A number of physiologically important catecholamines have been successfully analysed by gas chromatography.[7] Beckett, *et al.*[8] reported that catecholamine-like derivatives, ephedrine and related compounds, were resolved as their conversion to N–TFA-L-prolyl derivatives. Examination of the present results shows that the peaks of epinephrine, norepinephrine, metanephrine and normetanephrine, except for dopamine, are not observed. This may be considered that N–TFA-L-prolyl-catecholamines can not be trimethylsilylated because of steric interference, considering from the result that the peaks of trimethylsilylated N–TFA-L-prolyl dopamine are observed.

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UDC 547.233.04 : 547.239.1.04

Reaction of N-(Alkoxymethyl)dialkylamines and N,N'-Methylenebisdialkylamines with Isocyanides

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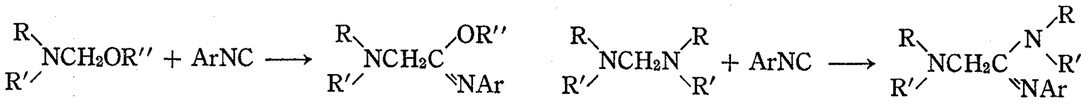
(Received July 15, 1974)

It has been found that N-(alkoxymethyl)dialkylamines and N,N'-methylenebisdialkylamines react with isocyanides, effecting 1,1-addition by suffering split of one of the methylene carbon-heteroatom bonds. The reactions furnish the corresponding imidates and amidines as the products which are not otherwise obtainable.

The representative pattern of the isocyanide reactions has been known as the 1,1-addition to the isocyanide carbon, where the presence of the copper catalyst is generally preferable. On inspection of these papers this addition reaction is limited to that of protic materials such as amine,[2] alcohol,[3] thioalcohol,[4] phosphine[5] and silane.[6] We have now found that, in the absence of the copper catalyst, N-(alkoxymethyl)dialkylamines and N,N'-methylenebisdialkylamines react with isocyanide resulting in the 1,1-adduct formation by suffering split of one of the methylene carbon-heteroatom bonds. A number of N-(alkoxymethyl)dialkylamines and N,N'-methylenebisdialkylamines were allowed to react with phenylisocyanides in 1:1 molar proportion by refluxing their toluene solution. The corresponding imidates and amidines were obtained as the 1,1-adduct product, which are shown in Table I with their yields. These



$$\genfrac{}{}{0pt}{}{R\diagdown}{R'\diagup}NCH_2OR'' + ArNC \longrightarrow \genfrac{}{}{0pt}{}{R\diagdown}{R'\diagup}NCH_2C\genfrac{}{}{0pt}{}{\diagup OR''}{\diagdown\!\!\diagdown NAr} \qquad \genfrac{}{}{0pt}{}{R\diagdown}{R'\diagup}NCH_2N\genfrac{}{}{0pt}{}{\diagup R}{\diagdown R'} + ArNC \longrightarrow \genfrac{}{}{0pt}{}{R\diagdown}{R'\diagup}NCH_2C\genfrac{}{}{0pt}{}{\diagup N\genfrac{}{}{0pt}{}{\diagup R}{\diagdown R'}}{\diagdown\!\!\diagdown NAr}$$

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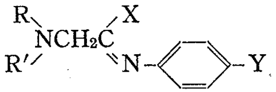
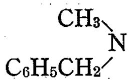
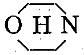
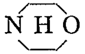
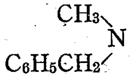
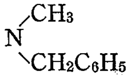
TABLE I



$R \backslash N / R'$	X	Y	Yield (%)	bp [°C(mmHg)]	n_D (°C)	IR $\nu_{C=N}^{liquid}$ (cm⁻¹)	UV λ_{max}^{EtOH} mμ (log ε)	NMR $>NCH_2C<$ τ in $CDCl_3$	Formula	Analysis (%) Found (Calcd.) C	H	N
	OC_2H_5	H	38	142—144 (5.0)	1.5282 (20)	1669	—	6.92	$C_{15}H_{22}ON_2$	72.77 (73.13)	9.01 (9.01)	11.84 (11.37)
	OC_3H_7	H	33	123—124 (0.4)	1.5245 (20)	1668	—	6.98	$C_{16}H_{24}ON_2$	73.83 (73.80)	9.27 (9.29)	10.81 (10.76)
	OC_4H_9	H	23	130—131 (0.5)	1.5286 (17)	1666	—	6.93	$C_{17}H_{26}ON_2$	74.38 (74.41)	9.33 (9.55)	10.43 (10.21)
	OC_4H_9	OCH_3	34	148 (0.12)	1.5298 (25)	1664	—	6.96	$C_{18}H_{28}O_2N_2$	71.29 (71.01)	9.26 (9.27)	9.18 (9.20)
	OC_4H_9	CH_3	26	135—136 (0.03)	1.5230 (22)	1670	—	7.02	$C_{18}H_{28}ON_2$	74.66 (74.95)	9.79 (9.79)	9.87 (9.71)
	OC_4H_9	Cl	23	158—159 (0.3)	1.5302 (25)	1666	—	7.01	$C_{17}H_{25}ON_2Cl$	66.14 (66.10)	7.84 (8.15)	9.39 (9.07)
	OC_4H_9	H	11	144—145 (1.0)	1.5180 (15)	1668	—	6.95	$C_{16}H_{24}O_2N_2$	70.04 (69.53)	8.59 (8.75)	10.50 (10.14)
 $(CH_3)(C_6H_5CH_2)N$	OC_4H_9	H	20	134—136 (0.1)	1.5450 (15)	1668	—	6.85	$C_{20}H_{26}ON_2$	77.30 (77.38)	8.66 (8.44)	8.68 (9.03)
		H	41	142—143 (0.1)	1.5536 (18)	1628[a]	247.5 (4.20)	7.00	$C_{18}H_{27}N_3$	75.57 (75.74)	8.96 (9.54)	14.53 (14.72)
		H	27	mp 137—139 prisms (benzene)		1614[a]	242 (4.24)	6.91	$C_{16}H_{23}O_2N_3$	66.72 (66.41)	7.87 (8.01)	14.19 (14.52)
 $(CH_3)(C_6H_5CH_2)N$	 $N(CH_3)(CH_2C_6H_5)$	H	25	190—192 (0.04)	1.6090 (18)	1630[a]	243 (4.11)	6.78	$C_{24}H_{27}N_3$	80.36 (80.63)	7.25 (7.61)	11.84 (11.76)

a) measured in $CHCl_3$ solution

products were identified by noting well correspondence of their infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra with their structures as can be seen in Table I. The following chemical behaviors as for the representative products are also agreeable with their structures. Butyl N-phenyl-4-morpholineacetimidate reacted with morpholine to give 4-(N-phenyl-4-morpholineacetimidoyl)morpholine. Butyl N-phenyl-1-piperidineacetimidate was hydrolyzed in refluxing hydrochloric acid to give 1-piperidineacetic acid and aniline. All the products listed in Table I have not been described previously. Thus, the reactions provide a new way for synthesis of the imidate and amidine derivatives of 2-(dialkylamino)acetic acid which are not otherwise easily obtainable.

In the above 1,1-addition reaction the reaction site, the methylene carbon-oxygen bond of N-(alkoxymethyl)dialkylamine, is agreeable with that of the nucleophilic substitution reactions known as to this type of the compounds.[7] On the analogy, N-(dialkylaminomethyl)-amide is expected to react at the site of the methylene carbon-amide nitrogen bond. However, an attempt to carry out the reaction of N-(piperidinomethyl)phthalimide with phenylisocyanide failed, presumably owing to its low reactivity.

Experimental[8]

Reaction of N-(Alkoxymethyl)dialkylamines and N,N′-Methylenebisdialkylamines with Isocyanides——The products shown in Table I were obtained from the reactions between the corresponding isocyanides and methylene compounds by the following general procedure. For the reaction the starting materials were used after freshly distilled. A solution of 0.1 mole of N-(alkoxymethyl)dialkylamine or N,N′-methylenebisdialkylamine and 0.1 mole of isocyanide in 50 ml of toluene was refluxed for 10 hr with stirring. The reaction solution was concentrated under reduced pressure to remove toluene and the unreacted materials, and the residual oil was submitted to distillation under high reduced pressure to give the corresponding imidate or amidine product. Yields of the products and their analytical and spectral data are recorded in Table I.

Reaction of Butyl N-Phenyl-4-morpholineacetimidate with Morpholine——A solution of 2.7 g of butyl N-phenyl-4-morpholineacetimidate and 0.9 g of morpholine in 5 ml of toluene was refluxed for 5 hr with stirring. The reaction solution was concentrated to dryness under reduced pressure. Recrystallization of the resulting crystalline residue from benzene gave prisms, mp 137—139°, which were identified as 4-(N-phenyl-4-morpholineacetimidoyl)morpholine by comparison of their IR and UV spectra with an authentic sample and by mixed melting point test. Yield, 0.9 g (30%).

Hydrolysis of Butyl N-Phenyl-1-piperidineacetimidate with Hydrochloric Acid——A solution of 5.5 g of butyl N-phenyl-1-piperidineacetimidate in 55 ml of 10% aq. HCl was refluxed for 2 hr with stirring. The solution was concentrated under reduced pressure and the resulting residue was extracted several times with hot acetone. Concentration of the acetone solution gave aniline hydrochloride, mp 190—193°, weighing 1.9 g (74%). The acetone insoluble residue was recrystallized from EtOH to give needles, which were identified as 1-piperidineacetic acid hydrochloride, mp 210—212° (lit.[9] mp 215—216°), weighing 2.7 g (75%). IR $\nu_{\mathrm{CO}}^{\mathrm{KBr}}$ 1754 cm^{-1}. *Anal.* Calcd. for $C_7H_{14}O_2NCl$: C, 46.78; H, 7.85; N, 7.79. Found: C, 46.96; H, 7.74; N, 7.75.

Acknowledgement We thank Mr. K. Narita and the other members of the Analysis Center of this college for microanalyses and NMR measurements.

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[8] All melting and boiling points are uncorrected. Spectra herein reported were determined with a Hitachi EPI-G2 IR spectrophotometer, a Hitachi EPS-3T UV spectrophotometer, and a JEOL JNM-C-60H NMR spectrometer using tetramethylsilane as an internal standard.

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