

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.

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

Three Series of N-Substituted Aliphatic Amides¹

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) —NHCH₂CH₂OH, (b) —N(CH₂CH₂OH)₂ and (c) —NHCH₂CH(OH)CH₃. 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 Fränkel³ who gave 67° as m. p. and by Wenker⁵ who obtained it as an uncrystallizable liquid. The melting points are given in Tables I and II and plotted in Fig. 1.

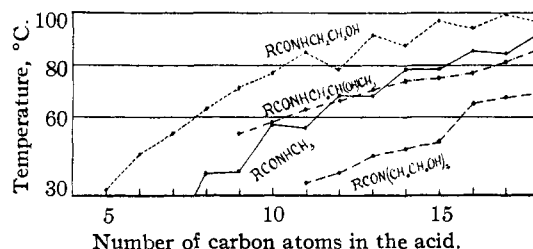


Fig. 1.—Melting points of the N-substituted amides.

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

(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.

TABLE I

PHYSICAL PROPERTIES AND ANALYSES OF N-ETHANOL AMIDES

No. C atoms in acid	M. p., °C.	n_D^{20}	B. p., °C.	Mm.	Yield, %	% Nitrogen	
						Calcd.	Found
1	Glass	1.4785	150-155	2 ^a	65	15.73	15.61
2	40	1.4710	155-160	2-3 ^a	87	13.60	13.40
3	Glass	1.4681	160-168	1-2 ^a	89	11.98	11.93
4	Glass	1.4672	155-162	1-1.5	78	10.69	10.60
5	32.0	1.4642	192	6	84	9.65	9.63
6	46.0				91	8.80	8.83
7	53.6				87	8.08	8.00
8	63.2				85	7.51	7.46
9	71.6				88	6.97	6.93
10	77.1				82	6.51	6.50
11	84.8				86	6.10	6.06
12	78.2				90	5.77	5.79
13	91.8				87	5.45	5.41
14	87.4				80	5.17	5.13
15	97.0				81	4.91	4.86
16	94.4				84	4.67	4.70
17	99.2				84	4.47	4.44
18	96.1				86	4.28	4.20

^a Ref. (5) gives for no. 1, b. p. 191-193° (10 mm.), d_4^{25} 1.180; for no. 2 b. p. 195-196° (10 mm.), d_4^{25} 1.115; for no. 3 b. p. 201-203° (10 mm.), d_4^{25} 1.071. Ref 3 gives m. p. for no. 2 of 63-65° while we found 40° from a heating and cooling curve.

invert at no. 14. The melting points of the N-diethanol amides appear to rise in groups of three. Pharmacological results have been pub-

TABLE II

MELTING POINTS AND ANALYSES

No. C atoms in acid	Diethanol amides			Isopropanol amides		
	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
9	Glass	53.8	6.52	6.50
10	Glass	58.1	6.10	6.00
11	34.9	5.13	5.08	63.1	5.76	5.70
12	38.7	4.88	4.81	66.6	5.45	5.43
13	45.3	4.66	4.64	71.0	5.17	5.15
14	47.9	4.44	4.40	74.2	4.91	4.87
15	50.9	4.25	4.20	75.1	4.75	4.69
16	65.1	4.08	4.00	78.2	4.53	4.54
17	67.9	3.93	3.88	82.0	4.34	4.30
18	69.7	3.79	3.75	86.1	4.15	4.13

lished.⁹ For the ninth members of the four series of N-substituted amides the activities are in the order: RCONHCH₃ > RCONHCH₂CH₂-OH > RCON(CH₂CH₂OH)₂ > RCONHCH₂CH(OH)CH₃.

Summary

The N-ethanol amides of the normal acids from formic to stearic have been prepared and characterized. The corresponding N-diethanol and N-isopropanol amides have been made of the higher acids. Comparative pharmacological effects are also reported.

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(9) Macht and D'Alelio, *Am. J. Pharmacol.*, **116**, 104 (1936).

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Alkenyl Derivatives of Fluorescein

BY CHARLES D. HURD AND LOUIS SCHMERLING¹

Surprisingly few O-alkylated derivatives of fluorescein have been prepared. Only the methyl and ethyl derivatives are reported in the literature, but they have been investigated by many workers² chiefly because of the confusion arising from difficulties involved in their purification. In the present study, the allyl, pentenyl and hexenyl derivatives were synthesized. The various types involved are the "ether ester" (A), the "diether" (B), the "monoether" (C) and the "monoester" (D).

Two general methods of synthesis were used. In the first, fluorescein was reacted with the

(1) Parke, Davis and Company Fellow, 1933-1935.

(2) Fischer and Hepp, *Ber.*, **27**, 2790 (1894); **28**, 396 (1895); **46**, 1951 (1913); Nietzki and Schroeter, *ibid.*, **28**, 44 (1895); Herzog and Meyer, *ibid.*, **28**, 3258 (1895); Kehrman and Dingler, *ibid.*, **42**, 810 (1909); **46**, 3028 (1913); **47**, 84 (1914); von Liebig, *J. prakt. Chem.*, **85**, 97, 241 (1912); **86**, 472 (1912); **88**, 26 (1913); *Ber.*, **46** 3593 (1913).

