Treatment of Dihalide IIa with Other Reagents. (Table II).—The experiments listed in Table II with lithium amide, potassium anilide, dipotassio phenylacetate, and dipotassiobenzoylacetone in liquid ammonia were carried out in a manner similar to that described with potassium amide and potassium diphenylmethide. The experiment with phenylmagnesium bromide in ether was carried out in a manner similar to that with phenyllithium. Potassium anilide was prepared by adding aniline to a molecular equivalent of potassium amide in liquid ammonia. Dipotassio phenylacetate[18] and dipotassiobenzoylacetone[19] were prepared by adding phenylacetic acid and benzoylacetone, respectively, two molecular equivalents of potassium amide in liquid ammonia.

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[18] See C. R. Hauser, D. Lednicer, and W. R. Brasen, *J. Am. Chem. Soc.*, **80**, 4345 (1958).

[19] See C. R. Hauser and T. M. Harris, *ibid.*, **80**, 6360 (1958).

Reactions of Cyclohexylisonitrile and Isobutyraldehyde with Various Nucleophiles and Catalysts

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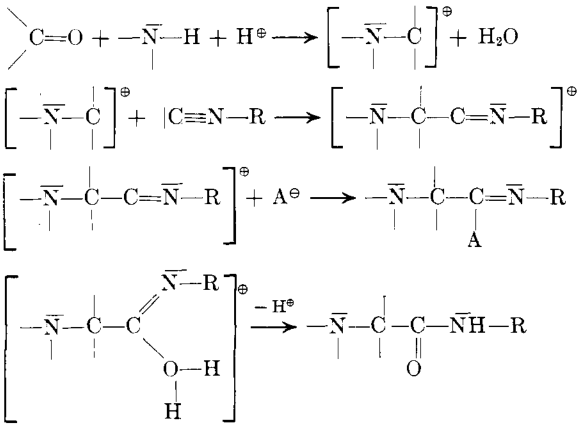
Cyclohexylisonitrile, isobutyraldehyde, and dimethylammonium acetate react to give N-cyclohexyl-α-dimethylaminoisovaleramide (I). By making slight variations in the reaction conditions one also can obtain N-cyclohexyl-α-hydroxyisovaleramide (II), N′-cyclohexyl-N,N-dimethyl-α-dimethylaminoisovaleramidine (III), and α-acetoxy-N-cyclohexylisovaleramide (IV). The Ugi and Passerini reactions are discussed.

In recent years Ugi and his co-workers have reported the results of a new reaction which gives great versatility to isonitriles as intermediates in organic syntheses.[1-4] This reaction serves usefully in the syntheses of such varied structures as α-aminoamides, dipeptides, β-lactams, thioamides, and tetrazoles. The ensuing reaction scheme was suggested by Ugi, and fairly well explains the observed facts. One may imagine an aldehyde or ketone to react with an amine, an isonitrile, and a nucleophile ($A^{\ominus}$) in the following way.



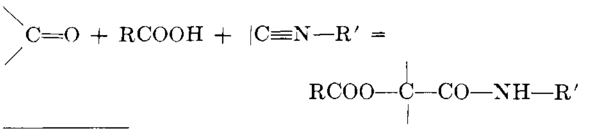
$$>C{=}O + -\bar{N}{-}H + H^{\oplus} \longrightarrow \left[-\bar{N}{-}\overset{|}{\underset{|}{C}}\right]^{\oplus} + H_2O \qquad (1)$$

$$\left[-\bar{N}{-}\overset{|}{\underset{|}{C}}\right]^{\oplus} + |C{\equiv}N{-}R \longrightarrow \left[-\bar{N}{-}\overset{|}{\underset{|}{C}}{-}C{=}\bar{N}{-}R\right]^{\oplus} \qquad (2)$$

$$\left[-\bar{N}{-}\overset{|}{\underset{|}{C}}{-}C{=}\bar{N}{-}R\right]^{\oplus} + A^{\ominus} \longrightarrow -\bar{N}{-}\overset{|}{\underset{|}{C}}{-}\underset{A}{\underset{|}{C}}{=}\bar{N}{-}R \qquad (3)$$

$$\left[-\bar{N}{-}\overset{|}{\underset{|}{C}}{-}C\begin{matrix}\nearrow \bar{N}{-}R\\ \searrow O{-}\underset{H}{\underset{|}{H}}\end{matrix}\right]^{\oplus} \xrightarrow{-H^{\oplus}} -\bar{N}{-}\overset{|}{\underset{|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}\bar{N}H{-}R \qquad (4)$$

In reaction 3 the imino product is most often a reactive intermediate, and a further reaction occurs to give a stable product. For example, when the nucleophile $A^{\ominus}$ is water the loss of a proton leads to an α-aminoamide (reaction 4). Nearly forty years prior to this work Passerini discovered that isonitriles, carbonyl compounds, and carboxylic acids react slowly to give α-acyloxyamides.[5]



$$>C{=}O + RCOOH + |C{\equiv}N{-}R' = RCOO{-}\overset{|}{\underset{|}{C}}{-}CO{-}NH{-}R' \qquad (5)$$

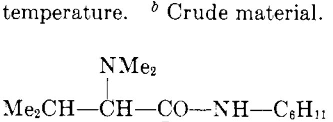
As part of a larger research program in these laboratories it was desired to synthesize N-cyclohexyl-α-dimethylaminoisovaleramide (I), and it seemed convenient to use the Ugi reaction for this purpose. At the beginning of this project only the preliminary report of this reaction had been published,[1] and it was not clear what the optimum conditions for the synthesis of I would be. To establish this point isobutyraldehyde, dimethylamine, and cyclohexylisonitrile were allowed to react under a set of varying conditions. The results of these studies are summarized in Table I.

Table I

Ugi Reactions[a]

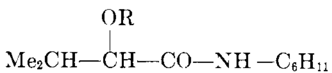
Expt.	Catalyst	Moles	Me_2NH, moles	Products (yield, %)
1	None	. . .	0.02	None
2	$Me_2NH \cdot HCl$	0.01	None	I (32[b]); II (32[b])
3	$Me_2NH \cdot HCl$	.01	.01	III (70)
4	AcOH	.02	.02	I (94); IV (6[b])
5	AcOH	.01	.01	I (35); IV (41)

[a] Reaction of 0.01 mole of isobutyraldehyde and 0.01 mole of cyclohexylisonitrile in 25.0 cc. of absolute methanol at room temperature. [b] Crude material.



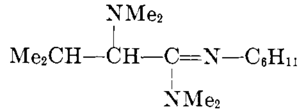
$$Me_2CH{-}\overset{NMe_2}{\overset{|}{C}}H{-}CO{-}NH{-}C_6H_{11}$$

I



$$Me_2CH{-}\overset{OR}{\overset{|}{C}}H{-}CO{-}NH{-}C_6H_{11}$$

II, R = H
IV, R = Ac
V, R = CHO



$$Me_2CH{-}\overset{NMe_2}{\overset{|}{C}}H{-}\underset{NMe_2}{\underset{|}{C}}{=}N{-}C_6H_{11}$$

III

It is evident from these studies that I is best obtained when a twofold excess of dimethylammonium acetate is used (experiment 4). Surprisingly, however, three other products were obtained in substantial yield when the nature of the catalyst was only slightly modified.

Experiment 1 illustrates the necessity of an acid catalyst for the reactions presently under investigation. However, since acids react directly with isonitriles to

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[1] I. Ugi and C. Steinbrueckner, *Angew. Chem.*, **72**, 267 (1960).

[2] Review: I. Ugi, *Angew. Chem. Intern. Ed. Engl.*, **1**, 8 (1962).

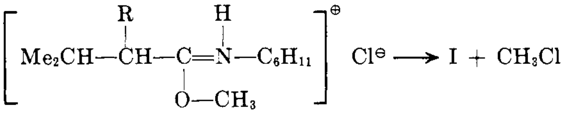
[3] I. Ugi and U. Fetzer, *Ber.*, **94**, 1116 (1961).

[4] I. Ugi and R. Meyr, *ibid.*, **94**, 2229 (1961).

[5] M. Passerini, *Gazz. chim. ital.*, **51** (II), 126 (1921); *Chem. Abstr.*; **16**, 555 (1922).

form formamidines[6] care must be taken to select conditions which do not favor this important side reaction. This is usually done by employing weak acids such as amine hydrochlorides and carboxylic acids. When dimethylamine hydrochloride was the catalyst (experiment 2) the desired product I was obtained in only 32% yield along with the neutral product II also in 32% yield. Evidently this latter compound is the result of a Passerini reaction competing with the Ugi reaction. With free dimethylamine present in the reaction mixture (experiment 3) the Passerini side reaction becomes inconsequential, but the product is the amidine III instead of the desired I. Apparently in this case the water and methanol cannot successfully compete with the more nucleophilic dimethylamine in reaction 3. The amidine so formed is a stable product in its own right and undergoes no further reaction.

Because anhydrous methanol was used as the solvent in these studies, there can be little doubt that the imino ester hydrochloride VI is the important intermediate leading to I in experiment 2. It is known that imino ester hydrochlorides decompose fairly rapidly in polar solvents at room temperature to give amides and alkyl chlorides.[7,8]

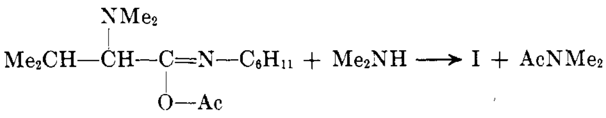


$$\left[\mathrm{Me_2CH{-}\overset{R}{C}H{-}\underset{O-CH_3}{C}{=}\overset{H}{N}{-}C_6H_{11}}\right]^{\oplus} \mathrm{Cl^{\ominus} \longrightarrow I + CH_3Cl} \qquad (6)$$

VI, R = NMe_2
VII, R = OH

By an analogous process II is obtained from VII. Since in the present case the reaction solution was allowed to stand overnight, there was adequate time for such reactions to go to completion.

The discrepancy in the yields of I and IV noted in experiments 4 and 5 was unexpected, and deserves some explanation. In these cases I most likely arises from the intermediate imino anhydride VIII by reaction with dimethylamine.



$$\mathrm{Me_2CH{-}\overset{NMe_2}{C}H{-}\underset{O-Ac}{C}{=}N{-}C_6H_{11} + Me_2NH \longrightarrow I + AcNMe_2} \qquad (7)$$

VIII

Since two moles of dimethylamine are consumed in this reaction for each mole of other reactants, the yield of I in experiment 5 is less than half that otherwise expected. Once the amine is used up, the remainder of the aldehyde and isonitrile go on to react with the excess acetic acid to give the Passerini product IV in nearly equivalent yield. In experiment 4, where there was sufficient dimethylamine, the yield of I was nearly quantitative and IV was detected in only negligible amounts. This rationalization requires acetate ion to compete successfully with dimethylamine as the nucleophile in reaction 3; otherwise the amidine III should be the product. Considering that more than 99% of the amine will be bound in its cationic form, this conjecture becomes plausible. One additional assumption must be made: the intermediate VIII must react with free dimethylamine (in equilibrium with its cationic form) at a rate that is very much faster than the rate at which VIII is formed.

In order to understand better the formation of the neutral products II and IV a brief investigation of the Passerini reaction was made. In the same manner as before equimolar solutions of isobutyraldehyde and cyclohexylisonitrile were treated with acids of differing strength and character. The results of these experiments are summarized in Table II.

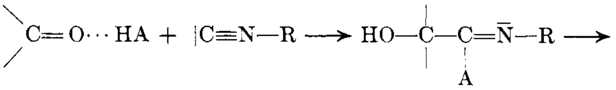
Table II

Passerini Reactions[a]

Expt.	Catalyst	Moles	Products (yield, %)
6	$Me_3N{\cdot}HCl$	0.01	II (35[b])
7	AcOH	.02	IV (69)
8	HCOOH	.02	V (20)
9	HCl	.01	$C_6H_{11}NH_2$[c]

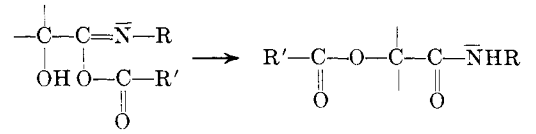
[a] Reaction of 0.01 mole of isobutyraldehyde and 0.01 mole cyclohexylisonitrile in 25.0 cc. of absolute methanol at room temperature. [b] Crude material. [c] A rapid exothermic reaction in which other products were obtained but not identified.

Several mechanisms have been proposed for the Passerini reaction,[9,10] but the most comprehensive is one suggested by Ugi and Meyr.[4] These authors have generalized the reaction as shown.



$$\mathrm{{>}C{=}O\cdots HA + |C{\equiv}N{-}R \longrightarrow HO{-}\overset{|}{\underset{|}{C}}{-}\underset{A}{C}{=}\bar{N}{-}R \longrightarrow Products} \qquad (8)$$

Where HA is a carboxylic acid, an imino-anhydride is initially obtained, but this intermediate then rearranges by intramolecular acyl migration to give the usual Passerini product.



$$\mathrm{{-}\underset{OH}{\overset{|}{C}}{-}\underset{O-\underset{O}{\overset{\|}{C}}-R'}{C}{=}\bar{N}{-}R \longrightarrow R'{-}\underset{O}{\overset{\|}{C}}{-}O{-}\overset{|}{\underset{|}{C}}{-}\underset{O}{\overset{\|}{C}}{-}\bar{N}HR} \qquad (9)$$

From the foregoing and the results of the present work it seems evident that the dimethyl- and trimethylammonium ions also must be added to the class of acids which catalyze the Passerini reaction (albeit poorly). However, it does not appear absolutely necessary that the conjugate base of these catalysts appear in the product as according to the Ugi–Meyr scheme.

Experiment 7 using acetic acid gives an excellent yield of the expected product IV. However, when a stronger acid is employed, such as formic acid in experiment 8, the yield of α-acyloxyamide begins to fall, and other products begin to appear. In the extreme case of experiment 9, where hydrochloric acid is the catalyst, no Passerini type product could be detected.

Each of the cases that have been discussed so far has involved hydrogen ions (or hydrogen bonds) as the activating principle. The question of whether there are any aprotic reagents for reactions of the type presently under consideration naturally arises. An interesting possibility in this regard is the use of acylating agents. Conceivably α-acyloxyamides or related products could arise from following sequence of events.

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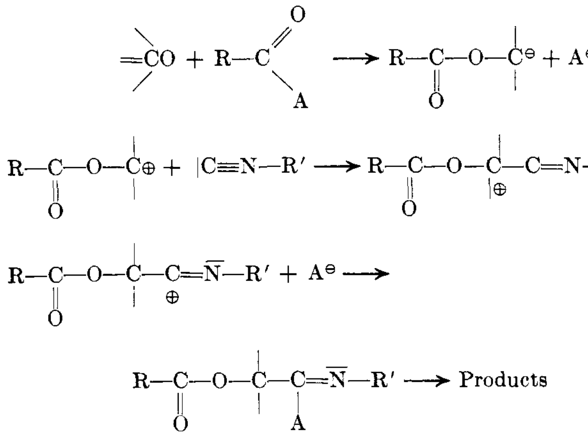
(6) M. Passerini, *Gazz. chim. ital.*, **52**, 250 (1922); *Chem. Abstr.*, **17**, 1632 (1923).

(7) S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **73**, 2233 (1951).

(8) D. J. Morgan, *Chem. Ind.* (London), 854 (1959).

(9) M. Passerini, *Gazz. chim. ital.*, **51** (II), 181 (1921); *Chem. Abstr.*, **16**, 556 (1922).

(10) R. H. Baker and D. Stanonis, *J. Am. Chem. Soc.*, **73**, 699 (1951).



$$>C{=}O + R{-}C(=O){-}A \longrightarrow R{-}C(=O){-}O{-}C^{\ominus} + A^{\ominus} \quad (10)$$

$$R{-}C(=O){-}O{-}C^{\oplus} + |C{\equiv}N{-}R' \longrightarrow R{-}C(=O){-}O{-}C{-}\overset{\oplus}{C}{=}N{-}R' \quad (11)$$

$$R{-}C(=O){-}O{-}C{-}\overset{\oplus}{C}{=}\bar{N}{-}R' + A^{\ominus} \longrightarrow R{-}C(=O){-}O{-}C{-}C(A){=}\bar{N}{-}R' \longrightarrow \text{Products} \quad (12)$$

Accordingly, this hypothesis was tested by studying reaction of isobutyraldehyde and cyclohexylisonitrile with acetyl chloride, acetic anhydride, and acetoformic anhydride as the acylating agents. The results of this investigation are summarized in Table III.

TABLE III[a]

Expt.	Reactant	Moles	Products (yield, %)
10	AcCl	0.01	Complex mixture
11	Ac_2O	.01	IV (75[b])
12	AcOCHO	.01	IV, V[c]

[a] Reactions of 0.01 mole of isobutyraldehyde and 0.01 mole of cyclohexylisonitrile in 25.0 cc. of chloroform at room temperature with various acylating agents. [b] Crude material. [c] Ratio of IV to V was about 2:1 as estimated from the infrared spectrum of the crude reaction mixture.

In these reactions isonitrile was always added last to the solution, and this was done usually after the other components had stood for some minutes. By this means a direct reaction of the isonitrile with the acylating agent was avoided.[3]

Experiment 10 gave a complex mixture of products, and none of them could be sufficiently purified for proper identification. More encouraging, however, were the results of experiment 11 in which an excellent yield of IV was obtained. Finally, in experiment 12, acetoformic anhydride was employed with the hope that the product might be solely or mostly the α-formyloxyamide V. If this were the case, then the difficulties met in attempting to make V by the conditions of experiment 8 would be obviated. The reaction went very rapidly and gave a quantitative yield of acyloxyamides, but unfortunately the product consisted of a 2:1 mixture of IV and V.

Experimental[11]

N-Cyclohexyl-α-dimethylaminoisovaleramide (I).—A solution of 0.92 cc. (0.01 mole) of isobutyraldehyde, 1.2 cc. (0.02 mole) of acetic acid, 10 cc. of 2 *M* dimethylamine in methanol, and 5.0 cc. of methanol was treated with 1.2 cc. (0.01 mole) of cyclohexylisonitrile.[12] After the solution had stood for 90 min. the volatile components were evaporated under reduced pressure, to give a crystalline residue. This material was shaken in a mixture of ethyl ether and 1 *N* hydrochloric acid. The ether phase was dried over anhydrous sodium sulfate, filtered, and evaporated to give 0.15 g. (6%) of crude IV (determined by its infrared spectrum). The aqueous solution was made alkaline by the addition of 1 *N* potassium hydroxide and the organic material was extracted from this solution with ethyl ether. The extract was dried, filtered, and evaporated to give colorless crystals of I; yield, 2.12 g. (94%); m.p. 132–133°. The product was recrystallized from hexane to give an analytical sample, m.p. 132–133°.

Anal. Calcd. for $C_{13}H_{26}N_2O$ (226.36): C, 68.98; H, 11.58; N, 12.38. Found: C, 68.97; H, 11.36; N, 11.90.

N′-Cyclohexyl-N,N-dimethyl-α-dimethylaminoisovaleramidine (III).—A solution of 8.2 g. (0.1 mole) of dimethylamine hydrochloride, 50 cc. of 2 *M* dimethylamine in methanol, 9.2 cc. (0.1 mole) of isobutyraldehyde, and 50 cc. of methanol was treated with 10.9 g. (0.1 mole) of cyclohexylisonitrile. The solution became immediately warm and after 30 min. it was at room temperature again. The volatile components were evaporated under reduced pressure, and the oily residue was shaken in a mixture of 200 cc. of water and 50 cc. of ethyl ether. The ether phase contained only 1 g. of neutral material which was discarded. The aqueous phase was made basic by the addition of 20 cc. of 10 *N* potassium hydroxide. An oily phase appeared in the solution and it was extracted with ether. The ether extract was dried over anhydrous sodium sulfate, filtered, and evaporated to give a residue which was then fractionally distilled. The product III was obtained as a clear oil; yield, 18.1 g. (72%); b.p. 102–103° (1.0 mm.); $n^{25}D$ 1.4894; ν_{max} 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{31}N_3$ (253.42): C, 71.09; H, 12.33; N, 16.58. Found: C, 70.86; H, 12.00; N, 16.54.

α-Acetoxy-N-cyclohexylisovaleramide (IV). (A) Acetic Acid.—A solution of 0.92 cc. (0.01 mole) of isobutyraldehyde, 1.2 cc. (0.02 mole) of acetic acid, and 25 cc. of methanol was treated with 1.2 cc. (0.01 mole) of cyclohexylisonitrile. After 7 hr. the volatile components were evaporated under reduced pressure to give a colorless crystalline residue; yield, 2.82 g.; m.p. 114–118°. The crude product was recrystallized from hexane–benzene to give pure crystalline IV; yield, 1.65 g. (69%); m.p. 121–122°.

Anal. Calcd. for $C_{13}H_{23}NO_3$ (241.32): C, 64.70; H, 9.61; N, 5.81. Found: C, 64.67; H, 9.56; N, 6.07.

(B) Acetic Anhydride.—A solution of 0.92 cc. (0.01 mole) of isobutyraldehyde, 25 cc. of chloroform, and 1.02 g. (0.01 mole) of acetic anhydride was treated with 1.2 cc. (0.01 mole) of cyclohexylisonitrile. After standing overnight 1.0 cc. of methanol was added and the volatile materials were evaporated to give a colorless crystalline residue; yield, 1.80 g. (75%); m.p. 110–115°; m.m.p. with IV prepared in part A, 116–119°.

N-Cyclohexyl-α-hydroxyisovaleramide (II).—A solution of 600 mg. (0.0025 mole) of IV, 15 cc. of methanol, and 2.5 cc. of 1 *N* potassium hydroxide was allowed to stand at room temperature for 2 days. A small amount of insoluble material was filtered and the filtrate was evaporated under reduced pressure to give colorless crystals of II; yield, 386 mg. (76%); m.p. 127–128°. An analytical sample was prepared by recrystallization from hexane–benzene, m.p. 129–131°.

Anal. Calcd. for $C_{11}H_{21}NO_2$ (199.29): C, 66.29; H, 10.62; N, 7.03. Found: C, 66.13; H, 10.35; N, 7.10.

N-Cyclohexyl-α-formyloxyisovaleramide (V).—A solution of 0.92 cc. (0.01 mole) of isobutyraldehyde, 0.75 cc. (0.02 mole) of formic acid, and 25 cc. of methanol at room temperature was treated with 1.2 cc. of cyclohexylisonitrile. After standing overnight the solution was filtered to remove a small amount of insoluble material and the filtrate was evaporated under reduced pressure to give 1.84 g. of a red-brown oil. This was taken up in ethyl ether and was then washed twice with water. The ether phase was dried over anhydrous sodium sulfate, filtered, and evaporated to give 1.55 g. of a semicrystalline substance. Two recrystallizations from hexane–benzene gave a pure crystalline sample of V; yield, 446 mg. (20%); m.p. 94–95°.

Anal. Calcd. for $C_{12}H_{21}NO_3$ (227.30): C, 63.41; H, 9.31; N, 6.16. Found: C, 63.64; H, 9.33; N, 6.20.

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[11] All melting points and boiling points are uncorrected.

[12] I. Ugi and R. Meyr, *Ber.*, **93**, 239 (1960).