mole of acetyl bromide, the ratio remaining constant for 22 hours. This result corresponds to a product containing 0.64 mole of ethyl acetate per mole of acetic acid and differs sufficiently from the value of this ratio which was observed by Farkas, *et al.*,[2] to eliminate acetyl bromide as a possible intermediate in the oxidation reaction.

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The Synthesis of 2-Ethylhexanol-1-C^{14} and Esters[1]

BY JOSEPH L. KALINSKY AND ALLAN WEINSTEIN

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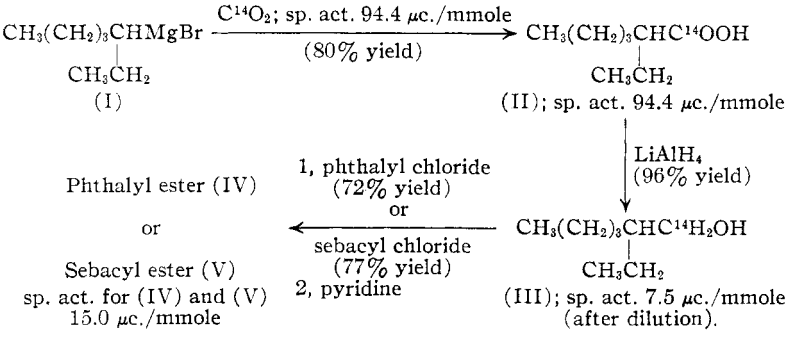
The sebacyl and phthalyl esters of 2-ethylhexanol-1-C^{14} were required at this Laboratory for the evaluation of primary plasticizers and synthetic lubricants using radioisotope-tracer techniques. These syntheses were accomplished by the radiocarbonation of 3-heptylmagnesium bromide (I), using a method similar to that of Dauben, Reid and Yankwich,[2] followed by lithium aluminum hydride reduction of the resulting 2-ethylcaproic acid-1-C^{14} (II). The 2-ethylhexanol-1-C^{14} (III) produced was esterified by the acid chloride–pyridine technique.



The alcohol and esters so obtained were identical in physical properties (including infrared spectra) with the pure unlabeled compounds.[3]

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(1) The opinions or assertions herein are those of the authors, and are not to be construed as reflecting the views of the Navy Department or the Naval Service at large.

(2) (a) W. G. Dauben, J. C. Reid and P. E. Yankwich, *Anal. Chem.*, **19**, 828 (1947); (b) M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert and P. E. Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 178.

(3) The full experimental details of the preparations described in this paper have been deposited as Document number 4229 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints or $1.25 for 35 mm. microfilm, payable to Chief, Photoduplication Service, Library of Congress.

Pungents. Fatty Acid Amides[1]

BY LEONARD M. RICE, CHARLES H. GROGAN, BERNARD H. ARMBRECHT AND E. EMMET REID

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Pungent principles or irritants have been discussed in recent reviews.[2,3] Although most of the pungents are amides, this is not always the case, as for example, gingerone and gingerol. In amides such as piperidine and chavicine the amine moiety is piperidine; in capsicin it is vanillylamine.

Staudinger, *et al.*,[4] studied the relationship of various acids with different amines with respect to pungency. They concluded that the amide linkage was necessary, since a salt did not give the same action. They prepared various amides of piperidine using fatty acids. With the lower or higher members of the fatty acid series they did not observe any peppers. Asano, *et al.*,[5] have expanded this work and found that the piperidides of the fatty acids were most pungent at pelargonic acid and that this pungency decreased in going up or down the series. It is interesting that furylvaleric piperidide has a strong taste. This acid, if split enzymatically, would approximate the C_9 length. Mitter and Ray[6] have found that with the acylated isobutylamines the highest degree of activity lies with the unsaturated fatty acids, 2-heptenoic and 2-nonenoic. Also when employing vanillylamine they found that the fatty acid moiety gave maximal pungency at the C_9-acid.

As part of our continuing study of various amides, we have found that the morpholides of fatty acids containing from seven to twelve carbon atoms are strong pungents. We have found in this series of morpholides that the greatest activity is produced when the fatty acid moiety is octanoic, nonanoic or decanoic. When the acid portion of the amide was either increased or decreased in length the activity was diminished. It was of interest to study the amine moiety in the most potent acid range in order to find out how essential the morpholine portion might be. When pelargonic acid was used, which exhibited maximum pungency in the morpholine series, and the heterocyclic part of the molecule was contracted to pyrrolidine or expanded to hexamethylenimine, the products obtained were almost devoid of pungency. In a like manner when diethylamine, dipropylamine or ethylpropylamine was substituted for morpholine, the resulting amides had very little pungency. It thus appears that the morpholides occupy a unique place in pungency not previously recognized. Indeed, the

(1) Supported by a grant from the Geschickter Fund for Medical Research, Inc.

(2) M. B. Jacobs, *Am. Perfumer*, **48**, #7, 60 (1946).

(3) S. Takata, *Koryo*, #4, 6 (1948).

(4) (a) H. Staudinger and H. Schneider, *Ber.*, **56**, 699 (1923); (b) H. Staudinger and F. Muller, *ibid.*, **56**, 711 (1923).

(5) (a) M. Asano and F. Nakatomi, *J. Pharm. Soc. Japan*, **53**, 174 (1933); *C. A.*, **27**, 2672, 2703 (1933); (b) M. Asano and T. Kanematsu, *J. Pharm. Soc. Japan*, **531**, 375 (1926); *C. A.*, **20**, 2844 (1926).

(6) P. C. Mitter and S. C. Ray, *J. Indian Chem. Soc.*, **14**, 421 (1937).

TABLE I

ACYLAMIDES $R-\overset{\overset{O}{\|}}{C}-R'$

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[c]	..	.954	1.4710	5.48	5.55	++++
$C_{11}H_{23}$	Morpholino	$C_{16}H_{31}NO_2$	23–24.5[c]	..	.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.