mate of total unsaturation than do the molar absorptivities.

Acknowledgment.—We thank G. E. Secor for elemental analyses, R. E. Lundin for the n.m.r. spectra and their interpretation, Jane S. Nelson for samples of methyl 12-hydroxyoctadecanoate and methyl 12-oxooctadecanoate, Richard E. Knowles for methyl 14-hydroxy-*cis*-11-eicosenoate, Charles F. Krewson for trivernolin and methyl *cis*-9,10-epoxyoctadecanoate, T. L. Ward for methyl sterculate, and Bernard Freedman for methyl 12-oxo-*cis*-9-octadecenoate.

Amidation of Esters with Amides in the Presence of Methoxide Ion

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Received January 29, 1965

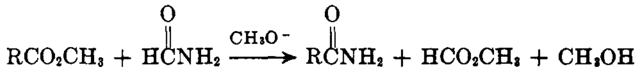
Methyl esters have been found to undergo amidation when treated with formamide or N-methylformamide in the presence of catalytic amounts of sodium methoxide. In addition to the new amide, other reaction products are methyl formate and methyl alcohol. Carbon monoxide is an additional product with N-methylformamide. Amidation also can be effected with esters other than methyl esters and with amides other than formamides. Amide anions are the actual reactive species with the ester. In this regard, the sodium salts of formamide and N-methylformamide are efficient catalysts. The amidation mechanism appears to consist of a complex series of reversible addition–elimination steps which include N-acylformamides and N-acylamides as reaction intermediates.

The conversion of carboxylic acid derivatives to one another by the action of appropriate nucleophiles has been one of the more extensively studied classes of chemical reactions.[2] In view of this, it is surprising to find that the reaction of amide anions with other carboxylic acid derivatives has received only limited attention. With one exception, the published results appear to deal entirely with intramolecular amidation by a neighboring amide function. Most of the reports have been concerned with demonstrating neighboring-group participation,[3-7] with only one study specifically utilizing the ring closure for synthetic purposes.[8] The one reference to intermolecular amidation describes only limited use of the reaction for synthesis.[9]

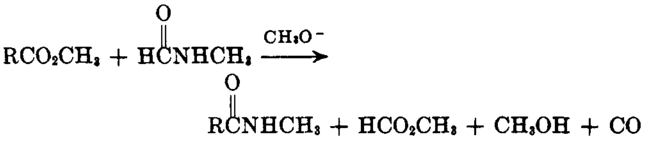
This paper reports our investigation of the reaction of amides with esters in the presence of catalytic amounts of methoxide ion, and discusses our cursory examination of the amidation mechanism for formamides. A unique decarbonylation reaction of a formyl imide also is reported.

Results and Discussion

Amidation Reactions Promoted by Methoxide Ion.—Preliminary experiments revealed that the reactions of formamide and N-methylformamide with esters in the presence of sodium methoxide proceed quite differently. These results prompted us to scrutinize the details of the reactions, as well as to investigate the synthetic scope.



$$\mathrm{RCO_2CH_3 + H\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow{CH_3O^-} R\overset{O}{\overset{\|}{C}}NH_2 + HCO_2CH_3 + CH_3OH}$$



$$\mathrm{RCO_2CH_3 + H\overset{O}{\overset{\|}{C}}NHCH_3 \xrightarrow{CH_3O^-} R\overset{O}{\overset{\|}{C}}NHCH_3 + HCO_2CH_3 + CH_3OH + CO}$$

Germane to a study of these reactions was the observation that mixtures of the reactants were not completely homogeneous. The very low solubility of sodium methoxide in aprotic solvents made difficult the examination of the reactions in a nonreactive solvent under strictly comparable homogeneous conditions. For this reason, the reactions for this preliminary investigation were carried out in the absence of solvent under one set of conditions. This standard set of conditions consisted of stirring an equal molar mixture of the anhydrous ester and amide with 5 mole % sodium methoxide (based on amide) at a bath temperature of 94–96° for 23 (or 72) hr. As the reaction proceeded, the low-boiling products were allowed to distil through a short column packed with Heli-Pak into a trap cooled with Dry Ice and acetone. The volume of any gas evolved was estimated with a gas buret assembly similar to one described by Wiberg.[10] Following the heating period, the remaining volatile products were removed under vacuum. Product analysis of both the low- and high-boiling products was by gas phase chromatography. Identification was made by comparison of the individual components with samples of the known compounds. Representative results for the reactions of a number of esters with formamide and N-methylformamide are collected in Tables I and II. The yields are estimated to be accurate to within *ca.* ±2%, based on checks with known mixtures of the products. Carbon monoxide gas was identified by the infrared spectrum which consisted of a doublet absorption at 4.65 and 4.76[11] μ. From each reaction,

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[1] To whom communications should be sent.

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[10] K. B. Wiberg, "Laboratory Techniques in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 228.

[11] (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 130; (b) National Academy of Sciences–National Bureau of Standards Infrared Compound Card, Serial No. 829.

TABLE I

REACTION OF ESTERS WITH FORMAMIDE AT 94–96°

Expt. no.	Reaction time, hr.	R of RCO_2CH_3	Catalyst: Charged as	Catalyst: Mole, %	Products, % yield: HCO_2CH_3	Products, % yield: CH_3OH	Products, % yield: CO	Products, % yield: $RCONH_2$	% recovered RCO_2CH_3
1	23	$(CH_3)_2CH$	$Na^+\overset{-}{O}CH_3$	5.2	49	5	0	53	41
2	72	$(CH_3)_2CH$	$Na^+\overset{-}{O}CH_3$	5.4	55[a]	7	Trace[b]	74	26
3	23	$(CH_3)_2CH$	$Na^+\overset{-}{N}H\overset{\overset{O}{\|}}{C}H$	5.0	49	4	0	55	44
4	23	$CH_3(CH_2)_2$	$Na^+\overset{-}{O}CH_3$	5.3	45	7	0	53	42
5	72	C_6H_5	$Na^+\overset{-}{O}CH_3$	5.4	25	6	Trace[b]	31	..
6	23	CH_3CH_2[c]	$Na^+\overset{-}{O}CH_3$	5.2	2 (38)[d]	0[e] (6)[f]	0	50	52
7	3	...	$Na^+\overset{-}{O}CH_3$	13.3	0.1[g]	96.3[h]	0	..	..

[a] This yield is known to be low as methyl formate was detected in the gas buret assembly by infrared spectral examination. This resulted when the Dry Ice trap was allowed to warm during the extended period of reaction. [b] Carbon monoxide was just discernible by infrared spectroscopy, <1% yield. [c] Ethyl ester. [d] Ethyl formate. [e] Less than a 1% yield could have been easily detected. [f] Ethyl alcohol. [g] Just detectable. [h] Based on sodium methoxide.

TABLE II

REACTION OF ESTERS WITH N-METHYLFORMAMIDE AT 94–96°

Expt. no.	Reaction time, hr.	R of RCO_2CH_3	Catalyst: Charged as	Catalyst: Mole %	Products, % yield: HCO_2CH_3	Products, % yield: CH_3OH	Products, % yield: CO[a]	Products, % yield: $RCONHCH_3$	% recovered RCO_2CH_3
8	23	$(CH_3)_2CH$	$Na^+\bar{O}CH_3$	5.2	17	71	67	93	9
9	23	$(CH_3)_2CH$	$Na^+CH_3\bar{N}\overset{\overset{O}{\|}}{C}H$	4.3	17	63	68	82	18
10	23	$CH_2{=}CHCH_2CH_2$	$Na^+\bar{O}CH_3$	5.0	18	78	67	95	5
11	23	C_6H_5	$Na^+\bar{O}CH_3$	5.0	12	87	74	95	4
12	23[b]	...	$Na^+\bar{O}CH_3$	3.2	0	>90[c]	<1	100[d]	..

[a] Estimated accuracy of measurement is *ca.* ±10%. [b] Temperature, 107–108° for 23 hr. [c] Based on sodium methoxide. [d] Refers to recovered N-methylformamide.

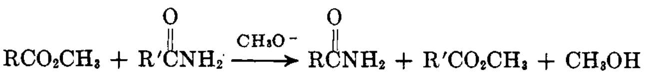
the product amide was isolated and identification was confirmed by melting point and infrared spectral comparison with an authentic sample.

For all of the cases with formamide, the reaction with ester did not appear to start appreciably until the bath temperature was near 90°. Initially the reaction mixture was three phased, with formamide and the ester being immiscible. As the reaction proceeded the mixture became one phase. With N-methylformamide, the ester and amide were miscible but sodium methoxide was initially insoluble. In these cases the reaction began at *ca.* 50° and became vigorous at 65°. As the reaction began to subside the temperature was raised slowly to 95°.

The amidation of esters with formamide and N-methylformamide in the presence of methoxide ion appears to be general. With N-methylformamide the reaction is especially facile. For the esters investigated the conversion to new amide was almost quantitative in less than 3 hr. at 95°. In the case of formamide considerably more vigorous conditions are required. The conversions were only *ca.* 50–55% after 23 hr. at 95° even though the reaction mixture was homogeneous for 18–20 hr. Conversions were increased by longer reaction time, or by reaction at higher temperatures.

While methyl esters were used in the investigation, other alkyl esters appear to react similarly. This can be seen by expt. 6, Table I, for an ethyl ester.

It appears that amidation also can be extended successfully to other amides, with analogous results. For instance, treatment of methyl isobutyrate with acetamide under the above standard conditions afforded isobutyramide in 59% yield. Methyl acetate and methyl alcohol also were formed in 56 and 7% yields, respectively.



$$RCO_2CH_3 + R'\overset{\overset{O}{\|}}{C}NH_2 \xrightarrow{CH_3O^-} R\overset{\overset{O}{\|}}{C}NH_2 + R'CO_2CH_3 + CH_3OH$$

Reaction Intermediates.—*A priori* considerations suggested that the amidation reactions may proceed through N-acylformamides (see Scheme I) as reaction intermediates. In this connection, N-isobutyrylformamide (VI) and N-methyl-N-isobutyrylformamide (VII) were prepared by acylation of formamide and N-methylformamide with an isobutyryl chloride–pyridine complex (in chloroform) at −30 to −40°.[12] The n.m.r. and infrared spectra were in complete accord with the structures assigned to VI and VII.

Treatment of VI and VII with sodium methoxide further confirmed the above structural assignments. This was carried out by treating the N-acylformamide with an equal molar amount of sodium methoxide under the standard conditions of the amidation reaction (*vide supra*). For both cases the reaction started out in a

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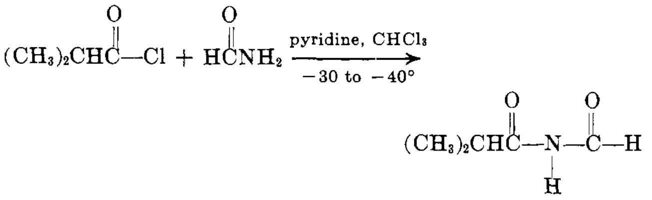
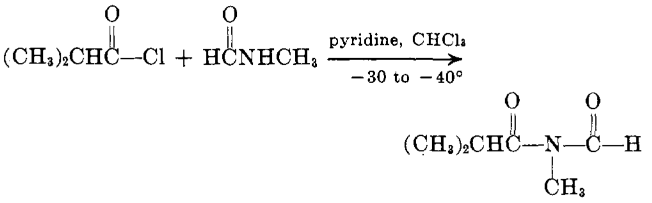
[12] The procedure was adapted from the preparation of similar compounds reported by Q. E. Thompson [*J. Am. Chem. Soc.*, **73**, 5841 (1951)].



$$(\mathrm{CH_3})_2\mathrm{CH}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\!-\!\mathrm{Cl} + \mathrm{H}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{NH_2} \xrightarrow[-30\ \text{to}\ -40°]{\text{pyridine, CHCl}_3} (\mathrm{CH_3})_2\mathrm{CH}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\!-\!\underset{\mathrm{H}}{\underset{|}{\mathrm{N}}}\!-\!\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\!-\!\mathrm{H}$$

VI

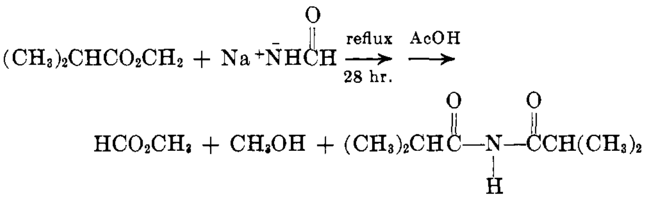


$$(\mathrm{CH_3})_2\mathrm{CH}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\!-\!\mathrm{Cl} + \mathrm{H}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{NHCH_3} \xrightarrow[-30\ \text{to}\ -40°]{\text{pyridine, CHCl}_3} (\mathrm{CH_3})_2\mathrm{CH}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\!-\!\underset{\mathrm{CH_3}}{\underset{|}{\mathrm{N}}}\!-\!\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\!-\!\mathrm{H}$$

VII

semisolid state and ended up as an essentially solid mass. From VI were obtained methyl isobutyrate (26%), methyl formate (2%), methyl alcohol (39%), formamide (26%), and only a trace of carbon monoxide (<1%).[13] The N-acylformamide VII gave methyl isobutyrate (20%), methyl formate (4%), methyl alcohol (36%), N-methylformamide (24%), and a major amount of carbon monoxide (40%).[13]

In an experiment aimed at the isolation of intermediates from the reaction of esters with amide anions, excess methyl isobutyrate was refluxed in the presence of the sodium salt of formamide for 28 hr. The low-boiling products formed were allowed to distil slowly through a short Heli-Pak column into a trap cooled with Dry Ice–acetone. Gas phase chromatographic analysis of the latter showed the formation of methyl alcohol (47%) and methyl formate (23%). Carbon monoxide could not be detected. After the reflux period, the remaining methyl isobutyrate was removed under vacuum. Treatment of the residue with the calculated equivalent of acetic acid, followed by extraction with hot hexane afforded N-isobutyrylisobutyramide (VIII) in 20% yield. This N-acylamide was identified by the n.m.r. spectrum. The identification was confirmed by melting point and infrared spectral comparisons with authentic VIII prepared by acylation of isobutyramide with an isobutyryl chloride–pyridine complex at −40°.



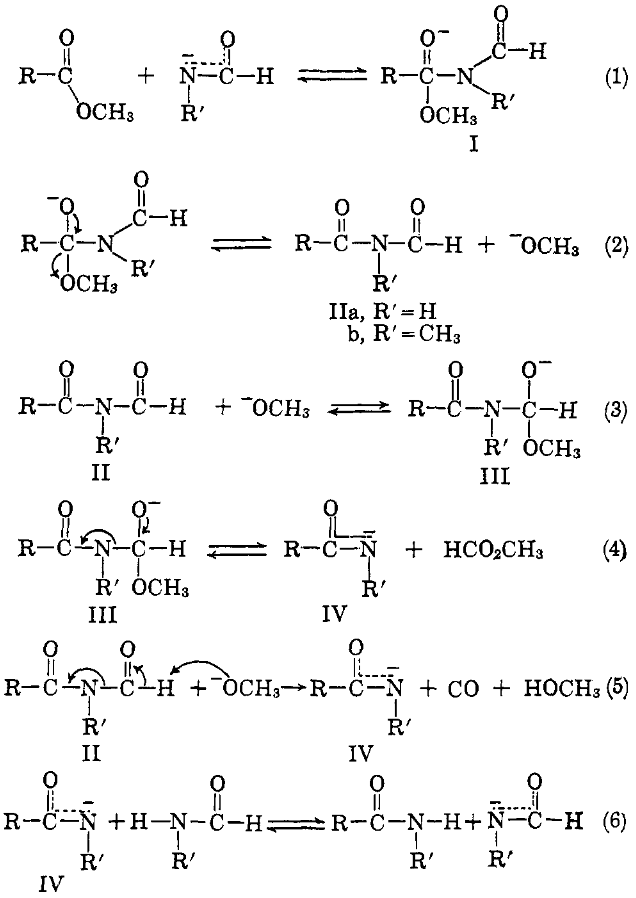
$$(\mathrm{CH_3})_2\mathrm{CHCO_2CH_2} + \mathrm{Na^+\bar{N}H}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H} \xrightarrow[28\ \text{hr.}]{\text{reflux}} \xrightarrow{\text{AcOH}} \mathrm{HCO_2CH_3} + \mathrm{CH_3OH} + (\mathrm{CH_3})_2\mathrm{CH}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\!-\!\underset{\mathrm{H}}{\underset{|}{\mathrm{N}}}\!-\!\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH(CH_3)_2}$$

VIII

Reaction Mechanisms.—The complexity of the methoxide ion promoted amidation of esters with formamide and N-methylformamide did not appear to allow a ready examination of the mechanistic details by simple kinetic methods. However, an analysis of the product data does permit the formulation of a reasonable reaction mechanism which leads to the observed product results.

SCHEME I

AMIDATION REACTION MECHANISM



Experiments 1, 3 (Table I), 8, and 9 (Table II) compare the product yields for reactions induced with sodium methoxide and with the sodium salts of formamide and N-methylformamide. Within experimental error, the results are identical for methoxide ion and the amide anion. This serves to indicate that the function of methoxide ion is to generate formamide anions, and that the latter are the actual reacting species. Consistent with this is the observation that formamide is a somewhat stronger acid than methyl alcohol.[14]

Based upon analogy with other well-documented reactions of carboxylic acid derivatives with nucleophiles,[2] the amidation reaction undoubtedly is multistep, involving some addition–elimination sequences. A mechanistic formulation which accounts for the observed products is summarized in Scheme I. As indicated, the initial step can be formulated as eq. 1. An attractive step 2 involves elimination of methoxide ion from I to form the N-acylformamide II as a reaction intermediate. There are two conceivable ways by which methoxide ion could convert II to the product amide. First of all, there is the expected addition of methoxide ion to the formyl carbonyl carbon shown in step 3, followed by the elimination of methyl formate in step 4 to give the product amide anion IV. Secondly, abstraction of the formyl hydrogen by methoxide ion

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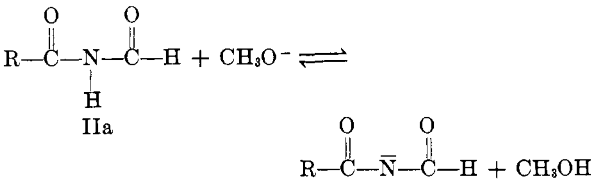
[13] Isobutyramide and N-methylisobutyramide had nearly the same retention times as VI and VII, respectively, with several different gas phase chromatographic columns. We made no further attempt to obtain exact analyses for these products since our main objective in this preliminary mechanistic investigation was to see if treatment of VI and VII with methoxide ion afforded the same products as the two corresponding amidation reactions.

[14] Measured in isopropyl alcohol solvent by J. Hine and M. Hine [*J. Am. Chem. Soc.*, **74**, 5266 (1952)].

(step 5) undoubtedly would lead to loss of carbon monoxide and formation of IV.[15] For amidation with formamide, product from IIa *via* step 5 is almost nil. In the case of N-methylformamide, product from IIb through step 5 occurs to the extent of *ca.* 70%. Propagation would follow from step 6 by the reaction of product anion IV with the starting formamide.

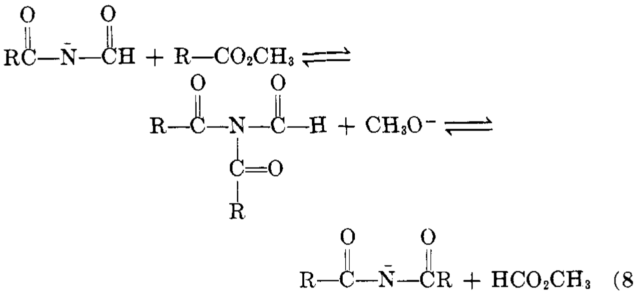
Support for the intervention of intermediates like IIa and IIb is provided by the finding that treatment of N-isobutyrylformamide (VI) and N-methyl-N-isobutyrylformamide (VII) with sodium methoxide afforded the same products as the amidation reactions. Particularly relevant to this point is the observation that carbon monoxide was just detectable (<1%) from VI, but was formed in substantial yield from VII.[16] The fact that methyl isobutyrate was formed in both cases also substantiates the reversibility indicated in steps 1–4. That the over-all product compositions differ from the amidation results is not surprising in view of the considerable dissimilarity in the reaction media.

Additional corroborating evidence for the intervention of N-acylamide intermediates is furnished by the identification of methyl alcohol, methyl formate, and N-isobutyrylisobutyramide (VIII) as products from the reaction of methyl isobutyrate with formamide anion. The isolation of VIII also implies that the total reaction mechanism for formamide is more complicated than represented in Scheme I. The close correspondence between the yields of VIII and methyl formate suggests that VIII is formed from a reaction between the anion of VI and methyl isobutyrate. This can be summarized for the general case by eq. 7 and 8. Once again, it is mechanistically significant that carbon monoxide does not result from the above reaction.



IIa

$$\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}\underset{H}{\underset{|}{N}}{-}\overset{O}{\overset{\|}{C}}{-}H + CH_3O^- \rightleftharpoons R{-}\overset{O}{\overset{\|}{C}}{-}\bar{N}{-}\overset{O}{\overset{\|}{C}}{-}H + CH_3OH} \qquad (7)$$



$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}\bar{N}{-}\overset{O}{\overset{\|}{C}}H + R{-}CO_2CH_3 \rightleftharpoons R{-}\overset{O}{\overset{\|}{C}}{-}\underset{\underset{R}{\underset{|}{C=O}}}{\underset{|}{N}}{-}\overset{O}{\overset{\|}{C}}{-}H + CH_3O^- \rightleftharpoons R{-}\overset{O}{\overset{\|}{C}}{-}\bar{N}{-}\overset{O}{\overset{\|}{C}}R + HCO_2CH_3} \qquad (8)$$

It is interesting that the N-acylformamides VI and VII (and IIa and IIb in general) partition so differently with methoxide ion. This supplies at least a partial explanation for the difference in the facility of amidation with formamide and N-methylformamide. For N-methylformamide, the decarbonylation in step 5 provides the one irreversible sequence in the course of the reaction. This is essentially absent in the case of formamide. The reason for the difference in partitioning is of considerable theoretical interest. However, the information presently available concerning the properties of compounds like VI and VII is not sufficient for singling out the factor(s) which controls this difference.

Experimental

Materials.—The esters used in this study were, or were made from, commercially available materials. These esters were dried with anhydrous magnesium sulfate, fractionally distilled, and checked for dryness by Karl Fischer titration. Formamide (Baker and Adamson) and N-methylformamide (Eastman) were doubly distilled under reduced pressure and shown to be anhydrous by Karl Fischer titration. Sodium methoxide was commercial material (Olin Mathieson Chemical Corp.), minimum purity 95%. The authentic sample of isobutyramide, *n*-butyramide, and benzamide were Eastman products. Propionamide was from Matheson Coleman and Bell. Authentic N-methyl-4-pentenamide was supplied by Dr. T. W. Hutton of this laboratory, b.p. 119–120° (8 mm.). The other standard compounds were synthesized as described below.

Gas Chromatography.—Analytical gas phase chromatography was done on an Aerograph Model A-350-B. The carrier gas was Airco helium. The low-boiling products were analyzed with a 0.25 in. × 6 ft. column packed with 20% Carbowax on Chromosorb P. For the high-boiling amides two different columns were used. One was 6 ft. and the other 12 ft.; both were packed with 5% Ucon on Fluoropak (Fluorocarbon Co.). Compounds were identified by comparison of retention times with authentic samples. For the quantitative analysis, control experiment with known mixtures indicated that the accuracy was *ca.* ±2%.

N.m.r. Spectral Analysis.—All n.m.r. spectra were obtained on a Varian Associates Model HR-60 spectrophotometer.

Sodium Salts of Formamide and N-Methylformamide.—An equal molar mixture of purified formamide and sodium hydride (51% in mineral oil) in 1,2-dimethoxyethane (monoglyme), which had been distilled from lithium aluminum hydride, was stirred and hydrogen was vigorously evolved. After the initial gas evolution slowed, the mixture was stirred and heated under reflux for 21 hr. The white sodium salt of formamide was filtered in a drybox under dry nitrogen and washed repeatedly with anhydrous ether; neut. equiv. 67.7 (calcd. 67.03).

The sodium salt of N-methylformamide was prepared in an entirely analogous fashion; neut. equiv. 80.4 (calcd. 81.05).

N-Methylisobutyramide.—To a cooled (10°), stirred mixture of 13.9 g. (0.2 mole) of methylamine hydrochloride, 16 g. (0.4 mole) of sodium hydroxide, and 85 ml. of water was added dropwise 21.2 g. (0.2 mole) of isobutyryl chloride. After addition the reaction mixture was extracted with ether and the extract was dried with magnesium sulfate. Removal of the ether and distillation under reduced pressure afforded 15 g. (75%) of N-methylisobutyramide, b.p. 64–65° (0.4 mm.), lit.[17] b.p. 120–121° (27 mm.).

Anal. Calcd. for $C_5H_{11}NO$: C, 59.36; H, 10.96; N, 13.85. Found: C, 59.55; H, 10.92; N, 13.99.

N-Isobutyrylformamide (VI).—To 10.6 g. (0.1 mole) of isobutyryl chloride in 75 ml. of chloroform at −40° was slowly added 10 ml. of anhydrous pyridine. A solution of 4.5 g. (0.1 mole) of purified formamide in 25 ml. of anhydrous reagent grade acetone was added with stirring to the acid chloride–pyridine complex as the temperature was held at −30 to −40°. Following addition the reaction mixture was held around −40° for 2 hr. and then stored overnight at 0°. The solvent was removed on a rotatory evaporator under reduced pressure. The residue was extracted three times with boiling ether. Removal of the combined extracts left a white crystalline solid. Recrystallization from hexane gave 5.7 g. (50%) of VI, m.p. 61–64°. Further recrystallization from hexane afforded pure VI, m.p. 64.5–65.5°.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.44; H, 7.83; N, 12.21.

The n.m.r. spectrum (in CCl_4) showed the isopropyl group doublet and complex multiplet at τ 8.76 (6) and 7.43 (1), the

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[15] A conceivable alternative to the concerted abstraction of the formyl hydrogen implied in step 5 would involve the intermediate formation of R-CO-NR-CO:⁻ and then loss of carbon monoxide.

[16] As regards carbon monoxide formation, it is also significant that neither formamide nor N-methylformamide yield this product upon treatment with methoxide ion under the reaction conditions (expt. 7 and 12).

[17] S. M. McElvain and C. L. Stevens, *J. Am. Chem. Soc.*, **69**, 2663 (1947).

formyl hydrogen doublet at 0.98 (1), and the unresolved N–H resonance at *ca.* −0.2 (1).

N-Methyl-N-isobutyrylformamide (VII).—The procedure was identical with that described above for the preparation of VI. From 23.3 g. (0.22 mole) of isobutyryl chloride, 12.9 g. (0.22 mole) of purified N-methylformamide, and 20 ml. of pyridine there was obtained 20 g. (70%) of VII, b.p. 66.5–68° (3.6 mm.). Redistillation provided VII, 98% pure (g.p.c.), b.p. 68.5–69° (3.5 mm.).

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.51; H, 8.59; N, 11.13.

The n.m.r. spectrum (in CCl_4) showed the isopropyl group doublet and multiplet at τ 8.81 (6) and 6.77 (1), the N-CH_3 hydrogens as a sharp singlet at 7.00 (3), and the formyl hydrogen at 0.80 (1).

N-Isobutyrylisobutyramide (VIII).—From a procedure analogous to the one described for VI, N-isobutyrylisobutyramide (VIII) was obtained in 15% yield, m.p. 176.5–177°. This material was shown to be identical with the m.p. 176–177° product isolated from the reaction of sodium formamide with methyl isobutyrate (*vide infra*) by mixture melting point (176.5–177°) and infrared spectral comparison.

Amidation of Esters with Formamide in the Presence of Methoxide Ion.—All of the experiments were carried out in the same apparatus under analogous conditions. Experiment 1 is representative of the procedure. A one-necked, 20-ml., round-bottomed flask which contained a Teflon-covered magnetic stirring bar was connected to a 6-in. column packed with No. 3013 Heli-Pak; the column was fitted with a distilling head which was connected through a Dry Ice–acetone cooled trap to a 500-ml.-volume gas buret assembly similar to one described by Wiberg.[10] A mixture of 50.8 g. (0.05 mole) of methyl isobutyrate, 2.27 g. (0.05 mole) of purified formamide, and 0.14 g. (0.0026 mole) of sodium methoxide was placed in the round-bottomed flask. These reactants were stirred and heated at 94–96° for 23 hr. As the reaction proceeded, methyl formate and methyl alcohol were allowed to distil into the trap. After about 3 hr. the mixture became essentially homogeneous. Following the heating period, the remaining volatile materials were collected in the cold trap under reduced pressure (*ca.* 80° and 10 mm.) and analyzed by gas phase chromatography. The results were 1.45 g. (49%) of methyl formate, 0.07 g. (5%) of methyl alcohol, and 2.08 g. (41%) of methyl isobutyrate. The residue was dissolved in *ca.* 8 ml. of methyl alcohol; analysis by gas phase chromatography showed 2.29 g. (53%) of isobutyramide. Any gas evolved was purged from the buret system into a 4-cm. gas cell and subjected to infrared analysis. No absorptions were found. In a control experiment it was determined that a 1% yield of carbon monoxide was readily detectable.

In another experiment, the stripped concentrate was treated with boiling ethyl acetate, filtered, and cooled. Isobutyramide separated out as white platelets, m.p. 126–128° (lit. m.p. 126–128°), m.m.p. 26–128°. The infrared spectra of the product and authentic isobutyramide were identical.

The product amides from the other esters examined were recovered and in each case identification was confirmed (Table III). Recovered yields by the usual recrystallization techniques were only a few per cent below the g.p.c. values given in Table I.

TABLE III

Expt. no.	Compd.	M.p., °C.	Comparison with authentic amide	
			M.m.p., °C.	Infrared spectrum
4	*n*-Butyramide	115–116	115–116	Identical
5	Benzamide	128–128.5	128–128.5	Identical
6	Propionamide	78–80	79–81	Identical

Amidation of Esters with N-Methylformamide in the Presence of Methoxide Ion.—The experiments were carried out in the apparatus described above for the formamide reaction. A representative procedure is illustrated by expt. 8. To a solution of 2.62 g. (0.025 mole) of methyl isobutyrate and 1.47 g. (0.025 mole) of purified N-methylformamide was added 0.070 g. (1.3 mmoles) of sodium methoxide. The reactants were stirred and heated slowly. At *ca.* 50° reaction started, and gas evolution became rapid at *ca.* 65°. The mercury leveling bulb of the gas buret assembly was moved as necessary to keep the internal and external pressures balanced. As the reaction subsided, the temperature was taken to 94–96°, and held there for a total time of 23 hr. Gas evolution essentially ceased after *ca.* 3 hr. Methyl formate and methyl alcohol were allowed to distil into the cold trap. The remaining low-boiling materials were removed under vacuum and collected in the trap. Analysis by gas phase chromatography showed methyl formate, 0.26 g. (17%); methyl alcohol, 0.57 g. (71%); and methyl isobutyrate, 0.23 g. (9%). The residue, when dissolved in 5 ml. of methyl alcohol, analyzed (g.p.c.) as 2.38 g. (93%) of N-methylisobutyramide. Total gas evolution was 403 ml., corresponding to a 67% yield of carbon monoxide. The gas was identified as carbon monoxide by the infrared spectrum (4-cm. cell) which consisted of a doublet absorption at 4.65 and 4.76 μ.[11]

In another experiment, the high-boiling concentrate was distilled *in vacuo*, b.p. 65–66° (0.5 mm.). The infrared spectra of the product and authentic N-methylisobutyramide were identical.

The product amides from the other two esters investigated were recovered and identification was confirmed (Table IV). Isolated yields for the recovered amides were only a few per cent below the g.p.c. values given in Table II.

TABLE IV

Expt. no.	Compd.	M.p., °C.	Comparison with authentic amide	
			M.m.p., °C.	Infrared spectrum
10	N-Methyl-4-pentenamide			Identical
11	N-Methylbenzamide	80.5–81.5	80.5–81.5	Identical

Reaction of Methyl Isobutyrate and N-Methylformamide in the Presence of Sodium N-Methylformamide.—In expt. 9 sodium N-methylformamide was substituted for sodium methoxide; otherwise the reaction was carried out exactly as described above. It was observed that gas evolution began immediately, at room temperature. The product yields are recorded in Table II.

Reaction of Methyl Isobutyrate with Sodium Formamide.—Using the amidation reaction apparatus (*vide supra*), a mixture of 8.85 g. of methyl isobutyrate and 1.36 g. (0.023 mole) of sodium formamide was stirred and heated at reflux for 28 hr. The low-boiling products were collected in the cold trap. After the period of reflux the excess methyl isobutyrate was distilled into the trap under reduced pressure. Analysis (g.p.c.) showed 0.31 g. (23%) of methyl formate and 0.34 g. (47%) of methyl alcohol. No carbon monoxide was detected by infrared analysis.

The solid residue was treated with 1.38 g. (0.023 mole) of acetic acid in 100 ml. of hexane. Extraction of the neutralized residue with three 100-ml. portions of boiling hexane afforded 0.71 g. (20%) of N-isobutyrylisobutyramide (VIII), m.p. 164–169°. Recrystallization from acetone gave an analytical sample, m.p. 176.0–176.5°.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.98; H, 9.42; N, 8.91.

The n.m.r. spectrum (in $DCCl_3$) showed the isopropyl group doublet and multiplet at τ 8.81 (12) and 6.52 (2), and the very broad N–H absorption at *ca.* 1.2 (1).

Amidation of Methyl Isobutyrate with Acetamide.—A mixture of 5.04 g. (0.05 mole) of methyl isobutyrate, 2.95 g. (0.05 mole) of acetamide, and 0.14 g. (0.0026 mole) of sodium methoxide was stirred and heated at 94–96° in the amidation apparatus (*vide supra*) for 23 hr. Following the heating period, the remaining volatiles were collected in the cold trap under vacuum. Analysis (g.p.c.) of the latter revealed 2.04 g. (56%) of methyl acetate, 0.11 g. (7%) of methyl alcohol, and 1.59 g. (32%) of methyl isobutyrate. The residue was dissolved in 8 ml. of methyl alcohol and the isobutyramide content determined by g.p.c. was 2.52 g. (59%).

Treatment of N-Isobutyrylformamide (VI) with Sodium Methoxide.—A mixture of 2.60 g. (0.023 mole) of VI and 1.25 g. (0.023 mole) of sodium methoxide was stirred and heated at 94–96° in the amidation setup (*vide supra*) for 23 hr. Initially the mixture was semisolid, but became a solid mass as the reaction proceeded. The volatile products were recovered by vacuum evaporation into the cold trap. Analysis (g.p.c.) indicated 0.02 g. (2%) of methyl formate, 0.28 g. (39%) of methyl alcohol, and 0.59 g. (26%) of methyl isobutyrate. The solid residue was dissolved in 8 ml. of methyl alcohol and then neutralized with 1.38 g. (0.023 mole) of acetic acid. Gas phase chromatographic analysis showed a formamide content of 0.27 g. (26%). Under the conditions of analysis isobutyramide could not be distinguished from VI.[13] Infrared analysis of the gas in the buret system indicated a trace (<1%) of carbon monoxide; no other gas was observed.

Treatment of N-Methyl-N-isobutyrylformamide (VII) with Sodium Methoxide.—Treatment of VII with sodium methoxide was conducted as described for VI. From 2.83 g. (0.021 mole) of VII and 1.11 g. (0.021 mole) of sodium methoxide were obtained 0.04 g. (4%) of methyl formate, 0.24 g. (36%) of methyl alcohol, and 0.43 g. (20%) of methyl isobutyrate. The yield of N-methylformamide amounted to 24%. N-Methylisobutyramide and VII had the same retention time with the g.p.c. column used for analysis.[13] It was observed that gas evolution began immediately upon mixing the reactants. Infrared analysis showed the gas to be solely carbon monoxide. The total amount of carbon monoxide evolved was 207 ml. (40%).

Acknowledgment.—The authors wish to thank Dr. Keith S. McCallum, Mr. Francis L. Jackson, and Mr. Sandy H. Venable of the Rohm and Haas Company for special assistance with the n.m.r. and infrared spectral aspects of this work.

Chemistry of Imidoyl and Amide Chlorides. II.[1] On the Preparation and Properties of the N-Mono- and N,N-Dialkyl-Substituted Amide Halides[2,3]

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Received November 3, 1964

From a number of N-alkylimidoyl chlorides and HCl, HBr, DCl, and DBr, a series of N-monoalkylamide halides (N-alkylimidoyl chloride hydro or deuterio halides) was prepared. This is the first instance of the preparation and description of this type of compound. Certain new N,N-dialkyl-substituted amide chlorides were prepared from the corresponding N,N-disubstituted 2-furamides with $COCl_2$, or, in less pure form, with PCl_5. The amide chlorides were identified also as N,N′-disubstituted or N,N,N′-trisubstituted amidines by reaction with the corresponding primary amines. On the basis of infrared spectra and other properties the amide chlorides appear to have an immonium salt structure.

By the reaction of N-ethyl-2-furamide with phosphorus pentachloride Wallach[5] prepared a very hygroscopic product, analysis of which approximated that required for the amide chloride, $C_4H_3O \cdot CCl_2NHC_2H_5$. The compound, however, was not further characterized. From N-phenylbenzimidoyl chloride and hydrogen iodide Lander and Laws[6] obtained a mixed amide halide and suggested a covalent structure, $C_6H_5CClINHC_6H_5$. Subsequently, a number of contradicting structure assignments have been reported. In accord with Stephen's[7] results N-phenylbenzimidoyl chloride reacted with 2 moles of hydrogen chloride to give a covalent amide chloride salt, $[C_6H_5CCl_2NH_2C_6H_5]^+Cl^-$, whereas Bosshard and Zollinger[8] suggested an immonium chloride hydrochloride structure, $[C_6H_5C(Cl){=}NH\text{-}C_6H_5]^+HCl_2^-$ for this compound. Klages[9] reported that the addition of 2 moles of hydrogen bromide to N-methylbenzimidoyl chloride gave an "imidoyl chloride hydrobromide," while the addition of 3 moles of hydrogen chloride produced an "imidoyl chloride sesquihydrochloride." The structures of the compounds, however, were not specified. To the addition products of hydrogen halides with nitriles, in the presence of a metal salt, Meerwein[10] assigned an immonium salt structure, $[RC(Cl){=}NH_2]^+(MeCl_{n+1})^-$. This is in contrast to the nitrilium salt structure assigned to similar compounds by Hantzsch.[11]

Owing to the growing interest in amide chlorides and related compounds,[12] we have examined the addition reaction of hydrogen and deuterium halides to N-alkyl- and N-aryl-2-furimidoyl chlorides. From our data, in contrast to the previous reports,[7-11] the N-alkylamide halides appear to be the only stable addition products. Under the same conditions, N-aryl-2-furimidoyl chlorides reacted with hydrogen chloride to give products which were crystalline but spontaneously dissociated at room temperature and atmospheric pressure.

As we have found earlier,[1] N-aryl-2-furamides react with phosphorus pentachloride with the evolution of hydrogen chloride to form N-aryl-2-furimidoyl chlorides. However, N-methyl-, N-ethyl-, and N-isopropyl-2-furamides reacted with the formation of the corresponding amide chloride as crystalline solids sensitive to moisture but stable in a dry atmosphere. We found the amide chlorides to be practically insoluble in nonpolar solvents and were unable to prepare analytically pure samples by this method, except in the case of compound I, which could be purified by vacuum sublimation, and proved to be identical with the amide chloride prepared by the hydrogen chloride procedure.

In a sealed capillary tube, under nitrogen, the prepared amide halides were observed to melt sharply without decomposition. The ease of addition of hydrogen halides to the N-alkyl-2-furimidoyl chlorides, and the fact that the derived amide halides were insoluble in nonpolar solvents and were easily dehydro-

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(1) Part I: V. Hahn and M. Grdinić, to be published.

(2) Studies in the Furan Series. X. Part IX: see ref. 1.

(3) This paper is abstracted from part of the doctoral thesis of Marcel Grdinić, submitted to the University of Zagreb, Zagreb, Yugoslavia, in partial fulfillment of the requirements for the degree of Doctor of Chemistry (Ph.D.), July 1959.

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