o-(α-phenylallyl)-phenol, unadmixed with any o-cinnamylphenol. Similarly, o-cinnamylphenol, prepared by direct alkylation of phenol, was free from o-(α-phenylallyl)-phenol.

Study of the rearrangement behavior of mixtures of allyl β-naphthyl ether with cinnamyl phenyl ether or 2-hexenyl phenyl ether showed that the rearrangement of allyl aryl ethers is intramolecular.

Resorcinol 2-hexenyl monoether and other hexenylresorcinols were prepared.

By use of a molecular still the polymeric products formed during pyrolysis of phenyl allyl ether were separated into a dimer and trimer of o-allylphenol. Considerable evidence supports o-(2-(o-allylphenoxy)-propyl)-phenol as the structure of the dimer.

EVANSTON, ILL. RECEIVED SEPTEMBER 21, 1936

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

A Series of N-Methyl Amides[1]

BY G. F. D'ALELIO[2] AND E. EMMET REID

In order to bring out the analogies of the N-monomethyl amides to the acids we have prepared the series from the normal acids, formic to stearic. Although some of these are recorded in the literature the data on all except the acetyl are fragmentary. We have compared a number of preparation methods which have been proposed for N-alkyl amides and have investigated some of their reactions. The physical properties of our compounds are given in Tables I and II and their melting points, along with those of the corresponding acids are plotted in Fig. 1. Using Swietoslawski's[3] values for the other elements the average value for the atomic refraction of nitro-

TABLE I

PHYSICAL PROPERTIES AND ANALYSES OF THE N-METHYL AMIDES

No.	B. p. °C.	Press., mm.	M. p. amide, °C.	M. p. acid, °C.	Diff.	Nitrogen, % Found	Calcd.
1	131.0	90	− 5.4	8.4	−13.8	23.64	23.72
2	140.5	90	28.0	16.6	11.4	19.05	19.17
3	146.0	90	−43.0	−20.8	−22.2	16.03	15.90
4	156.0	90	− 5.2	− 5.5	− 0.3	13.81	13.86
5	169.0	90	−25.5	−34.0	8.5	12.09	12.17
6	183.0	90	13.6	− 3.9	17.5	10.78	10.85
7	151.0	15	14.0	− 8.9	22.9	9.67	9.79
8	161.5	15	38.9	16.3	22.6	8.84	8.91
9	175.0	15	39.1	12.3	26.8	8.11	8.18
10	...	..	57.3	32.0	25.3	7.54	7.56
11	...	..	56.0	27.8	28.2	6.99	7.03
12	...	..	68.4	43.2	25.2	6.60	6.57
13	...	..	68.2	41.5	26.7	6.05	6.12
14	...	..	78.4	53.9	24.5	5.74	5.81
15	...	..	78.3	52.3	26.0	5.43	5.48
16	...	..	85.5	61.8	23.7	5.17	5.20
17	...	..	84.8	60.7	24.1	4.87	4.94
18	...	..	92.1	68.8	23.3	4.62	4.71

TABLE II

PHYSICAL PROPERTIES OF THE N-METHYL AMIDES OF THE LOWER ACIDS

No. of C atoms in acid	n^{20}_D	d^0_4	d^{25}_4	d^{35}_4	Mol. ref. Found	Calcd.
1	1.4300	1.0114	0.9961	...	15.23	15.30
2	1.4301[a]	...	.9571	0.9481	20.51	19.91
3	1.4345	0.9508	.9304	...	24.64	24.51
4	1.4365	.9308	.9108	...	29.05	29.11
5	1.4401	.9239	.9033	...	33.61	33.72
6	1.4431	...	.8925	.8849	37.77	38.32
7	1.4450[b]	...	.8869	.8795	42.99	42.99

[a] The values for N-methyl acetamide were determined also over the following range of temperatures, n^t_D where t = 35, 1.4253; 33, 1.4263; 32, 1.4268; 31, 1.4272; 30, 1.4277; 29, 1.4282; 28, 1.4286; 27, 1.4290; 26, 1.4294. [b] Franchimont and Klobbie, *Rec. trav. chim.*, **6**, 247 (1887), give sp. gr. 0.895 at 15° or 0.894^{15}_4. Their product had m. p. 9° and b. p. 265.6–266.5° at 758 mm.

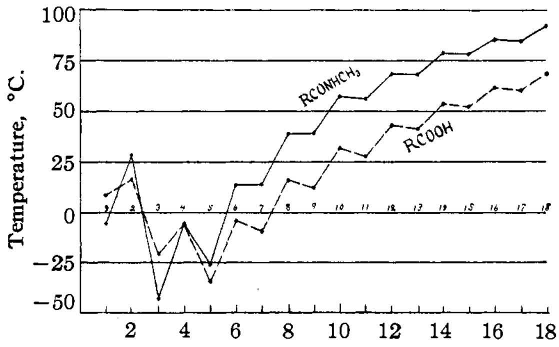

Fig. 1.—Melting points of acids and of their N-methyl amides.

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(1) From a part of the Ph.D. dissertation of G. F. D'Alelio, June, 1935.

(2) The Charles J. O'Malley Fellow of Boston College.

(3) Swietoslawski, THIS JOURNAL, **42**, 1945 (1920).

gen in these amides is 2.76. The curves for the melting points of these amides and of the acids are strikingly alike. The liquid N-methyl amides resemble the acids in viscosity. The lower members of the series are practically tasteless, but a peppery taste appears with the fourth and reaches a maximum value with the tenth, which has an intense burning taste and numbs the tongue. The toxicities increase likewise. Nos. 7, 8 and 9 are local anesthetics.[4]

Chemical Reactions

The mono-methyl amides, like acetamide,[5] form two types of hydrochlorides (a) $RCONHCH_3 \cdot HCl$ and (b) $(RCONHCH_3)_2 \cdot HCl$. In a non-polar solvent type (a) salts are formed, while in the absence of any solvent, type (b) result. Melting points and analyses of our preparations appear in Table III.

TABLE III

MELTING POINTS AND ANALYSES OF THE HYDROCHLORIDES OF THE METHYL AMIDES

	Melting points, °C.		Chlorine, %	
No.	$RCONHCH_3HCl$	$(RCONHCH_3)_2HCl$	Calcd.	Found
1	82.8–85.0	......	37.13	37.00
2	67.2–69.4	......	32.42	32.50
3	....	84–85	19.43	19.38
4	....	106.4–108	16.83	16.79
5	....	17–20	14.85	14.79
6	....	—1 to 3	13.40	13.15
7	....	32–34	12.03	12.00
8	....	38–40	11.00	10.90

Sodium reacts readily with formamide[6] but hardly at all with its N-methyl derivative or with other N-methyl amides at room temperature. It does react with their solutions in boiling toluene. Amides form mercury derivatives[7] but the N-methylamides do not. Treatment of N-methyl acetamide with nitrous acid converts it into its nitroso compound, b. p. 116.3°, m. p. −8.5°, n^{25}_D 1.4415, d^0_4 1.1007, d^{25}_4 1.0709, mol. refr. 25.10, calcd. 25.32. Refluxing N-methyl acetamide with acetic anhydride gives N-methyldiacetamide,[8] b. p. 194.2°, m. p. −46.8°, n^{25}_D 1.4502, d^0_4 1.0904, d^{25}_4 1.0663, mol. refr. 28.9, calcd. 27.9. With phosphorus pentoxide a complicated reaction occurs: N-methyldiacetamide is formed in 19% yield. N-Bromo-N-methyl acetamide is obtained readily as light yellow prisms, m. p. 123.5° but is very unstable, readily giving up its bromine. It does not undergo the Hofmann[8] degradation which accords with the prediction of Stieglitz.[9]

Experimental

Preparation of N-Methyl Amides.—The most generally useful method was to drop the acid chloride very slowly, with constant stirring, into three moles of amine[10] in concentrated aqueous solution. For the first nine members the temperature was kept at −20 to −10° during the addition. The methyl amides were caused to separate by the addition of solid caustic potash to the mixture. The separated amide was dried over caustic potash, and distilled. For the higher members a large excess of amine was used, and cooling was effected by tap water. Troublesome emulsions result unless the acid chloride is added at an extremely slow rate At the completion of the reaction the mixture was placed in a separatory funnel, the aqueous layer drawn off, and the amide taken up in benzene or ether. The solution was dried and the amide recovered by evaporation of the solvent and then recrystallized from anhydrous methanol. The yields run from 85 to 95%. Similar yields of the lower amides were obtained when the amine was passed into a solution of the acid chloride in dry toluene at −10° followed by the addition of 20% sodium hydroxide solution.

For comparison various other methods of preparing amides were tried. The reaction of dry methylamine on esters proved to be very slow but with an excess of the aqueous amine 68% of the heptamide was obtained after several days. From the sodium salt of an acid and methylamine hydrochloride as recommended by Verley[11] and Menschutkin[12] a good yield of the crude amide was obtained but it was difficult to purify. Acetamide[13] and its sodium salt[14] were methylated, yields 50–60%. The methyl amides of formic and acetic were obtained by passing the amine through the heated acids.[15]

N-Nitroso-N-methyl Acetamide.—To one mole of methyl acetamide and three moles of sodium nitrite dissolved in a minimum amount of water, concentrated hydrochloric acid was added slowly. When the reaction was complete the mixture was cooled, the oily layer separated, dried and distilled. On five runs the yields varied from 74–80%. *Anal.* % N calcd. 27.45; found 27.41.

N-Methyl Diacetamide.—N-Methyl acetamide was refluxed with 2.8 moles of acetic anhydride and the product fractionated in a precision still, yield 68%. *Anal.* % N calcd. 12.17; found 12.14.

N-Bromo-N-methyl Acetamide.—To 0.1 mole of N-methyl acetamide in 25 cc. of anhydrous ethyl acetate, 0.15 mole of bromine was added. Silver oxide was added slowly with rapid stirring until the bromine color disap-

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[4] Macht and D'Alelio, *Am. J. Physiol.*, **116**, 104 (1936).

[5] Titherly, *J. Chem. Soc.*, **79**, 411 (1901); Holden, *ibid.*, **101**, 1875 (1912); Pinner, *Ber.*, **25**, 1435 (1882).

[6] P. A. Magill, *Ind. Eng. Chem.*, **26**, 612 (1934).

[7] Strecker, *Ann.*, **103**, 324 (1858); Markownikoff, *Z. Chem.*, **6**, 533 (1863).

[8] A. W. Hofmann, *Ber.*, **18**, 2734 (1885); **19**, 1822 (1886); **35**, 3579 (1902).

[9] J. Stieglitz, *Am. Chem. J.*, **18**, 751 (1896); **29**, 48 (1903).

[10] Our thanks are due to E. I. du Pont de Nemours & Co., for a cylinder of methylamine.

[11] Verley, *Bull. soc. chim.*, [3] **9**, 691 (1893).

[12] Menschutkin, *Ber.*. **17**, 848 (1884).

[13] Nicholas and Erickson, THIS JOURNAL, **48**, 2174 (1926).

[14] Walsh and Titherley, *J. Chem. Soc.*, **79**, 402 (1901).

[15] Mitchell and Reid, THIS JOURNAL, **53**, 1879 (1931).

peared, the temperature being kept below 50°. The silver bromide was filtered off and the solution evaporated *in vacuo*. The resulting oil crystallized on standing in a vacuum desiccator. The crystals were washed free of bromine with carbon tetrachloride. *Anal.* % Br calcd. 52.58; found 52.60.

Thanks are due to Dr. John R. Ruhoff and Dr. Jane Dick Mayer for samples of the higher acids and esters.

Summary

N-Methyl amides of the acids from formic to stearic have been prepared and some of their physical and pharmacological properties determined. Some of them are local anesthetics and possess a peppery taste. Derivatives of some of them have been made.

BALTIMORE, MARYLAND RECEIVED NOVEMBER 14, 1936

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Three Series of N-Substituted Aliphatic Amides[1]

BY G. F. D'ALELIO AND E. EMMET REID

In a previous article,[2] a series of N-methyl amides has been described. This investigation considers three series involving the same normal aliphatic acids, their hydroxyls being replaced by the groups (a) $—NHCH_2CH_2OH$, (b) $—N(CH_2CH_2OH)_2$ and (c) $—NHCH_2CH(OH)CH_3$. Some acyl derivatives of aminoethanol have been described[3,4] and since the completion of our work, a communication describing the first three ethanol amides has appeared.[5]

All of our compounds were prepared by heating the ethyl esters of the acids, already reported,[6,7] with the amine.[8] For the first six members of series (a), the ester was refluxed with a 25% excess of ethanolamine for six hours and the product fractionated. For the remainder of this series, 2 g. of the ester with a 3% excess of the amine was heated at 160° for six to ten hours. The higher ethanol amides were washed with dilute hydrochloric acid and recrystallized from 95% ethanol or from anhydrous methanol.

The diethanol amides gave the most trouble; the lower members melt too low for crystallization, boil too high for fractionation and are too soluble in organic solvents and water With the higher members the reaction products solidified to waxes. These were dissolved in the minimum amount of methanol, 5 volumes of water added and the mixture saturated with sodium chloride. The precipitated amides were filtered off and kept four months in a vacuum desiccator over sulfuric acid. They could then be crystallized from methanol-ether mixtures; average yield 70%.

The higher isopropanol amides were readily prepared from the amine and the ester. The solids were recrystallized from methanol, average yield 85%.

N-Ethanol benzamide was prepared by heating equivalent quantities of ethyl benzoate and ethanolamine in a flask in an oil-bath at 150° until the calculated amount of alcohol had distilled off. The solidified product was spread on a porous plate, desiccated over sulfuric acid and recrystallized from acetone, yield 95%, m. p. 67.6°, N calcd. 8.48; found 8.39%. This compound was made by Fränkel[3] who gave 67° as m. p. and by Wenker[5] who obtained it as an uncrystallizable liquid. The melting points are given in Tables I and II and plotted in Fig. 1.

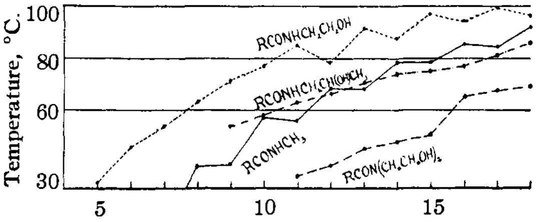

Fig. 1.—Melting points of the N-substituted amides.

The N-ethanol amides show slight alternation up to no. 11 where it suddenly becomes pronounced and then diminishes. This curve is the inverse of that of the N-methyl amides which is shown for comparison. The alternation is slight with the N-isopropanol amides and seems to

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[1] From a part of the Ph.D. dissertation of G. F. D'Alelio, Charles J. O'Malley Fellow of Boston College.

[2] G. F. D'Alelio and E. Emmet Reid, THIS JOURNAL, **59**, 109 (1937).

[3] Fränkel and Cornelius, *Ber.*, **51**, 1654–62 (1918).

[4] Knorr, *ibid.*, **36**, 1278 (1903).

[5] H. Wenker, THIS JOURNAL, **57**, 1079 (1935).

[6] Ruhoff and Reid, *ibid.*, **55**, 3827 (1933).

[7] Meyer and Reid, *ibid.*, **55**, 1583 (1933).

[8] Generously supplied by Carbide and Carbon Chemicals Corp.