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Reactions with 1-Benzotriazolecarboxylic Acid Chloride. I. Synthesis of the 2,6-Bis(hydroxymethyl)pyridinedicarbamates

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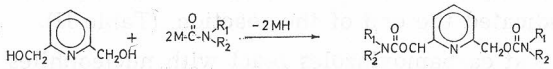
Some 2,6-bis(hydroxymethyl)pyridinedicarbamates VII were synthesized by reaction of pyridinedimethanole (I) with carbamoylazoles II—VI (azole=imidazole, benzimidazole, pyrazole, 1,2,4-triazole, benzotriazole). It is confirmed that this reaction proceed via an intermolecular elimination-addition acyl transfer mechanism including in the first step the formation of an isocyanate. Carbamoylbenzotriazoles VIa-i were prepared by aminolysis of 1-benzotriazolecarboxylic acid chloride (VIII) obtained from benzotriazole and phosgene.

It is known that pharmacologically active pyridinedimethanol carbamates VII, particulary 2,6-bis(hydroxymethyl)pyridine-di(*N*-methylcarbamate) (VIIa) »Pyribamate«, used in therapy of atherosclerosis, can be prepared directly in the reaction of pyridinedimethanol I either with isocyanates, carbamoylchlorides, S-methylcarbaminic acids[1], *O*-phenyl-methylcarbamate[2], dialkylureas[3], or with phosgene[1] and phenylchlorocarbonic acid[4], followed by aminolysis.

We wish to described the application of carbamoylazoles II—VI as reagents in the synthesis of the titled pyridinedimethanol carbamates VII according to the reaction Scheme 1.

SCHEME 1.

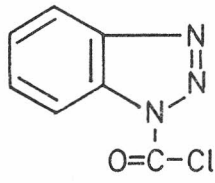


I II-VI VII

M=azole= imidazole (II), benzimidazole (III), pyrazole (IV), 1,2,4-triazole (V), benzotriazole (VI)

According to literature data, monosubstituted carbamoylazoles can be prepared from azoles and isocyanate[5–8], while disubstituted carbamoylazoles are obtained either in the reaction of carbonydiazoles with secondary amines[7] or by addition of carbamoylchlorides on azoles[7,9].

In searching for an efficient and simple synthesis which would be suitable to furnish both mono and disubstituted carbamoylazoles, we have studied a reaction of imidazole, benzimidazole and benzotriazole with phosgene in order to prepare corresponding 1-azolecarboxylic acid chlorides as key-intermediates.



VIII

Staab[10] has reported that azoles and phosgene react at a molar ratio 4 : 1 to yield quantitatively carbonyldiazoles. In our experiments, a large excess of phosgene was used. The reaction was carried out either at 60 °C by bubbling gaseous phosgene into the suspension of azole in toluene, or at 30 °C after adding the ether solution of azole to a 20% solution of phosgene in toluene. With imidazole and benzimidazole a mixture of corresponding hydrochlorides, carbonyldiazoles and the expected acid chlorides was obtained. On the other hand, the reaction of benzotriazole with phosgene under the same conditions afforded quantitatively a crystaline low-melting 1-benzotriazolecarboxylic acid chloride (VIII), as the only product. The IR spectrum of VIII with a carbonyl C=O at 1770 cm^{-1} and N=N double bond valent vibrations at 1600 cm^{-1} characteristic for 1-substituted benzotriazoles[11], fit a proposed structure.

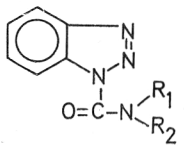
Chloride VIII reacts with various amines and hydrazines to give substituted carbamoylbenzotriazoles VI in high yields. The reaction is simple and rapid and was performed in benzene solution at ambient temperature with the addition of triethylamine or excess of amine as a hydrogen chloride scavenger. Even the crude chloride VIII can be used in this reaction step with the same effect. Some physical and chemical constants of compounds VIa-i are listed in Table I.

Carbamoylbenzotriazoles VIa, VId, VIe, as well as 1-*N*-methylcarbamoylimidazole (II), 1-*N*-methylcarbamoylbenzimidazole (III), 1-*N*-methylcarbamoylpyrazole (IV) and 1-*N*-methylcarbamoyl-1,2,4-triazole (V) were employed in the synthesis of pyridinedimethanol carbamates VII according to Scheme 1. The reactions were carried out by heating the reactants above melting temperature. The disappearance of carbamoylazoles, as checked by thin-layer chromatography (TLC), indicated the end of the reaction. (Table II).

It is known that carbamoylazoles react with nucleophiles by means of two mechanisms depending on the nature of the heterocyclic ring and substitution on carbamoyl nitrogen. Thus, aminolysis and hydrolysis[12] of monosubstituted carbamoylazoles proceed via an intermolecular elimination-addition acyl transfer mechanism including, in the first step the formation of an isocyanate, while disubstituted carbamoylazoles react by direct nucleophilic attack on the carbonyl[7]. In our opinion, the alcoholysis of primary carbamoylazoles also follows the first mechanism. The results indicate (Table II) a high reactivity of II and III and a low reactivity of IV, V, VIa, VId and VIe, which react with pyridinemethanol I only at elevated temperature (above 100 °C) and prolonged reaction time. The high reactivity of II and III can be explained by their easy dissociation into azole and isocyanate[7]. Carbamoylazoles of weakly basic heterocycles, such as pyrazole, 1,2,4-triazole and benzotriazole, do not dissociate at temperatures

TABLE I

Carbamoylbenzotriazoles



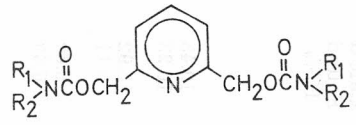
VI a-i

No	R_1	R_2	Reaction time/h	Yield %	M. p./°C	Cryst. from	Formula	Anal. C/%	Calc'd Found H/%	N/%
VIa	CH_3	H	1	75.4	117[a]					
VIb	n-C_4H_9	H	3	78.5	63[b]					
VIc	n-$C_{18}H_{37}$	H	2	66.0	70—1	EtOH	$C_{25}H_{43}N_4O$	72.24 72.24	10.43 10.23	13.48 13.60
VId	$CH(CH_3)_2$	H	1	94.8	73—4	Light petroleum	$C_{10}H_{12}N_4O$	58.81 59.02	5.92 6.11	27.44 27.28
VIe	cyclohexyl	H	1	70.0	73—4	Light petroleum	$C_{13}H_{16}N_4O$	63.91 64.07	6.60 6.69	22.93 22.89
VIf	C_6H_5	H	1	82.4	140[c]					
VIg	C_2H_5	C_2H_5	2	87.9[d]	165[e]		$C_{10}H_{14}N_4O$	58.23 57.99	6.84 6.68	27.17 27.05
VIh	NH—NH—C_6H_5	H	3	40.0	159	Benzene	$C_{13}H_{11}N_5O$	61.65 61.81	4.38 4.10	27.65 27.52
VIi	NH—1-azepinyl	H	2	88.0	98—101	Light petroleum	$C_{13}H_{17}N_5O$	60.21 60.09	6.61 6.56	27.00 27.25

[a] Lit[8] 116—117 °C; [b] Lit[7] 42 °C; [c] Lit[10b] 142 °C; [d] Extracted with light petroleum; [e] B. p. 0.6 mmHg

TABLE II

Synthesis of 2,6-Bis(hydraxymethyl)pyridinedicarbamates VII a—c



VII a-c

No.	Carbamoyl-azole	$R_1=$; $R_2=H$	reaction temp/°C	reaction time/h	method of isolation	yield/%	m. p./°C
VIIa	II	CH_3	95	2.0	A	96[a]	128—130[b]
VIIa	II	CH_3	95	0.5	A	95	129—130[b]
VIIa	III	CH_3	130	0.5	C	84	129[b]
VIIa	IV	CH_3	145	14.0	B	72	129—130[b]
VIIa	V	CH_3	145	10.0	B	64	132[b]
VIIa	VIa	CH_3	145	14.0	D	55	129—132[b]
VIIa	VIa	CH_3	145	4.0	D	60[c]	128—131
VIIb	VId	$CH(CH_3)_2$	145	24.0	D	36	132[d]
VIIb	VId	$CH(CH_3)_2$	145	4.0	D	45[c]	130[d]
VIIc	VIe	cyclohexyl	145	14.0	A	73	160[e]

[a] pyridine as a solvent; [b] Lit[1] 134 °C; [c] with addition of 0.1 mol of imidazole per mol of carbamoylbenzotriazole; [d] Lit[1] 131 °C; [e] Lit[1] 157 °C.

below 100 °C, whereas dissociation occurs at higher temperatures. This is established by heating VIa to 160 °C. The methylisocyanate liberated was absorbed in a suspension of imidazole in pyridine, and 1-*N*-methylcarbamoylimidazole (II) thus formed, was isolated. 1-*N*,*N*-Diethylcarbamoylbenzotriazole (VIg) which cannot produce the isocyanate, does not react with I at 150 °C. This fact confirms the proposed mechanism of alcoholysis via the dissociation into the azole and isocyanate. Zalikin et al.[13] have reported an activating influence of imidazole on the reaction of *n*-butanol with phenylisocyanate. We have obtained the same effect in the reaction of VIa and VId with I. Addition of catalytic amounts of imidazole shortened the reaction time significantly.

EXPERIMENTAL

IR spectra were determined by a Perkin-Elmer 257 spectrophotometer, and ^{1}H-NMR spectra were recorded by a Varian T-60 spectrometer in $CDCl_3$ using TMS as an internal standard. TLC was carried out on Merck Silica gel 60 F-254 plates (chloroform-methanal 10 : 1) and the spots were visualized under UV (254 nm) and by iodine vapors. Mps. and bps. are uncorrected.

1-N-*Methylcarbamoylimidazole* (II)

A mixture of imidazole (2.7 g, 40 mmol), benzene (36 ml) and methylisocyanate (3.6 ml, 60 mmol) was stirred without cooling for 1 h. Compound II was collected by filtration; 4.7 g (94%), m. p. 118—119 °C, after recrystallization from toluene: m. p. 119 °C.

Anal. $C_5H_7N_3O$ (125.13) calc'd.: C 48.00; H 5.64; N 33.58%
found: C 47.89; H 5.66; N 33.43%

IR spectrum: ν_{max} (KBr): 3350—3000 (NH assoc.), 1710 (C=O), 1550, 1290, 910, 800 and 720 cm^{-1}.
^{1}H-NMR: δ 2.9 (d, 3H, CH_3), 6.95 (s, 1H), 7.6 (m, 1H), 8.2 (s, 1H), 8.5 (d, 1H, NH).

1-N-Methylcarbamoylbenzimidazole (III)

Compound III was prepared according to Staab[7] from benzimidazole and methylisocyanate in 93% yield, m. p. 102 °C (ref[14] 94—98 °C).

1-N-Methylcarbamoylpyrazole (IV)

A mixture of pyrazole (2.7 g, 40 mmol), benzene (36 ml) and methylisocyanate (3.6 ml, 60 mmol) was stirred at room temperature for 1 h. Evaporation of the solvent in vacuo afforded IV (4.5 g, 90%), m. p. 44—46 °C; after recrystallization from light petroleum: m. p. 45—47 °C.

Anal. $C_5H_7N_3O$ (125.13) calc'd.: C 48.00; H 5.64; N 33.58%
found: C 48.03; H 5.51; N 33.60%.

IR spectrum: ν_{max} (nujol) 3400 (NH), 1760 (C=O) cm^{-1}.

1-N-Methylcarbamoyl-1,2,4-triazole (V)

Compound V was prepared as described for II in 98% yield; m. p. 147—149 °C (ref[15] 126—141 °C).

1-Benzotriazolecarboxylic Acid Chloride (VIII)

A. Phosgene was bubbled into a suspension of benzotriazole (1.19 g, 10 mmol) in toluene (30 ml) at 60 °C until a clear solution was obtained. Evaporation of the solvent at reduced pressure gave 1.79 g (98.8%) of crude VIII, m. p. 52—54 °C. Sample for analysis was crystallized from light petroleum; m. p. 54—55 °C.

Anal. $C_7H_4ClN_3O$ (181.58) calc'd.: Cl 19.53%
found: Cl 19.75%.

IR spectrum: ν_{max} (nujol) 1770 (C=O), 1600 (N=N) cm^{-1}.

B. A solution of benzotriazole (1.19 g, 10 mmol) in diethylether (55 ml) was added dropwise during 20 min to a 20% solution of phosgene in toluene (20 ml). The reaction mixture was stirred at room temperature, until a clear solution was obtained (approx. 2 h). Removal of the solvent at reduced pressure gave 1.77 g (96.8%) of VIII, m. p. 52 °C.

General Procedure for Preparation of Carbamoylbenzotriazoles VI*a-i*

To a solution of VIII (10 mmol) in benzene (15 ml) and triethylamine (10 mmol), the amine (10 mmol) was added. The mixture was stirred at room temperature for 30—60 min, and then evaporated in vacuo to drynes. Water was added to the residue and VI was extracted with chloroform (Table I). Compounds VIa-i exhibited characteristic IR bands (KBr) at 3400—3300 (NH), 1750—1730 (C=O) and 1600 (N=N) cm^{-1}. ^{1}H-NMR showed characteristic signals at 7.16 (NH), 7.4—7.5 and 8.1—8.2 ppm (aromatic protons of benzotriazole) and of corresponding protons for R_1 and R_2.

Thermic Dissociation of 1-N-Methylcarbamoylbenzotriazole (VI*a*)

A sample of VIa (2 g) was heated at 160 °C in a stream of nitrogen. Liberated methylisocyanate was introduced into a suspension of imidazole (1 g) in pyridine (5 ml). After 5 h, pyridine was distilled off and the solid residue crystalized from toluene to give II (0.5 g), m. p. 116—118 °C. The IR spectrum was identical with that of II, obtained from imidazole and authentic methylisocyanate.

General Procedure for Preparation of 2,6-Bis(hydroxymethyl)pyridinedicarbamates VII*a-c*

2,6-Bis(hydroxymethyl)pyridine[1] (I) (10 mmol) and carbamoylazole (20 mmol) were heated under conditions (temperature, time, method of isolation) given in Table II. Four procedures were applied to isolate the products:

A. Water (20 ml) was added to the reaction mixture, and concd. HCl to pH 5, and separated VII collected by filtration.

B. Water (20 ml) was added to the reaction mixture, and the separated VII collected by filtration.

C. Water (20 ml) was added to the reaction mixture, the insoluble azole filtered off, and the filtrate acidified with concd. HCl to pH 5. Carbamate VII separated on standing.

D. Water (10 ml) and a few drops of concd. HCl were added to the reaction mixture. The resulted clear solution was extracted with chloroform and the extract discarded. The aqueous solution was neutralized, and carbamate VII separated on standing.

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SAŽETAK

Reakcije klorida 1-benzotriazolkarboksilne kiseline. I. Sinteza 2,6-bis(hidroksimetil)-piridinkarbamata

I. Butula, M. V. Proštenik i V. Vela

2,6-Bis(hidroksimetil)piridindikarbamati VII sintetizirani su reakcijom piridindimetanola I s karbamoilazolima II—VI (azol= imidazol, benzimidazol, pirazol, 1,2,4-triazol, benzotriazol). Reakcija teče mehanizmom intermolekulskog eliminacijsko-adicijskog premještanja acila i u prvom stupnju uključuje nastajanje izocijanata. Karbamoilbenzotriazoli VIa-i pripravljeni su aminolizom klorida 1-benzotriazolkarboksilne kiseline (VIII) dobivenog iz benzotriazola i fosgena.

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