12}H_{23}NO_2S$ | 128–132 | 0.3 | 1.053 | 1.5023 | 5.71 | 5.51 | ++ |
| $C_7H_{15}$ | Hexamethylenimino | $C_{14}H_{27}NO$ | 93–96 | .01 | 0.932 | 1.4754 | 6.22 | 6.26 | + |
| $C_7H_{15}$ | Diethylamino | $C_{12}H_{25}NO$ | 80–82 | .15 | .869 | 1.4482 | 7.03 | 7.04 | ++ |
| $C_7H_{15}$ | Dipropylamino | $C_{14}H_{29}NO$ | 92–96 | .1 | .866 | 1.4501 | 6.16 | 6.20 | + |
| $C_8H_{17}$ | Pyrrolidino | $C_{13}H_{25}NO$ | 123–126 | .4 | .923 | 1.4650 | 6.63 | 6.57 | + |
| $C_8H_{17}$ | Hexamethylenimino | $C_{15}H_{29}NO$ | 100–110 | .06 | .922 | 1.4700 | 5.85 | 5.60 | + |
| $C_8H_{17}$[b] | Diethylamino | $C_{13}H_{27}NO$ | 94–98 | .16 | .866 | 1.4493 | 6.56 | 6.26 | ++ |
| $C_8H_{17}$ | Ethyl-*n*-propylamino | $C_{14}H_{29}NO$ | 104–108 | .15 | ... | 1.4498 | 6.16 | 6.44 | ++ |
| $C_8H_{17}$ | Dipropylamino | $C_{15}H_{31}NO$ | 114–118 | .3 | .862 | 1.4509 | 5.80 | 5.85 | ++ |
| $C_9H_{19}$ | Hexamethylenimino | $C_{16}H_{31}NO$ | 128–131 | .1 | .919 | 1.4751 | 5.53 | 5.17 | + |
| $C_9H_{19}$ | Diethylamino | $C_{14}H_{29}NO$ | 94–98 | .05 | .873 | 1.4505 | 6.16 | 6.45 | ++ |
| $C_9H_{19}$ | Dipropylamino | $C_{16}H_{33}NO$ | 129–132 | .2 | .865 | 1.4518 | 5.48 | 5.58 | ++ |

[a] L. Médard, *Bull. soc. chim.*, [5] **3**, 1343 (1936); b.p., 293°. [b] M. Montagne, *Ann. chim.*, **13**, 40 (1930); b.p., 167–169° at 10 mm. [c] Melting point. [d] + is very slight or negative, ++ slight, +++ hot not persistent, ++++ hot, +++++ very hot. [e] *Anal.* Calcd. for $C_{18}H_{35}NO_2$: C, 72.67; H, 11.86. Found: C, 72.35; H, 11.57. [f] *Anal.* Calcd. for $C_{20}H_{39}NO_2$: C, 73.61; H, 12.08. Found: C, 73.57; H, 11.80.

morpholides in the fatty acid series are much more potent peppers than the corresponding piperidides.

It is of interest to note that when a sulfur is introduced into the fatty acid chain the isoster also has a much decreased pungency. It is our observation that the pungency in the taste sensation may be due only to the stimulation of sensory nerves since these substances, when rubbed on the hands in low concentrations, produce the same effect which lasts for several hours.

The amides were prepared by the addition of an ethereal solution of the appropriate acyl chloride to a cold ethereal solution of the amide. Triethylamine was employed as a hydrogen chloride accepter.

### Experimental

The preparation of pelargonic morpholide will illustrate the method used for all compounds listed in Table I.

**Morpholide of Pelargonic Acid.**—Into a 3-necked reaction flask, fitted with stirrer, reflux condenser and dropping funnel, was placed a mixture of 0.5 mole of triethylamine and 0.5 mole of morpholine and 500 ml. of anhydrous ether. The mixture was cooled in an ice-bath to near 0°, stirring started, and a solution of 0.5 mole of pelargonyl chloride in 100 ml. of anhydrous ether added slowly. After all of the pelargonyl chloride had been added, the mixture was stirred for an additional hour and allowed to warm up to room temperature. The resulting slurry was filtered and the cake washed several times with dry ether. The filtrate and washings were washed with dilute acid, dilute alkali and finally with water. The ethereal solution was dried over anhydrous sodium sulfate and filtered. The ether was stripped off and the resulting oil vacuum distilled. A yield of 94% of product with b.p. 105–114° (0.1 mm.) was obtained.

**Evaluation of Pungency.**—To establish the presence or absence of pungency very small amounts of the pure amides were placed on the tip of the tongue. For amides that possessed weak pungency this amount was increased to a drop of the pure compound. For compounds found to possess pungency by this initial test, stock solutions of the amides were prepared in 40% ethanol to contain 100 mg./ml. Initially one drop of this solution was placed on the tip of the tongue. If little or no pungency was noted, increasing amounts of the stock solution up to 0.1 ml. were used. In the cases where pungency was noted on this test, the stock solution was serially diluted with water and the test repeated until no pungency could be noted by a majority of the tasters with a 0.1-ml. sample. In the cases of moderate to very strong pungents, where the effect persisted in some cases for hours, only one test was run each day in order to avoid abnormal responses.

Since the number of participants in these tests was limited to 7–10 persons, no statistical evaluation of the results is made. The tests were made primarily to establish the presence of pungency and to place approximately the maximum pungency reaction with respect to structure of the amide. Therefore, the relative orders of pungency assigned to the amides in Table I may be somewhat altered if standardized tests are made on a sufficiently large statistically random sample.

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## Open Chain Analogs of Morphine

BY ALFRED LÖFFLER AND DAVID GINSBURG

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Several excellent reviews describing various classes of analgesic compounds have appeared recently.[1,2] During the course of our work on morphine synthesis, it seemed desirable to utilize certain intermediates with the view of preparing potentially analgesic compounds containing a nitrogen atom on a carbon atom beta to a quaternary carbon atom. We wish to report the results obtained with

(1) E. J. Fellows and G. E. Ullyot, "Medicinal Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 390–437.

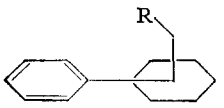
(2) J. Lee, *ibid.*, pp. 438–466.

2-phenylcyclohexanone and 1,2,3,4,4a,9,10,10a-octahydro-4-oxophenanthrene as starting materials.

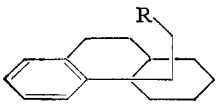
The N-methyl- and the N,N-dimethyl derivatives of 1-phenyl-1-(β-aminoethyl)-cyclohexane[3] and of 1,2,3,4,4a,9,10,10a-octahydro-4a-(β-aminoethyl)-phenanthrene[4] were prepared by mono-[5] and dimethylation[6] by well known procedures.

The amines were tested for analgesic activity through the courtesy of Dr. Nathan B. Eddy, Chief Pharmacologist of the U.S. Public Health Service. We are indebted to Dr. Eddy for allowing us to publish Table I.

TABLE I



| R | Analgesic effect, $ED_{50}$, mg./kg. | Remarks |
|---|---|---|
| $NH_2$ | | Not significant |
| $NHCH_3$ | 62.9 | Similar to morphine in onset (9 min.) and duration (151 min.) of effect |
| $N(CH_3)_2$ | 24.7 | Onset 9 min., duration 92 min.; less intense effect than morphine |



| | | |
|---|---|---|
| $NH_2$ | None | Hyperactivity at 80 mg./kg. and above |
| $NHCH_3$ | None | Convulsant in one of 10 at 80 mg./kg. |
| $N(CH_3)_2$ | 36.2 | Onset 15 min., duration 112 min.; less intense than morphine |

The phenylcyclohexanes are distinctly more effective than the phenanthrenes. In both groups, the analgesic effect is best with the dialkylamine. Preparation and testing of similar and more complex analogs are being continued.

### Experimental

**1-Phenyl-1-(β-methylaminoethyl)-cyclohexane.**—1-Phenylcyclohexaneethylamine hydrochloride[3] (2.4 g.) was dissolved in a small volume of water. The solution was basified and the free base taken up in ether. After evaporation of the ether, methyl formate (6 g.) was added and the mixture was refluxed for one hour. The excess solvent was removed and the residue was dissolved in dry ether (10 ml.). This solution was added with stirring to lithium aluminum hydride (1 g.) in dry ether (20 ml.). After refluxing of the ether had ceased, the solution was stirred at room temperature for 2 hr. Ethyl acetate was added to decompose the excess reagent. After addition of sodium hydroxide solution the clear ether solution was separated and the aqueous layer was extracted with two portions of ether. The combined ether extracts were shaken with 3 portions of 6 *N* hydrochloric acid (15 ml.). The combined acid extracts were evaporated to dryness *in vacuo*, the residue was basified and the free amine was again taken up in ether. The treatment with acid and evaporation were repeated. The residue was taken up in acetone; the solution deposited crystals after standing overnight. **The secondary amine hydrochloride** formed small colorless needles, m.p. 161–162° (acetone); the pure material weighed 0.6 g.

*Anal.* Calcd. for $C_{15}H_{24}NCl$: N, 5.5; Cl, 13.9. Found: N, 5.4; Cl, 13.9.

**1-Phenyl-1-(β-dimethylaminoethyl)-cyclohexane.**—1-Phenylcyclohexane-ethylamine hydrochloride (4.8 g.) was dissolved in water and basified to phenolphthalein with 40% sodium hydroxide. The amine was taken up in ether and the solvent was evaporated. To the residue was added at 0°, 90% formic acid (7.8 g.) and 30% formalin (3.5 ml.). The solution was heated on the steam-bath at 90–100° for 1 hr. during which time carbon dioxide was evolved. Heating was continued for an additional 12 hr. Concentrated hydrochloric acid (10 ml.) was added and heating on the steam-bath was continued for 2 hr. and the solution was then evaporated to dryness under reduced pressure. The solid residue was crystallized from acetone–petroleum ether, then twice from acetone. **The tertiary amine hydrochloride** melted at 178–180° (acetone). The pure material weighed 1.2 g.

*Anal.* Calcd. for $C_{16}H_{26}NCl$: N, 5.2; Cl, 13.2. Found: N, 5.2; Cl, 13.3.

**1,2,3,4,4a,9,10,10a-Octahydro-4a-(β-methylaminoethyl)-phenanthrene.—The hydrochloride** of this amine was prepared analogously[5] from 1,2,3,4,4a,9,10,10a-octahydro-4a-(β-aminoethyl)-phenanthrene.[4] It formed small colorless needles, m.p. 212° (acetone).

*Anal.* Calcd. for $C_{17}H_{26}NCl$: N, 5.0; Cl, 12.7. Found: N, 4.8; Cl, 12.7.

**The picrate** had m.p. 162–164° (ethanol).

*Anal.* Calcd. for $C_{23}H_{28}O_7N_4$: N, 11.9. Found: N, 11.7.

**1,2,3,4,4a,9,10,10a-Octahydro-4a-(β-dimethylaminoethyl)-phenanthrene.—The hydrochloride** was prepared analogously[6] from the corresponding primary amine. It formed colorless crystals, m.p. 207–208° (acetone–petroleum ether).

*Anal.* Calcd. for $C_{18}H_{28}NCl$: N, 4.8; Cl, 12.1. Found: N, 4.7; Cl, 12.0.

**The picrate** had m.p. 187–188° (ethanol). Ginsburg and Pappo[4] report m.p. 187–188.5° for this compound.

**Acknowledgment.**—We wish to thank Dr. L. F. Small and Dr. N. B. Eddy of the National Institutes of Health, Bethesda, Md., for their interest and coöperation.

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(3) W. E. Bachmann and E. J. Fornefeld, THIS JOURNAL, **73**, 51 (1951).

(4) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 1524 (1953).

(5) O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **34**, 2220 (1951).

(6) *Cf. Org. Syntheses*, **25**, 89 (1945).

## The Cyclohexyl and Cyclopentylmethyl Radicals

BY FRANK H. SEUBOLD, JR.[1]

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The aluminum chloride-catalyzed interconversion of cyclohexane and methylcyclopentane *via* the intermediate carbonium ions has been adequately demonstrated.[2] In view of the known rearrangement of the neophyl radical,[3] it was of interest to determine whether a similar rearrangement would occur in the cyclohexyl–cyclopentylmethyl radical system.

The di-*t*-butyl peroxide-catalyzed decompositions of cyclohexanecarboxaldehyde and cyclopentaneacetaldehyde in the liquid phase at 130 ± 5° gave as the only six-carbon atom products cyclohexane and methylcyclopentane, respectively. No evidence for rearrangement in either case was discovered, although hydrogen atom migration in the cyclopentylmethyl radical cannot be excluded.

As an example of a radical in which 1,2-hydrogen

(1) Union Oil Company, Research Center, Brea, California.

(2) H. Pines, L. Farkas Memorial Volume, Research Council of Israel, Special Publication No. 1, Jerusalem, 1952, summarizes the study of the mechanism of this isomerization.

(3) W. H. Urry and M. S. Kharasch, THIS JOURNAL, **66**, 1438, (1944); S. Winstein and F. H. Seubold, Jr., *ibid.*, **69**, 2916 (1947); F. H. Seubold, Jr., *ibid.*, **75**, 2532 (1953).