Anal. Calcd. for $C_{11}H_8O_3N_2$: C, 61.11; H, 3.73; N, 13.0. Found: C, 61.29; H, 3.83; N, 13.2.

Anil of Thiophene-2-aldehyde.—Aniline (4.65 g., 0.05 mole) and thiophene-2-aldehyde (5.60 g., 0.05 mole) were placed in a Claisen flask (10 ml.) and heated until a second phase separated. The water thus formed was removed by distillation under slightly reduced pressure, and the residue was distilled to give a pale yellow oil (8.85 g.), b.p. 122–125° (2 mm.). This oil crystallized with difficulty in the cold, m.p. 16°.

Anal. Calcd. for $C_{11}H_9NS$: C, 70.55; H, 4.85; N, 7.48; S, 17.12. Found: C, 70.82; H, 4.76; N, 7.22; S, 16.90.

Acknowledgment.—The authors are indebted to Dr. Carl T. Redemann of this Laboratory and Dr. Adalbert Elek of the Elek Micro Analytical Laboratories for analysis of the compounds obtained and to Mr. Elmer R. Streed of this Laboratory for the absorption spectra.

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[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

Molecular Compound Formation between Acetamide and Long-chain Saturated Fatty Acids

BY FRANK C. MAGNE AND EVALD L. SKAU

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The binary freezing point diagrams for each of the polymorphic forms of acetamide with lauric, myristic, palmitic and stearic acids have been constructed. These give conclusive evidence of molecular compound formation between acetamide and each of these acids. The general formula for these compounds is $RCOOH \cdot NH_2COCH_3$. Cryoscopic molecular weight determinations show that in dilute 1,4-dioxane solutions acetamide is 40.4% associated, myristic acid is not appreciably associated, and the equimolecular compounds of acetamide and the fatty acids are from 93.5 to about 97% dissociated depending upon the chain length of the fatty acid.

A review of all the published binary freezing point diagrams, in which one constituent is a long-chain saturated fatty acid, reveals that the only ones which showed molecular compound formation were those in which the second constituent is either a homologous fatty acid or one of the cholic acids. It has now been found that molecular compounds are also formed with acetamide. The nature and composition of these compounds are shown by binary freezing point diagrams which have been constructed for acetamide with lauric, myristic, palmitic and stearic acids, respectively.

Experimental

The pure fatty acids were recrystallized samples obtained through the usual fractional distillation of their methyl esters. Their freezing points by the Francis and Collins cooling curve method,[2] using a calibrated thermocouple instead of a thermometer, were as follows: lauric acid, 43.77°; myristic acid, 53.85°; palmitic acid, 62.45°; and stearic acid, 69.29°. The acetamide was the best Eastman Kodak Co. product[3] dried in vacuum over phosphorus pentoxide.

The freezing points were determined by the static method. For each composition weighed amounts of acetamide and the fatty acid were sealed in a glass tube. A glass bead was included to ensure efficient stirring as the sample tubes were turned end-over-end in a constant temperature bath. Two temperatures a few tenths of a degree apart were found, one at which the last crystals just disappeared and the other at which a few crystals remained undissolved after prolonged agitation. The freezing point was taken as the mean of these two temperatures corrected for both thermometer calibration and emergent stem. For compositions between 45 and 65% acetamide in the stearic acid system the difference in these two temperatures amounted to as much as 0.4°.

Results and Discussion

The data for the complete binary freezing point diagrams are given in Table I and are represented graphically in Fig. 1. In each system a molecular compound forms which has the general formula $RCOOH \cdot NH_2COCH_3$. On the acetamide side of the diagram two freezing points were obtainable. The full lines represent the temperatures at which the various liquid compositions are at equilibrium with the stable polymorphic form of acetamide; the broken lines represent the corresponding metastable equilibria between the liquid and either the equimolecular compound or the low-melting modification of acetamide, as the case may be. The higher freezing point was always obtained on the initial melting of the samples, as would be expected since they contained the stable modification. After the samples had been heated some degrees above this temperature, however, the freezing points invariably fell on the lower broken curve, and in order to obtain the higher freezing point again it was necessary to shock-chill the molten sample in a Dry Ice–alcohol mixture. Subsequent heating of the solid resulted in momentary local melting near the surface followed by rapid transformation to the higher melting form.

It is apparent from the figure that, in addition to the 50–50 composition, each system exhibits three invariant points at which the crystalline equimolecular compound is one of the phases. These points appear at lower and lower acetamide concentrations as the chain length of the fatty acid becomes shorter. For both the stearic and the palmitic acid systems all three of these invariant points represent eutectics, two being stable and one metastable. In the myristic and lauric acid systems they represent a stable eutectic, an incongruent melting point and a metastable eutectic. That is, the invariant point at which the solid phases are the equimolecular compound and the higher-melting form of acetamide is a eutectic point in the stearic acid system but, because of the shift to lower acetamide concentrations with shorter fatty acid chain length, it becomes an in-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) F. Francis and F. J. E. Collins, *J. Chem. Soc.*, 137 (1936).

(3) The mention of names of firms or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

TABLE I

BINARY FREEZING-POINT DATA[a]

Mole % acetamide	Freezing point, °C. Stable	Mole % acetamide	Freezing point, °C. Stable	Freezing point, °C. Metastable
	Acetamide–lauric acid system			
0.00	43.77	50.00[d]	51.5	43.6[d]
9.99	42.0	52.84	54.9	43.7
19.44	40.4	(54.2)[b]		(43.3)[b]
24.20[b]	39.4[b]	55.78		45.8
29.50	40.8	60.18	63.5	51.5
34.90	42.1	65.16	67.8	56.8
39.52	42.8	80.20	75.2	64.6
44.84	43.5	90.13	77.9	67.2
(45.2)[c]	(43.5)[c]	100.00	79.72	69.54
48.11	48.6			
	Acetamide–myristic acid system			
0.00	53.85	(50.00)[d]		(51.5)[d]
20.08	51.2	50.95	54.8	
25.06	50.0	51.73		51.4
30.29	48.9	53.34	58.3	51.3
(31.0)[b]	(48.7)[b]	55.18		51.2
31.58	48.9	56.91		51.1
33.49	49.4	(57.3)[b]		(51.0)[b]
34.92	49.8	60.01		54.3
35.91	50.1	65.02		59.0
40.21	50.9	65.47	70.4	59.3
40.48	50.8	69.67		62.3
47.83	51.4	75.56		65.1
48.08	51.4	81.79	77.1	66.9
(48.9)[c]	(51.5)[c]	84.82		67.5
49.81	53.5	84.96		67.6
		90.37	78.7	68.4
		100.00	79.72	69.54
	Acetamide–palmitic acid system			
0.00	62.45	(51.5)[b]	(59.0)[b]	
9.63	61.3	55.07	62.5	58.7
19.19	60.1	(61.8)[b]		(57.7)[b]
25.38	59.1	62.09		58.1
29.33	58.4	65.02	70.7	
(35.2)[b]	(57.2)[b]	65.48		61.0
39.17	58.0	80.09	77.1	67.1
44.61	58.8	89.90		68.7
49.81	59.1	100.00	79.72	69.54
(50.00)[d]	(59.1)[d]			
	Acetamide–stearic acid system			
0.00	69.29	52.09	65.4	
9.91	68.2	(52.9)[b]	(65.3)[b]	
19.72	66.9	54.65	67.4	65.3
24.88	66.2	60.18		65.2
34.84	64.7	64.56	73.7	64.7
(38.4)[b]	(64.0)[b]	(65.4)[b]		(64.7)[b]
40.71	64.5	80.11		68.3
44.77	64.7	90.10	79.5	69.1
49.26	65.4	100.00	79.72	69.54
(50.00)[d]	(65.4)[d]			

[a] The values in parentheses were obtained by graphical extrapolation. [b] Eutectic. [c] Incongruent melting point of 1:1 compound. [d] Congruent melting point of 1:1 compound.

congruent melting point for the myristic and lauric acid systems.

Since the higher-melting modification of acetamide does not usually appear after the samples have been heated well above the melting point, all the systems can thus be made to behave as if the upper acetamide curves did not exist and all the equimolecular compounds would then melt congruently.

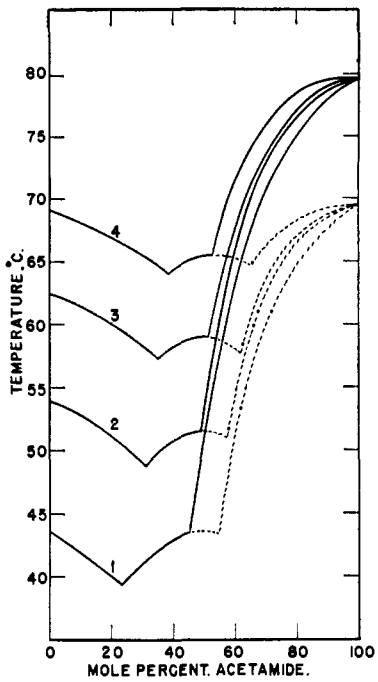

Fig. 1.—Binary freezing point diagrams for acetamide with: 1, lauric acid; 2, myristic acid; 3, palmitic acid; and 4, stearic acid.

Cryoscopic molecular weight determinations in 1,4-dioxane were made on each of the equimolecular compounds, on myristic acid, and on acetamide. The usual Beckmann apparatus was used, moisture being excluded from the system by means of a slight positive pressure of dry nitrogen. The results indicate that myristic acid is unassociated in dioxane, and it is safe to assume that this is also true of the other fatty acids considered. Acetamide, on the other hand, is 40.4% associated. Taking this into account calculations were made of the percentage dissociation of each of the 1:1 compounds in these dilute (approximately 0.03 molar) dioxane solutions. As shown in Table II the degree of dissociation is lowest for the lauric acid compound, 93.6%, and tends to increase as the chain length increases.

TABLE II

APPARENT MOLECULAR WEIGHTS IN 1,4-DIOXANE AND CALCULATED DEGREES OF ASSOCIATION OR DISSOCIATION

	Molecular weight Apparent	Molecular weight Theor.	Degree of Association,[a] %	Degree of Dissociation,[a] %
Acetamide	73.9	59.07	40.4	..
Myristic acid	231.1	228.37	..	..
Lauric acid–acetamide compound	148.5	259.38	..	93.6
Myristic acid–acetamide compound	163.5	287.64	..	95.2
Palmitic acid–acetamide compound	178.1	315.49	..	96.7
Stearic acid–acetamide compound	194.2	343.54	..	96.4

[a] Cryoscopic constant for dioxane: 4.63°/mole/1000 g.

Straight lines are obtained when the logarithm of the mole fraction of the fatty acid is plotted against the reciprocal of the absolute freezing temperature for that portion of the binary freezing point diagrams in which the fatty acid is the solid phase. The heats of fusion calculated from the slopes of these lines are 12,600 cal./mole for lauric acid, 15,800 for myristic acid, 18,900 for palmitic acid, and 20,900 for stearic acid. These are all considerably higher than the theoretical values: 8,750,[4] 10,750,[4] 13,100[5] and 16,350[6] cal./mole, respectively. Since the formation of the equimolecular compound would result in low calculated heats of fusion and the association of the acetamide would result in higher values, the association seems to be the predominant factor involved in these deviations.

It is apparent from Fig. 1 that the freezing point depression of either form of acetamide per mole % of added fatty acid is greater the shorter the chain length of the fatty acid. This is consistent with the idea that the degree of dissociation of the equimolecular compound decreases with a decrease in chain length of the fatty acid as was found to be the case in dioxane.

NEW ORLEANS, LOUISIANA

(4) W. E. Garner, F. C. Madden and J. E. Rushbrooke, *J. Chem. Soc.*, 2491 (1926).

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(6) W. S. Singleton, T. L. Ward and F. G. Dollear, *J. Am. Oil Chem. Soc.*, **27**, 143 (1950).

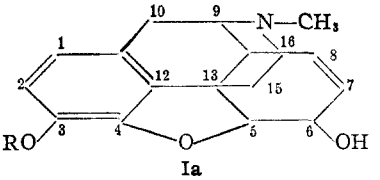
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

Stereochemical Studies in the Morphine Series. The Relative Configuration at Carbons Six and Thirteen[1]

BY HENRY RAPOPORT AND GEORGE B. PAYNE[2]

Dihydrocodeine and dihydroisocodeine were degraded to nitrogen-free products in order to establish the stereochemical relationship between the ethanamine chain at carbon 13 and the hydroxyl at carbon 6. While both compounds gave material in which the hydroxyl group had been methylated, only in the case of dihydroisocodeine was the compound resulting from alkylation of the hydroxyl with the ethane chain formed. On the basis of the formation of this cyclic ether, 6-codiran (VIII), the carbon-13 ethanamine chain and the carbon-6 hydroxyl were assigned the *cis*-configuration in isocodeine and hence the *trans* in codeine. The 13-carboxylic acids corresponding to codeine and isocodeine were also prepared from the respective 13-vinyl compounds, but lactonization could not be effected. Integrated with previous stereochemical evidence for carbons 5 and 6, this leads to the conclusion that the ethanamine chain at carbon 13 and the hydrogens at 5 and 6 are all *cis*.

The stereochemistry of morphine (Ia, R = H), with its five asymmetric centers and fused ring system, presents an interesting and as yet unsolved problem. Until recently, work on this subject had been confined to several deductions based on mechanistic interpretations. These were reviewed in our initial report[3] which advanced new experimental evidence for assignment of the relative configuration at carbons 5 and 6. In this report we wish to present work relating, stereochemically, the hydroxyl group at carbon 6 to the ethanamine chain at carbon 13. The quaternary carbon 13 affords an



Ia

excellent reference point, and it is the ultimate objective of these studies to relate configurations at carbons 9, 14, 5 and 6 to this center.

In seeking a reaction that might be dependent on the spatial relationship between the 6-hydroxyl and the ethanamine chain and hence reflect their relative configuration, a fruitful approach appeared to be the degradation, to nitrogen-free compounds, of codeine (Ia, R = CH_3) and isocodeine, epimeric alcohols differing only in the configuration at carbon 6. Recently[4] the observation was made that dihydrocodeine, when subjected to two successive Hofmann degradations, yielded an appreciable amount of material in which the 6-hydroxyl was converted to its methyl ether. Since the methyl group must have originated from the quaternary ammonium ion, this represents a reaction involving possible interaction between carbon 6 hydroxyl and carbon 13 ethanamine chain. If this were true, the nature and distribution of products might be influenced by the proximity of the reacting groups and the potentiality, in the *cis*-compound, for intramolecular reaction.

Also, on degradation to nitrogen-free material, compounds containing a free hydroxyl at carbon 4[5] or 14[6] have frequently formed cyclic ethers as degradation products. This may be considered as similar to the methyl ether formation cited above, alkylation of the hydroxyl taking place with the ethane chain rather than with the methyl group. In the case of codeine and isocodeine, such cyclic ether formation should occur only in the sterically favorable *cis*-compound to give structure VIII.

Consequently, the degradation products from dihydrocodeine and dihydroisocodeine (II)[7] have been examined in detail. The degradation of dihydrocodeine, following the sequence outlined in the

(1) Presented in part before the Division of Medicinal Chemistry, American Chemical Society, Cleveland, Ohio, April 10, 1951.

(2) U. S. Rubber Company Fellow, 1949–1950.

(3) H. Rapoport and G. B. Payne, *J. Org. Chem.*, **15**, 1093 (1950).

(4) H. Rapoport, *ibid.*, **13**, 714 (1948).

(5) L. Small and G. L. Browning, *ibid.*, **3**, 618 (1939); L. Small, *ibid.*, **7**, 158 (1942).

(6) C. Schöpf, *Ann.*, **452**, 249 (1927).

(7) In formulas II through XVI, the broken and solid lines at carbon 6 are used merely to designate the epimeric compounds. No stereochemical relationship with the rest of the molecule is intended.