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STUDIES OF ISOCYANIDES—III[1]

THE ADDITION OF N,N-DIALKYLAMIDE CHLORIDES TO ISOCYANIDES

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Abstract—The reaction of N,N-dimethyl- or N,N-pentamethylene-formamide chlorides with n-butyl, cyclohexyl, and 2,4-xylyl isocyanides results in the formation of 1:2-adducts which are readily converted by water to N,N′-disubstituted α-(dialkylamino)malonamides. In the case of N,N-dimethylamide chlorides of acetic, propionic, and benzoic acids, the products are the corresponding N-substituted α-ketoamides resulting from hydrolysis of 1:1-adducts and successive deamination. The yields range from 10 to 80% depending on the combinations of both reactants.

The nucleophilic character of isocyanides is due to a lone electron-pair on the terminal carbon. Thus, active carbonyl[2,3] and halogen[4] compounds (e.g. aldehydes, ketones, acyl halides, ketene, t-butyl hypochlorite and N-bromoamides) add to isocyanides, in the presence, if necessary, of certain acidic catalysts. It is likely that acids catalyse the reactions by converting these attacking agents into the more active carbonium or halogenonium salts. Recently, considerable attention has been devoted to studies on new carbonium salts[5,6] such as amide chlorides, carbamide chlorides, α-mercaptoformamide chlorides, and dimethyl sulphate salts of amides. The reactivity of these electrophilic compounds may be related to their ionization to α-dialkylamino carbonium ions, which are stabilized by resonance involving nitrogen. In fact, their ionic character has been proved by measurement of electric conductivity, appearance of a C═N band in the IR spectrum, and by their insolubility in non-polar solvents.[5] The behaviour of these carbonium salts towards various nucleophiles having no active hydrogens has not been studied. In a previous paper,[7] we have reported that the electrophilic attack of N,N-dimethylamide chlorides on the oxygen of cyclic ethers gives ω-chloroalkyl esters. This paper deals with the addition of the amide chlorides to the terminal carbon atom of isocyanides.

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[1] Part II, T. Shono, M. Kimura, Y. Ito, K, Nishida and R. Oda, *Bull. Chem. Soc. Japan*, **37**, 635 (1964).

[2] M. Passerini, *Gazz. Chim. Ital.* **51**, 181 (1921).

[3] I. Ugi, C. Steinbrückner and U. Fetzer, [a] *Chem. Ber.* **94**, 734 (1961); [b] *Ibid.* **94**, 1116 (1961); [c] *Ibid.* **94**, 2233 (1961).

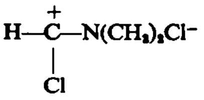
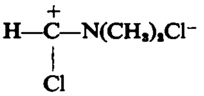
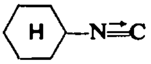
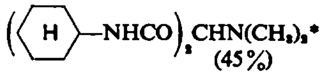
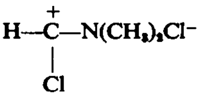
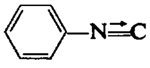
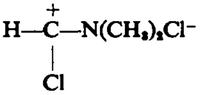
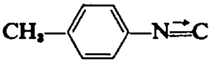
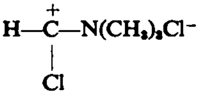
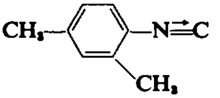
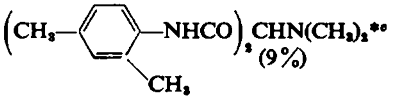
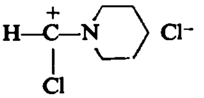
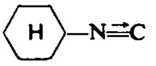
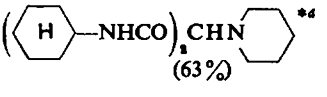
[4] M. Okano, Y. Ito, T. Shono and R. Oda, *Bull. Chem. Soc. Japan* **36**, 1314 (1963).

[5] H. Eilingsfeld, M. Seefelder and Weidinger, [a] *Angew. Chem.* **72**, 837 (1960); [b] *Chem. Ber.* **96**, 2671 (1963); [c] *Ibid.* **97**, 1232 (1964); [d] *Ibid.* **98**, 1293 (1965).

[6] H. Bredereck, F. Effenberger and G. Simchen, [a] *Chem. Ber.* **96**, 1350 (1963); [b] *Ibid.*, **97**, 1403; [c] *Ibid.* **97**, 3076 (1964); [d] *Ibid.* **97**, 3081 (1964).

[7] Y. Ito, S. Katsuragawa, M. Okano and R. Oda, *Tetrahedron Letters* 1321 (1965).

TABLE 1. THE REACTION OF N,N-DIALKYLFORMAMIDE CHLORIDES WITH ISOCYANIDES
Reaction conditions; amide chloride 0·05 mole; isocyanide 0·10 mole; solvent (dioxan) 200–300 ml; 15°, 15 hr.

Amide Chloride	Isocyanide	Product (Yield)	M.p.
 $H-\underset{Cl}{\overset{+}{C}}-N(CH_3)_2Cl^-$	$n-C_4H_9-N{\equiv}C$	$(C_4H_9NHCO)_2CHN(CH_3)_2$*[a] (27%)	130–132°
 $H-\underset{Cl}{\overset{+}{C}}-N(CH_3)_2Cl^-$			148–149°
 $H-\underset{Cl}{\overset{+}{C}}-N(CH_3)_2Cl^-$		Unreacted	
 $H-\underset{Cl}{\overset{+}{C}}-N(CH_3)_2Cl^-$		Unreacted	
 $H-\underset{Cl}{\overset{+}{C}}-N(CH_3)_2Cl^-$			
			190°

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[a] Found: C, 61·12; H, 10·43; N, 15·89. $C_{13}H_{27}N_3O_2$ requires: C, 60·66; H, 10·57; N, 13·33%.

[b] Found: C, 66·15; H, 10·29; N, 13·67. $C_{17}H_{31}N_3O_2$ requires: C, 65·98; H, 10·10; N, 1v·58. Its hydrochloride* (m.p. 232–233°), Found; C, 58·93; H, 9·17; N, 12·33; Cl, 10·74. $C_{17}H_{32}N_3O_2Cl$ requires: C, 59·03; H, 9·32; N, 12·15; Cl, 10·25%. Its ethyl bromide salt (m.p. 169–170°), Found: C, 54·78; H, 8·90; N, 9·96. $C_{19}H_{36}N_3O_2Br$ requires: C, 54·54; H, 8·67; N, 10·04%.

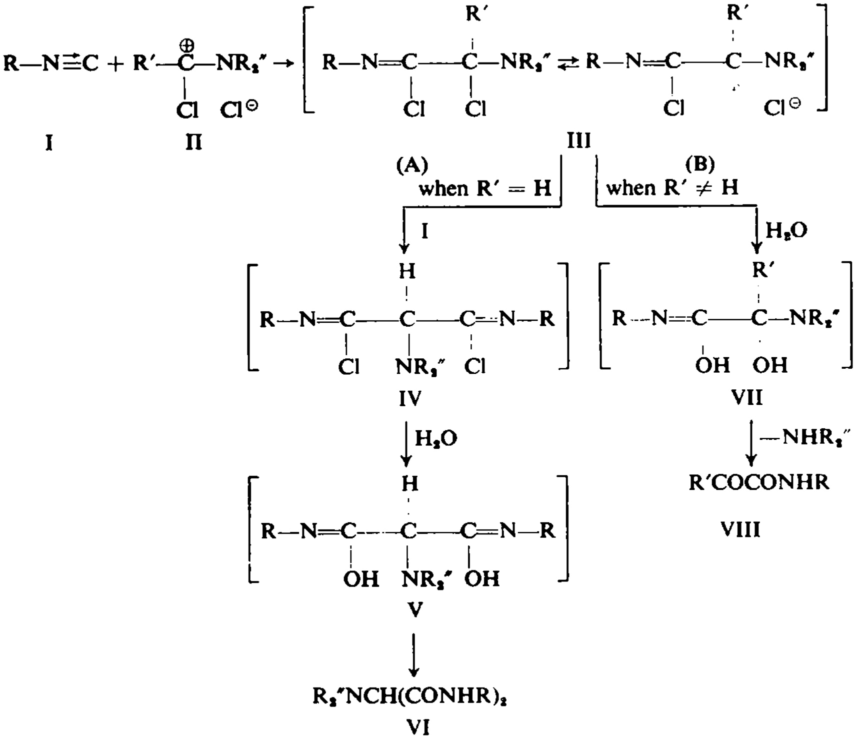
[c] Isolated as its hydrochloride* (m.p. 247–248°), Found: C, 65·10; H, 7·24; N, 10·56; Cl, 8·90; $C_{21}H_{28}N_3O_2Cl$ requires: C, 64·69; H, 7·24; N, 10·78; Cl, 9·09%.

[d] Found: C, 68·86; H, 10·19; N, 12·16. $C_{20}H_{35}N_3O_2$ requires: C, 68·73; H, 10·09; N, 12·02%.

* New compound.

The products obtained from the reaction mixtures by treatment with water depend on the acid component of the N,N-dialkylamide chlorides used. The reaction with dialkylformamide chlorides generally affords α-(dialkylamino)malonamides which correspond to 1:2-adducts of the amide chlorides and isocyanides; whereas, the reaction with other N,N-dialkylamide chlorides affords α-ketoamides which may be derived from 1:1-adducts of both reactants. The structures of these products were established by elemental analyses, IR spectra and in some instances by comparison with authentic samples prepared from acyl chlorides and isocyanides.

A most probable reaction scheme may be as follows. The initial intermediate may be the 1:1-adduct (III) formed by the attack of the cation II on the terminal carbon of I. The path A involving addition of the cation III to another molecule of I and subsequent hydrolysis gives VI. Another path B involving hydrolysis of III and successive deamination leads to VIII. Deamination after hydrolysis, which probably proceeds by an intramolecular sequence, has also been observed in the reactions of amide chlorides with dimethylaniline,[5a] phenylacetylene[5a] and cyclic ethers.[7]



Judging from the electronic effect, a cation III is less electrophilic than the corresponding cation II. In fact, the adduct isolated is generally of type VIII, not VI, except in the case of formamide chloride. Moreover, in the reaction of dimethylformamide chloride with cyclohexyl isocyanide in dioxan,[8] the presence of VIII was not detected and no variation in the yield of VI was observed, even when 100 mole % excess of the amide chloride was used. Perhaps such difference could be accounted for in the following way. When R' = H, the cation III would show the highest reactivity; whereas when R = CH_3, C_2H_5 or C_6H_5, the reactivity may be lowered due to the influence of the electron-donating alkyl (—I) or phenyl (—E) group. In the case of formamide chloride, its concentration in solution is very low because of its poor solubility[9] and, therefore, the reaction always proceeds under the condition where excess isocyanide is present.

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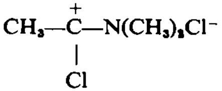
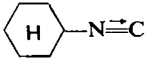
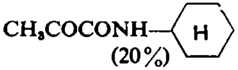
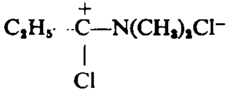
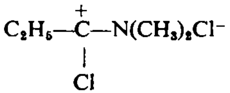
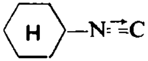
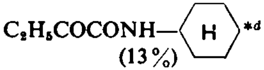
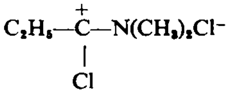
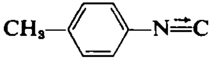
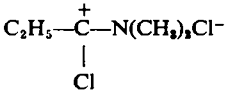
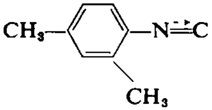
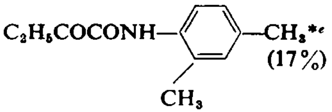
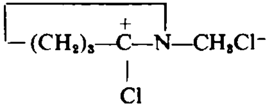
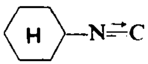
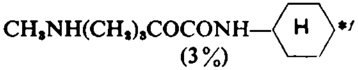
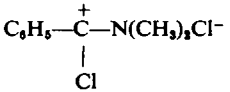
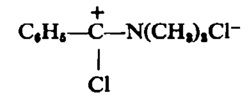
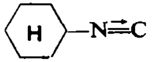
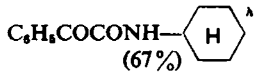
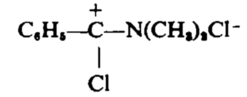
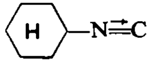
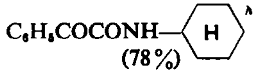
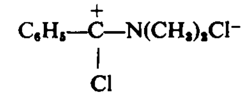
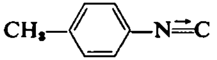
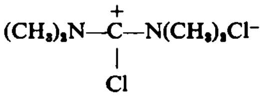
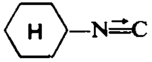
[8] Though somewhat higher solubility of the amide chloride in methylene dichloride than in dioxan was observed, the use of the former solvent resulted in the striking formation of tarry matter.

[9] A qualitative experiment showed that the solubility of N,N-dimethylamide chlorides in dioxan decreases in the order: R' = C_6H_5 > CH_3, C_2H_5 > H.

TABLE 2. THE REACTION OF N,N-DIALKYLAMIDE CHLORIDES OF ALIPHATIC AND BENZOIC ACIDS WITH ISOCYANIDES

Reaction conditions: amide chloride 0·10 mole; isocyanide 0·10 mole; solvent 200–300 ml; 15°, 15 hr.

Amide Chloride	Isocyanide	Solvent[a]	Product (Yield)	M.p. (b.p.)
 $CH_3{-}\underset{Cl}{\underset{\vert}{\overset{+}{C}}}{-}N(CH_3)_2Cl^-$		D	 CH$_3$COCONH— (20%)	75–76° [b]
 $C_2H_5{-}\underset{Cl}{\underset{\vert}{\overset{+}{C}}}{-}N(CH_3)_2Cl^-$	$n{-}C_4H_9{-}N\overset{\rightarrow}{=}C$	D	$C_6H_5COCONHC_4H_9$*[c] (11%)	(75–78°/3 mm)
 $C_2H_5{-}\underset{Cl}{\underset{\vert}{\overset{+}{C}}}{-}N(CH_3)_2Cl^-$		D	 C$_2$H$_5$COCONH— *[d] (13%)	62–63°
 $C_2H_5{-}\underset{Cl}{\underset{\vert}{\overset{+}{C}}}{-}N(CH_3)_2Cl^-$		A	Unreacted	
 $C_2H_5{-}\underset{Cl}{\underset{\vert}{\overset{+}{C}}}{-}N(CH_3)_2Cl^-$		A	 C$_2$H$_5$COCONH— —CH$_3$*[e] (17%)	112–113°
 $(CH_2)_3{-}\underset{Cl}{\underset{\vert}{\overset{+}{C}}}{-}N{-}CH_3Cl^-$		A	 CH$_3$NH(CH$_2$)$_3$COCONH— *[f] (3%)	
 $C_6H_5{-}\underset{Cl}{\underset{\vert}{\overset{+}{C}}}{-}N(CH_3)_2Cl^-$	$n{-}C_4H_9{-}N\overset{\rightarrow}{=}C$	D	$C_6H_5COCONHC_4H_9$*[g] (39%)	(95–100°/0·5 mm)

 $\mathrm{C_6H_5{-}}\underset{\mathrm{Cl}}{\overset{+}{\mathrm{C}}}\mathrm{{-}N(CH_3)_2Cl^-}$		D	 C$C_6H_5COCONH-$ (67%)[h]	115°[i]
 $\mathrm{C_6H_5{-}}\underset{\mathrm{Cl}}{\overset{+}{\mathrm{C}}}\mathrm{{-}N(CH_3)_2Cl^-}$		A	 $C_6H_5COCONH-$ (78%)[h]	115°[i]
 $\mathrm{C_6H_5{-}}\underset{\mathrm{Cl}}{\overset{+}{\mathrm{C}}}\mathrm{{-}N(CH_3)_2Cl^-}$		D	Unreacted	
 $\mathrm{(CH_3)_2N{-}}\underset{\mathrm{Cl}}{\overset{+}{\mathrm{C}}}\mathrm{{-}N(CH_3)_2Cl^-}$		A	Unreacted	

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[a] D: dioxan, A: acetonitrile.

[b] Reported m.p. 76–78° (Ref. 3*b*).

[c] Found: C, 61·43; H, 9·47; N, 9·41. $C_8H_{15}NO_2$ requires: C, 61·12; H, 9·62; N, 8·91%. Its 2,4-dinitrophenyl hydrazone* (m.p. 117–118°). Found: C, 49·92; H, 5·84; N, 20·93. $C_{14}H_{19}N_5O_6$ requires: C, 49·84; H, 5·68; N, 20·76%.

[d] Found: C, 65·81; H, 9·60; N, 7·41. $C_{10}H_{17}NO_2$ requires: C, 65·54; H, 9·35; N, 7·64%.

[e] Found: C, 70·58; H, 7·54; N, 7·18. $C_{12}H_{15}NO_2$ requires: C, 70·22; H, 7·37; N, 6·82%.

[f] Isolated as 2,4-dinitrophenyl hydrazone of its hydrochloride* (m.p. 223–224°). Found: C, 49·09; H, 6·40; N, 18·85. $C_{16}H_{27}N_6O_5Cl$ requires: C, 48·81; H, 6·14; N, 18·98%.

[g] Found: C, 70·78; H, 7·52; N, 6·60. $C_{12}H_{15}NO_2$ requires: C, 70·22; H, 7·37; N, 6·82%. Its 2,4-dinitrophenyl hydrazone (m.p. 188–189°). Found: C, 56·28; H, 4·74; N, 17·99. $C_{18}H_{19}N_5O_6$ requires: C, 56·10; H, 4·97; N, 18·17%.

[h] Its 2,4-dinitrophenyl hydrazone* (m.p. 230–231°). Found: C, 58·43; H, 5·35; N, 17·18. $C_{20}H_{21}N_5O_6$ requires: C, 58·38; H, 5·15; N, 17·02%.

[i] Reported m.p. 115° (Ref. 3*b*).

* New compound.

An attempt to obtain adducts from tetramethylcarbamide chloride was unsuccessful, no doubt due to the fact[5c] that the carbamide chlorides are less reactive than the amide chlorides.

It should be noted that, among the aromatic isocyanides employed, only 2,4-xylylisocyanide reacts with form- and propion-amide chlorides to yield the expected adducts.

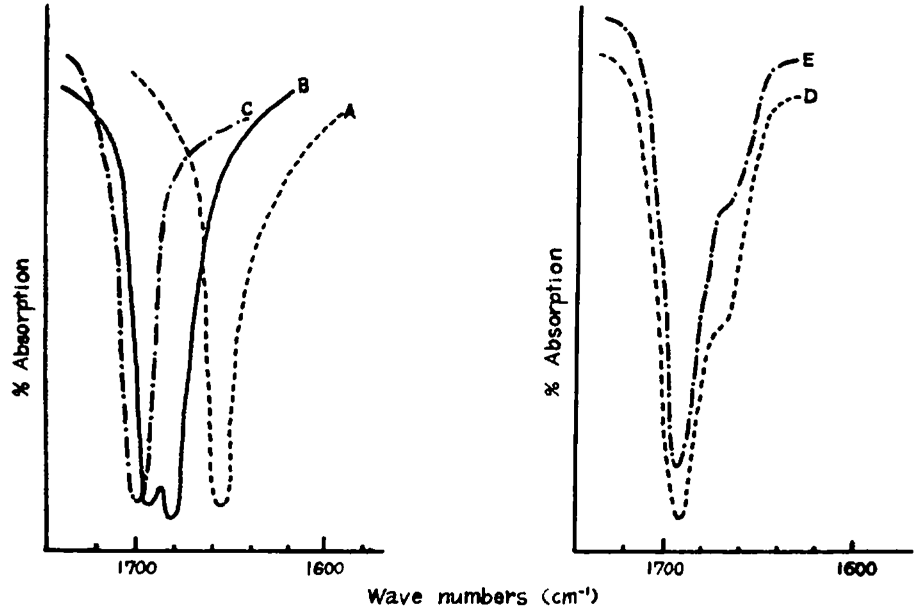
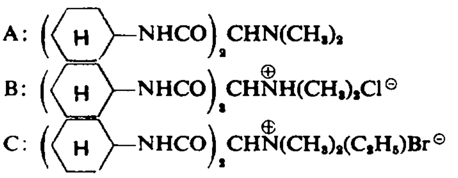
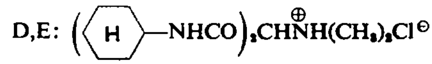


Fig. 1 IR spectra of N,N'-dicyclohexyl-α(dimethylamino)malonamide and its derivatives.



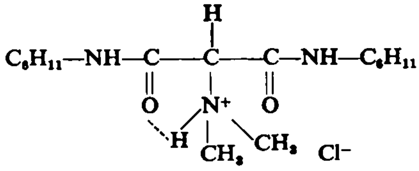


(in CHCl$_3$, conc. 0·25M and 0·05M, respectively)

(in Nujol)

This clearly results from the increase in the negative character at terminal carbon of the isocyanide due to the influence of the elctron-donating two methyl groups. The data also show that the activation by one methyl group only is insufficient.

As is seen in Fig. 1, both a free amine VI (R = cyclo-C_6H_{11} and R' = CH_3) and its ethyl bromide salt show a single carbonyl absorption at the expected position (1650–1700 cm^{-1}), whereas in the spectrum of its hydrochloride (in Nujol) two separated peaks appear near 1685 cm^{-1}. This is understood if we assume that a weak bond is formed between the hydrogen atom on the quaternary nitrogen and the oxygen of either one of two carbonyl groups. In fact, a marked decrease in the intensity of the lower-frequency band is observed when the spectrum was examined in dilute chloroform solution.



$$C_6H_{11}{-}NH{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{\underset{\underset{H\ \ CH_3\ \ CH_3}{\overset{|}{N^+}}}{C}}{-}\underset{\underset{O}{\|}}{C}{-}NH{-}C_6H_{11}\quad Cl^-$$

EXPERIMENTAL

Some representative examples are given below. Temps were not corrected.

Materials. All amide chlorides employed were synthesized by the reaction of the corresponding amides with phosgene,[5b] and all isocyanides were prepared from the corresponding formamides according to the procedure of Ugi and Meyr.[10]

The reaction of dialkylformamide chlorides with isocyanides

N,N′-*Dicyclohexyl-α-(dimethylamino)malonamide.* Into a mixture of 5·1 g (0·04 mole) dimethylformamide chloride and 200 ml dry dioxan, 8·7 g (0·08 mole) cyclohexylisocyanide was added dropwise with stirring which was continuted for 5 hr. The reaction was gently exothermic and the temp was maintained at about 15° by cooling with water and then the mixture was allowed to stand overnight. The reaction mixture was poured into 600 ml cold water. After 1 hr, Na_2CO_3 was added until the aqueous solution became alkaline, and the solution was then extracted with benzene. The extract was washed with water and dried. After evaporation of the benzene the crude product together with viscous brown matter was recrystallized from ethyl acetate. The yield of pure N,N′-dicyclohexyl-α-(dimethylamino)malonamide (m.p. 147–148°) was 5·5 g (45%), ν_{max} (in Nijol) 3310 (NH) and 1655 cm^{-1} (C=O). A mol. wt. determination by the cryoscopic method in benzene showed a value of 324 (Calc. 309).

Upon treatment of this amine with dry HCl and EtBr, the hydrochloride and the corresponding ammonium bromide were obtained in good yields, respectively.

N,N′-*Di(2,4-xylyl)-α-(dimethylamino)malonamide.* According to the procedure described above, 12·8, g (0·1 mole) dimethylformamide chloride was treated with 13·1 g (0·1 mole) 2,4-xylylisocyanide in 200 ml dry dioxan. The residue obtained by distillation of the solvent was dissolved in EtOH. Dry HCl gas was then passed into the EtOH solution, and the hydrochloride salt was recrystallized from EtOH yielding 1·8 g (9%) pure N,N′-di(2,4-xylyl)-α-(dimethylamino)malonamide hydrochloride (m.p. 247–2 8°), ν_{max} (in Nujol) 3180 (NH), 1700 and 1690 cm^{-1} (C=O).

The reaction of other dialkylamide chlorides with isocyanides

N-*Cyclohexylpyruvamide.* Into a stirred mixture of 10·5 g (0·074 mole) N,N-dimethylacetamide chloride and 200 ml dry dioxan, 8 g (0·074 mole) cyclohexyl isocyanide was added dropwise. Stirring was continued for additional 5 hr at 15°. The reaction mixture was allowed to stand overnight and then poured into 600 ml cold water. The aqueous solution was made alkaline with Na_2CO_3, and extracted with benzene. The benzene extract was washed and dried. After removal of the solvent, a tar-like residue was distilled *in vacuo*. The fraction b.p. 100–105°/2 mm was collected and solidified on cooling. The yield of N-cyclohexylpyruvamide (m.p. 75–76°) was 2·5 g (20%), ν_{max} (in Nujol) 3380 (NH), 1720 and ca. 1680 cm^{-1} (C=O).

An authentic sample used for structural confirmation was prepared by the reaction of cyclohexyl isocyanide with acetyl chloride.[8b]

N-*(2,4-Xylyl)-2-oxobutyramide.* In a similar way, 10 g (0·076 mole) 2,4-xylyl isocyanide was added to a solution of 12 g (0·076 mole) N,N-dimethylpropionamide chloride in 200 ml acetonitrile The working-up of the reaction mixture, as described above, gave a tarry product. It was extracted with hot ligroin several times and the combined extracts after being treated with Norit was evaporated. Recrystallization of the residue from ligroin afforded 2·6 g (17%) pure N-(2,4-xylyl)-2-oxobutyramide (m.p. 112–113°), ν_{max} (in Nujol) 3300 (NH), 1730 and 1670 cm^{-1} (C=O).

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

N-(*Cyclohexyl*)*benzoylformamide*. To a solution of 14·3 g (0·07 mole) N,N-dimethylbenzamide chloride in 200 ml dry acetonitrile, 7·7 g (0·07 mole) cyclohexylisocyanide was added dropwise with stirring which was continued at 15° for 5 hr. After the solution had stood overnight, it was poured into 600 ml ice water, and after 1 hr the precipitated crystalline material was recrystallized from 50% MeOH. The yield of N-(cyclohexyl)-benzoylformamide (m.p. 115°) was 12·5 g (78%), ν_{max} (in Nujol) 3300 (NH) and ca. 1660 cm^{-1} (two $C=O$ unresolved).