was allowed to stand at room temperature overnight. The reaction mixture was diluted with 5 ml of ethylene glycol, allowed to stand for 5 min, and concentrated on the steam bath to about 20 ml. The mixture was taken up in 600 ml of ether and 200 ml of ice-cold water, the layers were separated, and the aqueous phase was extracted first with 600 ml of ether and then with 300 ml of ether. The organic extracts were washed with three 200-ml portions of water, three 200-ml portions of ice-cold saturated sodium bicarbonate solution, and again with water to neutrality. The organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to leave 0.835 g of an oily residue.

Chromatographic purification of this product on 100 g of silica gel gave rise to 0.739 g of the desired formate **9a** which was obtained in the eluates with benzene–ethyl acetate (4:1). The compound could not be obtained in crystalline form. A typical chromatographic fraction contained, in addition to the formate **9a**, three trace impurities as shown by thin layer chromatographic analysis (silica gel, benzene–methanol 9:1). The compound **9a** had $[\alpha]^{24}\text{D}$ −4° (*c* 0.972); $\tilde{\nu}_{\max}$ 3605, 1720, 1170 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.92; H, 9.01.

3α,17β-Dihydroxy-13α-C-nor-5β-androstan-11-one (9b).—A solution of 0.729 g of the above-obtained product **9a** and 0.320 g of potassium carbonate in 25 ml of methanol and 3.5 ml of water was allowed to stand at room temperature for 5 days. The solution was diluted with 100 ml of distilled water and the methanol was removed under reduced pressure. The resulting crystalline suspension was cooled; the crystals were collected on a filter, washed with several small amounts of water, and dried to yield 0.466 g of compound. The turbid, aqueous filtrate was acidified with 2 *N* hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, filtered, and evaporated to leave 0.198 g of a solid residue. This material was shown to be identical with the above 0.466 g of product by infrared and nmr spectra and thin layer chromatography.

Chromatography of the above combined reaction product on 70 g of silica gel and two recrystallizations of the residues from the benzene–ethyl acetate (1:1) eluates from acetone–heptane gave rise to a first crop of 0.370 g of the desired C-nor ketone **9b**, of mp 184.5–185°. A second crop amounted to 0.156 g, mp 180–183°. The over-all yield of the ketone **9b** (both crops) from the lactone **6a** was 60%.

A part of the above first crop was recrystallized twice for analysis: mp 185–185.5°; $[\alpha]^{25}\text{D}$ +5° (*c* 1.01); $\tilde{\nu}_{\max}$ 3600, 1720 cm^{-1}.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.09, 73.90; H, 9.82, 9.66.

Registry No.—**2a**, 13976-62-0; **2b**, 13961-97-2; **3a**, 10437-34-0; **3b**, 13976-64-2; **3c**, 13976-65-3; **4**, 13976-66-4; **5a**, 10587-52-7; **5b**, 13976-68-6; **6a**, 10454-74-7; **6b**, 10454-75-8; **6c**, 13976-71-1; **7a**, 10454-76-9; **7b**, 10454-77-0; **8**, 13961-99-4; **9a**, 13962-00-0; **9b**, 13976-73-3; benzilic acid, 76-93-7.

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Selective Carbamylation with Methyl Isocyanate

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Reactions of methyl isocyanate ($CH_3N{=}C{=}O$), a fundamental decomposition product of some N-methylcarbamates, have been investigated. Nuclear magnetic resonance (nmr) was used to measure the end of the reaction in a sealed system. Reaction of $CH_3N{=}C{=}O$ with water proceeds slowly enough to be followed by nmr; no evidence was seen of large concentrations of CH_3ND_2 and CH_3NDCO_2D. Reaction of $CH_3N{=}C{=}O$ with 2-formylcyclohexanone, which can exist in three forms, yielded a fairly pure N-methylcarbamate. Nmr limited the derivation of the product to one of two possibilities. The *trans* structure was confirmed by reaction of $CH_3N{=}C{=}O$ with two other α-formyl ketones to yield a terminally substituted *trans* product; a small amount of pyridine was present, which may have shifted the equilibria. Reaction of $CH_3N{=}C{=}O$ with four aromatic ambident anions in pyridine at 100° yielded products indicating preferential attack on only one of the sites. 1,4-Naphthoquinone monoxime was carbamylated on the oxime to the exclusion of the ring products. The selective reaction of $CH_3N{=}C{=}O$ indicates that it has some steric requirements in the systems studied.

Many N-methylcarbamate esters of phenols, naphthols, ring hydroxylated heterocyclics, oximes, etc., act as insecticides probably by inhibiting esterases in a manner similar to the phosphate esters.[1,2] These carbamates are hydrolyzed to $CH_3N{=}C{=}O$ by various bases.[3,4] They are also pyrolyzed[5,6] and fragmented under electron impact[7] to yield $CH_3N{=}C{=}O$. Since $CH_3N{=}C{=}O$ appears to be a fundamental decomposition product of these carbamates, its reactions were further investigated in preparation for a study of the interaction of N-methylcarbamate insecticides with complex, living systems.

Although the reactivity of the $-N{=}C{=}O$ group in general has been reviewed,[8,9] the reactions of $CH_3N{=}C{=}O$ are associated mainly with the insecticide literature.[1,2] In reported syntheses of N-methylcar-

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(1) J. E. Casida, *Science*, **146**, 1011 (1964).

(2) W. R. Benson and H. A. Jones, *J. Assoc. Offic. Agr. Chemists*, **50**, 22 (1967).

(3) (a) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 3640 (1964); (b) A. Hassner and G. Nash, private communication; (c) M. L. Bender and R. B. Homer, *J. Org. Chem.*, **30**, 3975 (1965); (d) I. Christenson, *Acta Chem. Scand.*, **18**, 904 (1964).

(4) L. Dittert and T. Higuchi, *J. Pharm. Sci.*, **52**, 857 (1963).

(5) J. A. Aeschlimann and M. Reinert, *J. Pharmacol. Exptl. Therap.*, **43**, 413 (1931).

(6) J. G. Krishna, H. W. Dorough, and J. E. Casida, *J. Agr. Food Chem.*, **10**, 462 (1962).

(7) J. Damico and W. R. Benson, *J. Assoc. Offic. Agr. Chemists*, **48**, 344 (1965); J. B. Thomson, P. Brown, and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 4049 (1966).

(8) R. Pinner, *Plastics* (London), **11**, 257 (1947).

(9) (a) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **47**, 47 (1957); (b) P. Adams and F. A. Baron, *ibid.*, **65**, 567 (1965).

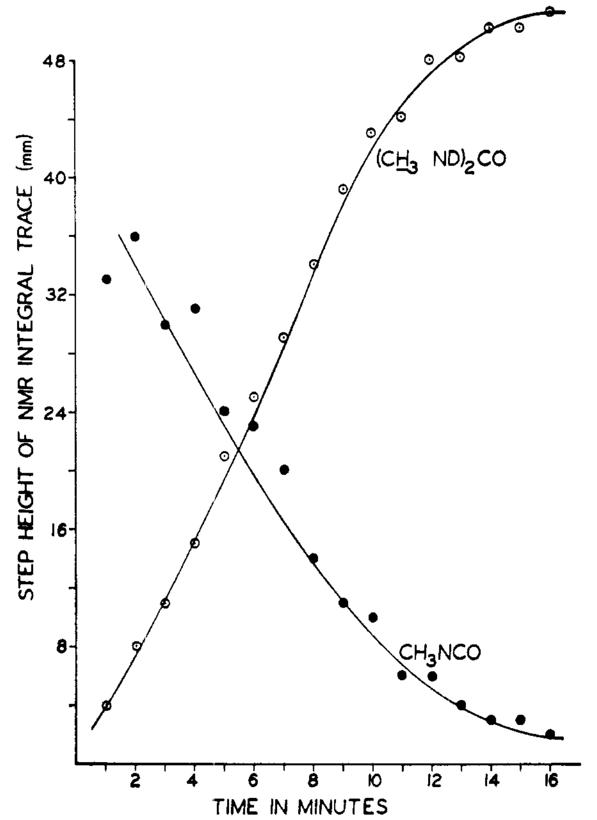


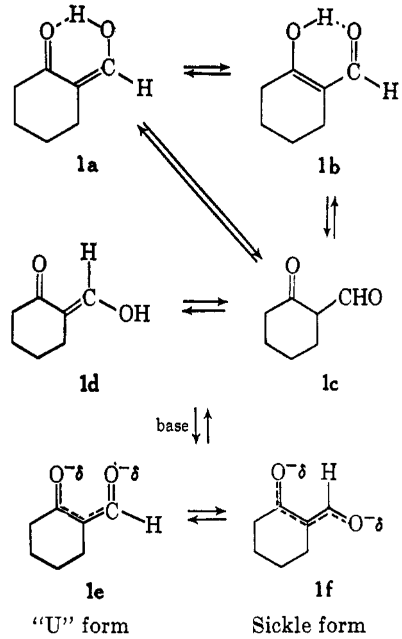
Figure 1.—Hydrolysis of methyl isocyanate in D_2O and acetone-d_6 as followed by nmr: $[D_2O]$ = 20 moles/l., $[CD_3COCD_3]$ = 5 moles/l., $[CH_3NCO]$ = 3.4 moles/l.

bamates *via* $CH_3N{=}C{=}O$,[10,11] the rate of product formation was not followed, mainly because the toxicity and volatility of $CH_3N{=}C{=}O$ often has required the use of a sealed system. The difficulty of measuring the end of the reaction in a sealed system was overcome in our work by using nmr. The disappearance of the $\mathit{CH}_3N{=}C{=}O$ peak at 183 Hz (nmr spectra were taken at 60 MHz; see Experimental Section) was followed, and the CH_3NHCO_2 doublet in the product generally was found to appear between 162 and 172 Hz (J_{HH} = 5 Hz). This range represents the absorptions and coupling constants for 20 aryl N-methylcarbamates. This technique was used to follow the formation of a number of carbamates in three systems.

Certain compounds were chosen for study of the chemistry of CH_3NCO because they give products that are easy to identify and because they demonstrate the stereochemistry involved. Later, we shall report on transesterification of carbamates with natural products.

First System.—Since water is the main component in living systems, the rate of reaction of $CH_3N{=}C{=}O$ with H_2O was demonstrated qualitatively. If the reaction were completed in a few seconds, it is unlikely that $CH_3N{=}C{=}O$ could remain intact long enough in an aqueous environment to react with an organic functional group. Methyl isocyanate was placed in contact with a large excess of deuterated water ($CH_3N{=}C{=}O : D_2O$, molar ratio of 1:6) together with some deuterated acetone to solubilize the $CH_3N{=}C{=}O$, and the reaction was followed by nmr. The crude results are given in Figure 1. During the reaction, no evidence of significant concentrations of CH_3ND_2 and CH_3NDCO_2D were found in the nmr spectra, a result which confirmed in part the reaction, $CH_3N{=}C{=}O + D_2O \rightarrow [CH_3NDCO_2D] \rightarrow [CO_2 + CH_3ND_2] \xrightarrow{CH_3NCO} CH_3NDC(O)NDCH_3$, reported by Naegel, *et al.*,[12] for phenyl isocyanate. It was also clear that $CH_3N{=}C{=}O$ was not instantly decomposed by water. Since $CH_3N{=}C{=}O$ reacts with amino groups nearly 200 times as fast as with hydroxyl groups,[8] the possibility becomes more likely that $CH_3N{=}C{=}O$ remains intact long enough to react with compounds other than H_2O in a living system.

Second System.—The second system studied was 2-formylcyclohexanone (**1**) which could exist in forms **a–f**.



Garbisch[13a] calculated the ratio of **1a**:**1b** to be 0.32. Deutsch and Deutsch[13b] calculated that **1** was entirely in the **1a** form. The nmr spectra of **1** in CCl_4, containing 8% DMSO at all concentrations tested (100%, 90%, 70%, . . . 10%), showed only one band in the vinyl hydrogen region.[13a] The reaction of **1** with $CH_3N{=}C{=}O$ in the presence of some base could lead to the three possible carbamates, **2a**, **2b**, and **2d**. Considering only the concentrations of the species in neutral solutions, the main products should be derived from **1a** and **1b**. Garbisch and Deutsch did not consider **1d**, but in more strained systems, this type of isomer, **1d**, was indeed found.[14] The reaction between **1** and $CH_3N{=}C{=}O$ took place with pyridine as a catalyst, yielding a sharp-melting solid **2**, which had (a) the expected infrared spectrum of an N-methylcarbamate[15] and (b) a predictable[7,16] mass spectrum (mol wt = 183).

In contrast to the starting material, the product **2**

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[10] M. J. Kolbezen, R. L. Metcalf, and T. R. Fukuto, *J. Agr. Food Chem.*, **2**, 864 (1954).

[11] H. W. Dorough and J. E. Casida, *ibid.*, **12**, 297 (1964).

[12] C. Naegel, A. Tyabji, L. Conrad, and F. Litwan, *Helv. Chim. Acta*, **21**, 1100 (1938).

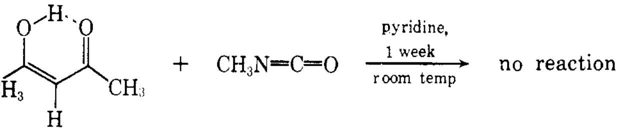
[13] (a) E. Garbisch, *J. Am. Chem. Soc.*, **85**, 1696 (1963); **87**, 505 (1965). (b) I. Deutsch and K. Deutsch, *Tetrahedron Letters*, No. 17, 1849 (1966).

[14] J. C. Richer and R. Clarke, *Can. J. Chem.*, **42**, 2073 (1964).

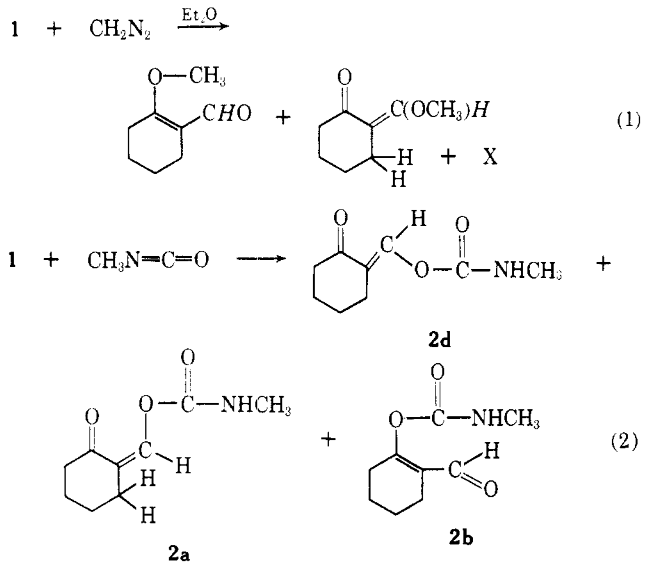
[15] J. T. Chen and W. R. Benson, *J. Assoc. Offic. Agr. Chemists*, **49**, 412 (1966).

[16] W. R. Benson and J. N. Damico, unpublished M. S. data.

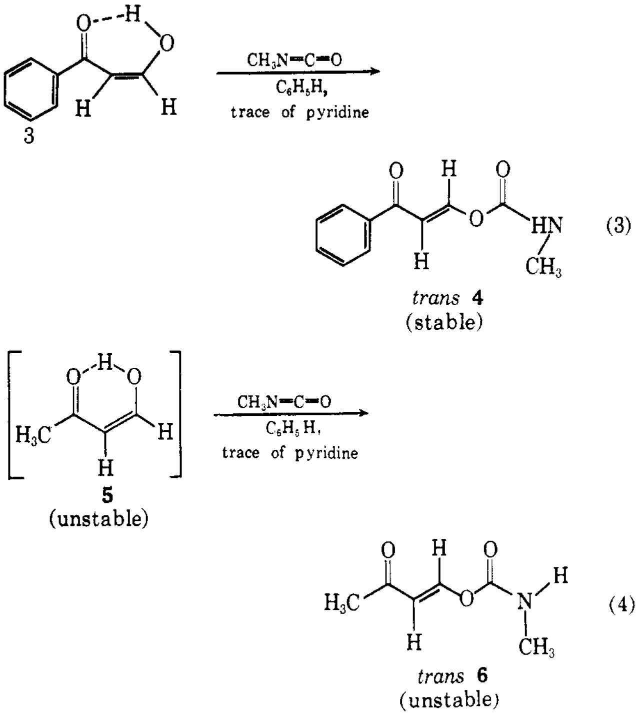
had only one rapidly exchanging H (on nitrogen), as shown by washing out NH with D_2O and base. In the nmr spectrum, no absorption in the aldehydic region was found, but a triplet appeared in the vinyl region. These and other bands conformed to the product expected from the carbamylation of **1a** and/or **1d**. To determine if the triplet was due to spin coupling or to chemical shifts in a mixture of isomers, the solution was examined at two radio frequencies (60 and 100 MHz). Since the triplet spacings were the same at these two frequencies, the triplet cannot arise from chemically shifted protons and, thus, not from the presence of isomers. From these and other data, it was concluded that a fairly pure product had been formed. The sluggish reactivity of the predominant form **1b** was understood somewhat better when 2,4-pentanedione under the same conditions had shown no reaction with $CH_3N{=}C{=}O$ after 1 week, shown by nmr.



We obtained further information on the triplet of **2a** or **2d** in the following way. The treatment of **1** with diazomethane (eq 1) gave three major products believed to be methyl ethers. The nmr spectrum of the products showed a singlet in the conjugated aldehydic hydrogen range and a triplet for the conjugated vinylic hydrogen. These results indicated that the CH_2 group at C-3 in **2a** and/or **2d** was probably causing the vinyl hydrogen absorption to split into a triplet. Such splitting has been reported[17] for a methylene in known *cis* and *trans* conformations.



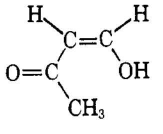
It was not possible to deduce from these data whether the OH group in **1a** reacted more rapidly with $CH_3N{=}C{=}O$ (eq 2) than did the OH group of **1d** to yield **2a** or **2d**. Therefore, we allowed $CH_3N{=}C{=}O$ to react with two other α-formyl ketones to see if any general principles could be formulated that would help us deduce the structure of **2**.

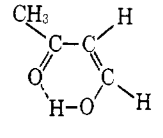


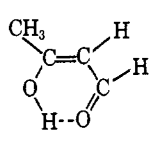
Lowe and Ferguson[18] suggested that the benzoylacetones tested were over 90% enolic in a nonpolar solvent and were enolized toward the phenyl group, and that a few per cent of nonchelated enol was present, also enolized toward the phenyl group. The percentage and direction of enolization were explained in terms of the relative amount of resonance stabilization associated with the cinnamoyl system, $ArC{=}CC{=}O$. Compound **3** should be subject to similar resonance considerations.

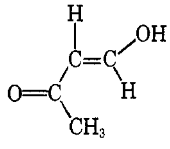
However, infrared and nmr data indicated that the product of carbamylation of **3** yielded the terminally substituted, *trans* product **4**. It must be remembered that a small amount of pyridine was present. This might upset equilibria in general as exemplified by **1e** and **1f**.

Equilibrium data from nmr studies reported for acetylacetaldehyde enol (**5**),[19] indicated that **5** exists mainly (in $CDCl_3$) as **5b** with some admixture from **5c**.


5a


5b


5c


5d

Forms **5a** and **5d** were not reported as present. Nevertheless, the product **6** was isolated, indicating that **5d** had reacted with $CH_3N{=}C{=}O$ (eq 4) as shown by nmr and infrared data.

From these two reactions, shown in eq 3 and 4, we infer that the pyridine may have caused partial carbanion formation leading to **1f**-type ambident ions.

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[17] D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, **29**, 1276 (1964).

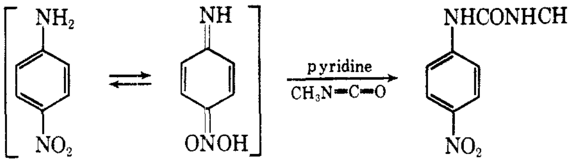
[18] J. V. Lowe, Jr., and L. N. Ferguson, *ibid.*, **30**, 3000 (1965).

[19] A. A. Bothner-By and R. K. Harris, *ibid.*, **30**, 254 (1965).

Also, formation of products from **1b**, **3**, and **5c** was probably not favored because of steric inhibition to **2b**, *cis*-**4**, and *cis*-**6**. The carbanions, if formed, could have assumed a "W" shape for **3** and **5** and a sickle shape for **1** in the three-plane, parallel, molecular orbital systems[20] so as to keep the charged oxygens as far apart as possible. Subsequent reactions with $CH_3N{=}C{=}O$ or a pyridine complex[21] yielded the carbamate.

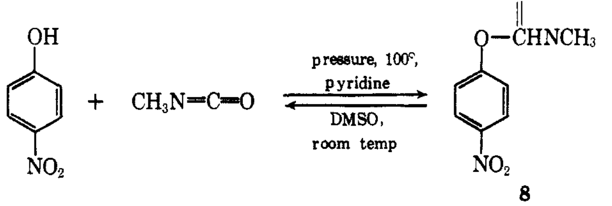
If these assumptions are true, then the reaction between **1** and $CH_3N{=}C{=}O$ with a trace of pyridine would lead to the *trans* product **2d** as given in eq 2 (from the **1f**, sickle form), rather than **2a** (from the **1e**, "U" form). From steric considerations, terminal vinyl hydroxy groups should be more reactive than secondary vinyl hydroxy groups but not necessarily to the exclusion of these secondary ester products. Pyridine could shift the reported equilibria of **1** and lead to the observed product **2d**. However, the neutral, rapid reacting CH_2N_2 may reflect the equilibrium of **1**.

Third System.—Four aromatic ambident anions in pyridine at 100° constituted the third system for carbamylation. Unlike some phenols and the previous vinyl hydroxy compounds, these compounds did not react at room temperature. More heat and pressure were necessary to effect reactions. Although in these studies we have found that pyridine, like other bases,[21] generally catalyzes carbamate formation, some amines have been reported to accelerate the thermal dissociation of carbamates[3b,22] at high temperatures. Pyridine, however, gave high yields in a closed system heated to 100°. With *p*-nitroaniline, the product of N-carbamylation prevailed over O-carbamylation to give **7** (eq 5). *p*-Nitrophenol might react with $CH_3N{=}C{=}O$ at two different oxygen atom positions. Even though the product melted 10° lower than that reported,[10] the elemental analysis was satisfactory for **8**. This compound **8** was stable in the solid state; however, when placed in dry DMSO, **8** rearranged to the starting materials, to a large extent, within 30 min.[23]



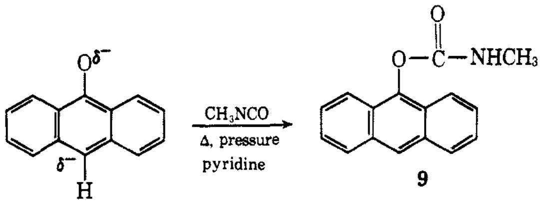
(5)

7

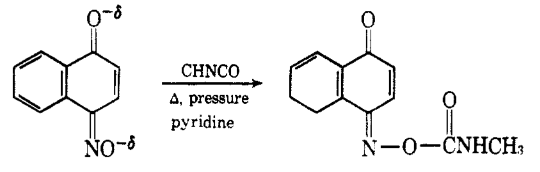


8

With 9-anthrone, the $CH_3N{=}C{=}O$ could react at two anion positions. The carbamate product **9** would be sterically hindered from having the planar carbamate group coplanar with the anthracene ring. Nevertheless, 9-anthryl N-methylcarbamate (**9**) formed exclusively.[24a] In the same manner as reported[24b] recently for the acetate, **10** formed on the oxime oxygen of 1,4-naphthoquinone monoxime, rather than on the ring oxygen, as shown by the presence of two carbonyl bands in the infrared spectrum.



9



10

In conclusion, methyl isocyanate reacted selectively with various ambident ions formed in solution containing pyridine. This indicates that $CH_3N{=}C{=}O$ has some steric requirements in all compounds studied. Further studies of the carbamylation process are in progress.

Experimental Section

Melting points are uncorrected and were determined on a hot stage equipped with a microscope. Proton nmr spectra were taken on a Varian A-60 spectrometer and lines are reported in hertz (Hz) downfield from tetramethylsilane, the internal reference standard. Elemental analyses were performed by Aldridge Associates and Co., Inc., Washington, D. C. Infrared spectra were taken on a Beckman IR-5 spectrometer and bands on peak positions are given in microns.

Hydrolysis of $CH_3N{=}C{=}O$.—Into an nmr sample tube were placed 0.20 ml (99% pure, 0.20 g, 0.010 mole) of D_2O and 0.20 ml (99% pure, 0.16 g, 0.0025 mole) of acetone-d_6. The two liquids were mixed. To this solution was added 0.10 ml (0.096 g, 0.0017 mole) of $CH_3N{=}C{=}O$, and the solution was swirled. The integral was determined every minute in the 200–150-Hz range. In previous runs it was determined that no other peaks appeared or disappeared except those attributed to $CH_3N{=}C{=}O$ and $CH_3NDC(O)NDCH_3$. Small, constant OH and CH peaks were observed but did not interfere. See Figure 1 for results.

2-(N-Methylcarbamyloxymethylene)cyclohexanone (2).—The 2-hydroxymethylenecyclohexanone was prepared by a method similar to that of Ainsworth.[25] Into 1 l. of benzene was placed 25.8 g (1.12 g-atoms) of finely cut sodium metal. The benzene was refluxed and 53 g (1.15 moles) of ethanol was added dropwise. After refluxing for 2 hr, the mixture was cooled to 5–7° and a mixture of ethyl formate (79.5 g, 1.07 moles) and cyclohexanone (98 g, 1.00 mole) was added dropwise. Vigorous stirring was necessary and an additional 2 l. of benzene was added as the sodium salt of 2-hydroxymethylenecyclohexanone (**1**) formed. After standing at room temperature over the weekend, the mixture was filtered, and the filter cake was broken and stirred with ether; the few remaining pieces of sodium were removed. The ether slurry was filtered and the filter cake was dried in a vacuum desiccator over P_2O_5. The salt was dissolved in 250 ml of water and acidified with 1:1 HCl, and the solution was cooled. Two layers formed. The upper layer was separated, and the lower, aqueous layer was extracted five times with ether, and the combined ether extracts and organic layer were dried over Na_2SO_4. When the solvent was

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[20] H. E. Zaugg and A. D. Shaefer, *J. Am. Chem. Soc.*, **87**, 1857 (1965).

[21] R. S. Bruenner and A. E. Oberth, *J. Org. Chem.*, **31**, 887 (1966).

[22] T. Mukaiyama and M. Iwanami, *J. Am. Chem. Soc.*, **79**, 73 (1957).

[23] N. Duy, W. R. Benson, and E. Lustig, unpublished data.

[24] (a) H. Muxfeldt, G. Grethe, and W. Rogalski, *J. Org. Chem.*, **31**, 2429 (1966); (b) W. R. Benson and R. Gajan, *ibid.*, **31**, 2498 (1966).

[25] C. Ainsworth, *Org. Syn.*, **4**, 536 (1963).

stripped off at reduced pressure, a red-brown oil remained. Vacuum distillation gave a clear, yellowish liquid (59.2 g, 47.0%), bp 37–40° (0.08–0.09 mm) (lit.[25] 70–72° at 5 mm), $n^{25}\text{D}$ 1.5115 (lit.[26] $n^{25}\text{D}$ 1.5110).

To 59 g (0.47 mole) of 2-hydroxymethylenecyclohexanone (**1**) in benzene solution were added 29 g (0.5 mole) of methyl isocyanate and 5 ml of anhydrous pyridine. The mixture was allowed to stand at room temperature for 1 hr and then tested for the presence of product by nmr. The appearance of the CH_3NH peak and the loss of the $CH_3N{=}C{=}O$ peak indicated that the reaction was completed. The benzene was removed by a Rinco flash evaporator. CCl_4 was added and the solution was chilled, yielding crystals. These were recrystallized from hot CCl_4 to give light yellow crystals, mp 106.2–107.8°.

Anal. Calcd for $C_9H_{13}NO_3$: C, 58.95; H, 7.15; N, 7.65. Found: C, 58.52; H, 6.85; N, 7.66.

The nmr spectrum showed a doublet at 167 Hz (J = 4.5 Hz) due to CH_3NH, a broad line at 415 Hz due to CH_3NH, and a 1:2:1 triplet at 477 Hz with a line separation of 2.2 Hz; this same separation was observed in a spectrum made on a Varian HR-100 spectrometer. The infrared spectrum showed the following peaks in microns (assignments are given): 2.93 (m), NH stretching; 3.29 (w), =CH; 5.68 (vs), C=O in carbamate; 5.93 (ms), conjugated C=O; 8.21 (ms), C—O—C; 8.48 (vs) and 9.11 (s) were not assigned.

Phenyl N-Methylcarbamyloxyvinyl Ketone (4).—Into 1 l. of benzene was placed 11.5 g (0.5 g-atom) of finely cut sodium. The benzene was refluxed and 100 ml (78.9 g, 1.72 moles) of ethanol was added dropwise. The mixture was refluxed for 2 hr and cooled to 5–7°. A mixture of ethyl formate (40 g, 0.54 mole) and methyl phenyl ketone (60 g, 0.50 mole) was added dropwise. After 6 hr of stirring at room temperature, the solid was filtered, washed with ether, and air dried to give 61 g (72%) of the yellow sodium salt of phenyl hydroxyvinyl ketone.

The salt was acidified with 1:1 H_2O–HCl (concentrated) and cooled, and the released ketone **3** was dissolved in benzene. Without further purification, this solution was treated with 5 ml of pyridine and 23 g (0.4 mole) of methyl isocyanate. The reaction mixture was allowed to stand overnight, during which time a crystalline solid formed. The solid was filtered and dissolved in hot $CHCl_3$; this solution was filtered and evaporated to 0.33 of its original volume. A light yellow solid precipitated and was filtered and air dried, mp 123–124.5°. More product was obtained from the further evaporation of the filtrate. The crystals appeared to be much more stable than the aliphatic products **2** and **6**.

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.27; H, 5.71; N, 6.79.

The nmr spectrum showed a doublet at 169 Hz (J = 4.5 Hz) due to CH_3NH, an AB quartet (J = 12.3 Hz, ω_A = 406.5 Hz, ω_B = 501.5 Hz) due to the *trans* vinyl proton absorptions, and a complex band from 445 to 484 Hz due to aromatic protons.

The infrared spectrum showed the following peaks (assignments are given): 3.00 (m), NH stretching; 5.62 (s), C=O in carbamate; 6.02 (m), C=O conjugated; 8.41 (s), C—O—C in carbamate; and 10.71 (s) μ, *trans*-CH out-of-plane deformation.

N-Methylcarbamyloxymethylene Acetone (6).—Finely cut sodium (25.8 g, 1.12 g-atoms) was placed in 1 l. of benzene. The benzene was heated to reflux and 53 g (1.15 moles) of ethanol was added dropwise. After 2 hr at reflux, the mixture was cooled to 5–7° and a mixture of ethyl formate (79.5 g, 1.07 moles) and acetone (58 g, 1.00 mole) was added dropwise. Vigorous stirring and addition of some extra benzene were necessary, since the brown mixture became very viscous as the sodium salt of hydroxymethylene acetone formed. After the solution was allowed to stand overnight, excess alcohol was added to remove the last traces of sodium. The solid was filtered, washed with ether, and dried in a vacuum desiccator over P_2O_5. The resulting light tan solid (83 g, 77% crude yield) was stirred with 500 ml of benzene and acidified with 300 ml of 10% H_2SO_4, while the reaction mixture was kept below 20°. The resulting layers were separated.

To the benzene solution of unstable hydroxymethylene acetone (**5**) were added 5 ml of pyridine and 22.8 g (0.4 mole) of cold methyl isocyanate. The reaction was allowed to proceed for 30 min and, because of a progressive browning, the solution was kept at −20° for 2 days. Warming the solution to the melting point of benzene (+6°) showed that crystals were present. They were filtered, yielding a pink powder, mp 75–85° dec. This material was very unstable at room temperature, both as the solid and in solution, but the solid was preserved for 2 weeks at −20° in a vial. No elemental analysis was made. A rapidly obtained nmr spectrum (DMSO-d_6) showed a doublet at 166 Hz (J = 45 Hz) due to the CH_3NH protons, and a pair of doublets (J = 16.6 Hz) due to the vinyl protons at 420 (O=C—CH=) and 442 Hz (=CH—O—C=O). The infrared spectrum was obtained and various bands were given the following assignments: 3.09 (ms), NH in carbamate; 5.64 (s), C=O in carbamate; 5.99 (ms) and 6.24 (m), C=C stretching; 6.10 (s), C=O conjugated; 6.48 (ms), NH deformation; 8.23 (s), C—O—C stretching in carbamate; and 10.55 (ms) μ, *trans* HC=CH. A band at 4.2 μ was later observed and spots developed in the KBr disk, both as a result of $CH_3N{=}C{=}O$ formation within the disk and its partial escape as a gas.

1-(*p*-Nitrophenyl)-3-methylurea (7).—In a 200-ml pressure bottle was placed a solution of 13.8 g (0.10 mole) of *p*-nitroaniline in 35 ml of anhydrous pyridine. Methyl isocyanate (7.6 g, 0.13 mole) was then rapidly added. No reaction occurred at room temperature after several hours. (In one experiment the aniline was recovered quantitatively.) The mixture was therefore heated on a steam bath for 1 hr. The cooling process caused crystals to form. The excess pyridine was decanted into water; the remaining crystals were filtered, washed with 100 ml of hexane, and air dried. The crude weight was 12 g. Another crop of crystals precipitated from the decanted pyridine. These crystals, after being filtered, washed, and dried, weighed 5 g; the total crude yield was 17 g (87%). Recrystallization from 95% ethanol gave yellow needles, mp 226–227° (capillary tube) with sublimation at 300–310° (melting point block) (lit.[26] 245–247°).

Anal. Calcd for $C_8H_9N_3O_3$: C, 49.22; H, 4.65; N, 21.53. Found: C, 49.02; H, 4.38; N, 21.61.

The infrared spectrum showed no unusual bands.

There were nmr signals at 163 (J = 4.5 Hz) due to CH_3NH–, a broadened quartet at 370–390 (J = 4.5 Hz) due to CH_3NH–, and an A_2B_2 pattern centered at 424 Hz. At 161 Hz (J = 4.5 Hz) another doublet appeared which was about $1/40$ as intense as the CH_3NH doublet.

***p*-Nitrophenyl N-Methylcarbamate (8).**—To 13.9 g (0.10 mole) of *p*-nitrophenol in pyridine in a 200-ml pressure bottle (A. H. Thomas, Catalog No. 2282) was added 4.8 g (0.08 mole) of methyl isocyanate; the reaction mixture was heated on a steam bath for 6.5 hr, and then allowed to cool. Yellow crystals formed, but when the reaction mixture was poured into water and filtered, a dark oil formed. This oil gradually crystallized. The crystals were washed thoroughly with water to remove the phenol and the pyridine. Crude yield, after air drying, was 15.8 g (84.5%). Several recrystallizations from methanol gave crystals melting at 151–153° (lit.[10] 160.5–162°).

Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.06; N, 14.29. Found: C, 49.08; H, 4.08; N, 14.02.

Nmr spectra taken over a period of several days showed that in DMSO-d_6 the product changed to other compounds. This reaction is under further investigation.

The infrared spectra of the compound in KBr and CS_2 showed characteristic bands which have been given various assignments.[15]

9-Anthryl N-Methylcarbamate (9).—To 16.3 g (0.084 mole) of anthrone in 50 ml of pyridine was added an excess (8 g, 0.14 mole) of methyl isocyanate. The mixture was heated in a pressure bottle on a steam bath for several hours. The crystals that formed were filtered, washed with water, and air dried to give 20.2 g (96%) of yellow solid, mp 233° dec.

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22. Found: C, 76.07; H, 5.47.

The nmr spectrum showed a doublet at 179 (J = 4.5 Hz), due to CH_3NH, and a complex absorption from 445 to 515 Hz. The infrared spectrum was given the following assignments: 3.03 (m), NH stretching; 5.88 (vs), C=O in carbamate; 6.55 (ms), NH deformation in carbamate; 8.09 (vs) and 8.96 (vs) μ, C—O—C stretching in the carbamate.

1,4-Naphthoquinone O-(N-Methylcarbamyl)monoxime (10).—To a 200-ml pressure bottle (as described in the preparation of **8**) were added 2.3 g (0.013 mole) of recrystallized 1,4-naphthoquinone monoxime (prepared by reacting equimolar quantities of 1,4-naphthoquinone and hydroxylamine hydrochloride in

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(26) R. C. O'Neill and A. J. Basso, U. S. Patent 2,787,574 (1957); *Chem. Abstr.*, **52**, 11364 (1958).

refluxing ethanol) and 3 ml of methyl isocyanate (3.1 g, 0.054 mole). The bottle was sealed, heated for 0.5 hr on a steam bath, cooled for 1 hr, and then opened. The solution had turned a deep red, and a gas evolved. Water was added slowly, causing a further evolution of gas and the precipitation of a yellow solid. The solid was filtered and recrystallized from 50% ethanol to give yellow needles, mp 160° dec.

Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.33; N, 12.17. Found: C, 62.87; H, 5.03; N, 13.08; also C, 63.36; H, 4.60; N, 9.38.

The infrared spectrum showed the following bands, which received the indicated assignments: 2.98 (ms) and 3.03 (sh), NH stretching; 3.43 (w) and 3.51 (sh), CH_3 stretching in NCH_3; 5.83 (s), C=O in carbamate; 6.04 (s), C=O in conjugation; 6.70 (s), C=C; 8.17 (s), C—O—C in carbamate; 10.46 (vs) μ, N—O stretching band in the oxime. The nmr spectrum (DMSO-d_6 solution) showed a doublet at 169.5 (J = 4.5 Hz) due to CH_3NH, an AB pattern (J = 10.6 Hz; ω_A = 404.5 Hz, ω_B = 480.0 Hz) due to protons on the quinone ring, and a complex absorption from 450 to 515 Hz due to the aromatic protons on the other ring.

Methylation of 2-Formylcyclohexanone.—About 63 ml of a solution of CH_2N_2 in ethyl ether (20 mg/ml) was added to 3.0 g (neat) of 2-formylcyclohexanone at 0°. The solution was allowed to warm gradually to 15°. Most of the ether was flash evaporated.

The nmr spectrum showed a 1:2:1 triplet at 423 Hz with a line separation of 2.2 Hz due to $—(CH_2—)C{=}C(O—)H$; it also showed two peaks for aldehydic protons (608 and 520 Hz), the cyclohexane proton peaks, and normal peaks for residual ethyl ether and OCH_3.

Attempted Carbamylation of Acetylacetone.—In a 125-ml conical flask were mixed 2.5 g (0.025 mole) of acetylacetone, 0.5 ml of pyridine, and 7.8 ml (0.027 mole) of 20% methyl isocyanate in ether. The mixture was shaken and allowed to stand at room temperature. After 6 days the nmr spectra of the solution indicated that only a trace of product, if any, was formed.

Registry No.—**2**, 13866-74-5; **4**, 13970-40-6; **6**, 13866-63-2; **7**, 13866-64-3; **8**, 5819-21-6; **9**, 10369-95-6; **10**, 13866-67-6; methyl isocyanate, 624-83-9.

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Conversions of Certain Amides into Nitriles by Means of *n*-Butyllithium[1]

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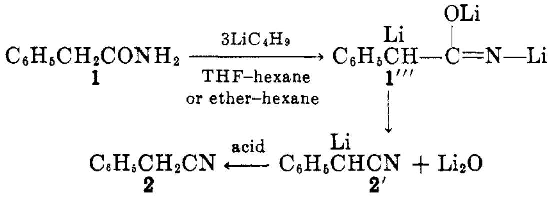
Phenyl- and diphenylacetamides were converted readily into the corresponding nitriles in good yields by means of three mole equivalents of *n*-butyllithium in inert solvents. The mechanism presumably involves β elimination of lithium oxide from an intermediate trilithioamide. However, *n*-heptamide afforded nitrile in ony a fair yield and benzamide in only trace amounts. Phenylacetamide was converted into nitrile in fair yield by lithium aluminum hydride, but potassium amide and lithium amide failed to effect the reaction.

It is well-known that amides can be dehydrated readily to form nitriles by means of acidic reagents[2] or by a combination of an acidic reagent and an amine such as tosyl chloride and pyridine.[3]

Although certain amides have been converted to nitriles with basic reagents, special procedures and/or relatively drastic conditions appear to have been employed. Some examples have involved benzamide with lithium aluminum hydride,[4,5] heptamide and benzamide with sodium hydroxide or potassium hydroxide (pyrolysis of sodio or potassio salt),[6] 2-methoxy-3-naphthamide with methylmagnesium iodide,[7] trimethylacetamide with *t*-butylmagnesium chloride in refluxing ether (16 hr),[8] and some hindered amides such as mesitamide with sodium hydroxide in refluxing ethylene glycol.[9]

It has now been found that phenyl- and diphenylacetamides can be converted readily to the corresponding nitriles by means of *n*-butyllithium which functions as a very strong base. Thus, phenylacetamide (**1**) reacted with 3 mol equiv of this reagent in tetrahydrofuran (THF)–hexane or ether–hexane to give phenylacetonitrile in good yield (45–77%). Presumably, **1** was trilithiated to form trilithioamide **1‴**, which decomposed to produce lithiophenylacetonitrile (**2′**) and lithium oxide (Scheme I).[10]

SCHEME I



$$C_6H_5CH_2CONH_2 \ (\mathbf{1}) \xrightarrow[\text{THF–hexane or ether–hexane}]{3LiC_4H_9} C_6H_5\overset{Li}{C}H—\overset{OLi}{C}{=}N—Li \ (\mathbf{1'''}) \longrightarrow C_6H_5\overset{Li}{C}HCN \ (\mathbf{2'}) + Li_2O \xrightarrow{\text{acid}} C_6H_5CH_2CN \ (\mathbf{2})$$

Evidence for formation of intermediate trilithioamide **1‴** was obtained by preparation and benzoylation of trilithioamide **1‴** at −80° to form the N-benzoyl derivative **3** and the dibenzoyl derivative **4** in yields of 30 and 14%, respectively (Scheme II).[10]

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[1] Supported by the Army Research Office (Durham) and by the National Science Foundation. A preliminary communication has appeared: E. M. Kaiser, R. L. Vaulx and C. R. Hauser, *Tetrahedron Letters*, **40**, 4833 (1966).

[2] D. T. Mowry, *Chem. Rev.*, **42**, 257 (1948).

[3] C. R. Stevens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **77**, 1701 (1955).

[4] M. S. Newman and T. Fukunaga, *ibid.* **82**, 693 (1960).

[5] (a) W. G. Brown, *Org. Reactions*, **6**, 484 (1955). The special conditions required for this reaction, which were not reported in detail in the original paper,[4] involved addition of 19 mmoles of a standardized 0.26 *M* solution of lithium aluminum hydride in THF to a solution of 5.0 mmoles of benzamide in THF at 30–35° during 90 min, gradual heating to reflux during 30 min, and final refluxing for 4 hr. (b) However, only spectroscopic amounts of the nitrile were obtained when the lithium aluminum hydride solution was added at 0–5°, and the reaction mixture was stirred at this temperature for several hours and then refluxed for 4 hr (Private communication from Dr. T. Fukunaga).

[6] See F. W. Bergestrom and W. C. Fernelius, *Chem. Rev.*, **12**, 133 (1933).

[7] K. Fries and K. Schimmelschmidt, *Ber.*, **B58**, 2835 (1925).

[8] F C. Whitmore, C. I. Noll, and V. C. Meunier, *J. Am. Chem. Soc.*, **61**, 683 (1939).

[9] L. Tsai, T. Miwa and M. S. Newman, *ibid.*, **79**, 2530 (1957).

[10] For convenience, mono- di-, and trilithio salts are designated by prime, double prime, and triple prime, respectively.