Acetylene Compounds of Potential Pharmacological Value

II. 4-Amino-2-butynyl Esters of Phenylcarbamic Acids

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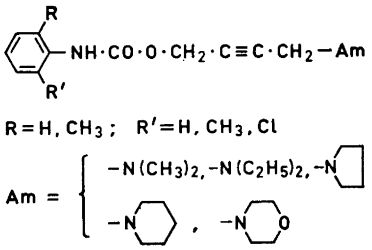
In continuation of our work on compounds of pharmacological interest derived from acetylene we have prepared a number of 4-tertiary-amino-2-butynyl esters of some substituted phenylcarbamic acids.



These new compounds, which were synthesised by reacting the substituted phenylisocyanate with the appropriate N-substituted 4-aminobutynol, are listed in Table 1.

In view of the pronounced local anesthetic effect exhibited by aminoalkyl esters of phenylcarbamic acids [1,2], the new compounds were tested for local anesthetic action on rabbit cornea, using lidocaine as the standard for comparison. All the compounds containing dimethylamine and morpholine as the amino component had low activities (0.1—0.7 times that of lidocaine), whereas those containing diethylamine pyrrolidine, and piperidine as the amino component exhibited considerable activity. The activity of these compounds was further enhanced when the phenyl group was substituted in the 2- and 6 positions. Thus, compounds 6, 7, 10, 11, 14, and 15 (see Table 1) showed activities of 1.2—3.3 times that of lidocaine. However, their high toxicity (LD 50 = 0.09—0.16 g/kg on subcutaneous injection in mice) precludes their use as local anesthetics.

Experimental. The 4-amino-2-butyn-1-ols used as starting materials were prepared as described in the previous paper in this series [3]. 2,6-Dimethylphenylisocyanate was prepared from the corresponding ethyl carbamate according to Dahlbom and Österberg [1].

2-Chloro-6-methylphenylisocyanate. Ethyl 2-chloro-6-methylphenylcarbamate [2] (107 g, 0.5 mole) was intimately mixed with phosphorus pentoxide (142 g, 1 mole) and the mixture distilled *in vacuo* affording a colourless oil (60 g, 72 %), b.p. 84—85°/10 mm; n_D^{23} 1.5548. (Found: C 57.4; H 3.80; N 8.27. Calc. for C_8H_6ClNO: C 57.3; H 3.61; N 8.36).

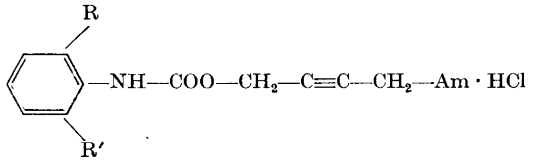
4-Amino-2-butynyl esters of the phenylcarbamic acids. The appropriate phenylisocyanate (0.05 mole) was dissolved together with the 4-amino-2-butyn-1-ol (0.05 mole) in benzene (25 ml), and the solution refluxed for 3 h. After cooling and diluting with ether (50 ml) the solution was treated with one equivalent of ethereal hydrogen chloride, whereupon the hydrochloride of the basic ester separated out. This was filtered off, recrystallised from an ethanol-ether mixture and dried at 50° and 0.05 mm Hg before analysis.

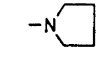
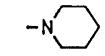
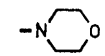
The physical constants and analytical data of the compounds prepared are collected in Table 1, the yields referring to the pure recrystallised products.

1. Dahlbom, R. and Österberg, L. E. *Acta Chem. Scand.* **9** (1955) 1553.
2. Dahlbom, R. and Misiorny, A. *Acta Chem. Scand.* **11** (1957) 1350.
3. Dahlbom, R. and Mollberg, R. *Acta Chem. Scand.* **17** (1963) 916.

Received December 19, 1961.

Table 1.



No.	R	R′	Am	Yield %	M.p. °C	Formula	Calculated %			Found %		
							C	H	N	C	H	N
1	H	H	$-N(CH_3)_2$	50	160.5—161.5	$C_{13}H_{16}N_2O_2 \cdot HCl$	58.1	6.38	10.4	58.0	6.35	10.2
2	CH_3	CH_3	$-N(CH_3)_2$	72	182.5—183.5	$C_{15}H_{20}N_2O_2 \cdot HCl$	60.7	7.13	9.44	60.6	7.06	9.26
3	CH_3	Cl	$-N(CH_3)_2$	86	171.5—172.5 (decomp.)	$C_{14}H_{17}ClN_2O_2 \cdot HCl$	53.0	5.72	8.89	52.8	5.79	8.46
4	H	H	$-N(C_2H_5)_2$	54	129.5—130.5	$C_{15}H_{20}N_2O_2 \cdot HCl$	60.7	7.13	9.44	60.7	7.13	9.45
5	CH_3	H	$-N(C_2H_5)_2$	82	129.5—131	$C_{16}H_{22}N_2O_2 \cdot HCl$	61.9	7.46	9.01	62.2	7.42	9.23
6	CH_3	CH_3	$-N(C_2H_5)_2$	61	175.5—176.5	$C_{17}H_{24}N_2O_2 \cdot HCl$	62.8	7.76	8.62	63.0	7.88	8.41
7	CH_3	Cl	$-N(C_2H_5)_2$	86	168—170 (decomp.)	$C_{16}H_{21}ClN_2O_2 \cdot HCl$	55.7	6.42	8.11	55.6	6.54	7.62
8	H	H		68	148.5—149.5	$C_{15}H_{18}N_2O_2 \cdot HCl$	61.1	6.51	9.50	60.9	6.56	9.26
9	CH_3	H		79	147.5—148 (decomp.)	$C_{16}H_{20}N_2O_2 \cdot HCl$	62.2	6.85	9.07	62.0	6.85	9.12
10	CH_3	CH_3		62	194—194.5 (decomp.)	$C_{17}H_{22}N_2O_2 \cdot HCl$	63.2	7.18	8.68	63.0	7.20	8.45
11	CH_3	Cl		77	184.5—185 (decomp.)	$C_{16}H_{19}ClN_2O_2 \cdot HCl$	56.0	5.87	8.16	56.1	5.96	7.96
12	H	H		65	174.5—175.5	$C_{16}H_{20}N_2O_2 \cdot HCl$	62.2	6.85	9.07	62.2	6.85	8.90
13	CH_3	H		57	177—178 (decomp.)	$C_{17}H_{22}N_2O_2 \cdot HCl$	63.2	7.18	8.68	63.0	7.21	8.71
14	CH_3	CH_3		80	192.5—193 (decomp.)	$C_{18}H_{24}N_2O_2 \cdot HCl$	64.2	7.48	8.32	64.4	7.66	8.24
15	CH_3	Cl		77	177—178 (decomp.)	$C_{17}H_{21}ClN_2O_2 \cdot HCl$	57.1	6.21	7.84	56.8	6.22	7.30
16	H	H		78	152.5—153	$C_{15}H_{18}N_2O_3 \cdot HCl$	58.0	6.16	9.01	58.0	6.29	9.00
17	CH_3	H		84	173.5—174.5 (decomp.)	$C_{16}H_{20}N_2O_3 \cdot HCl$	59.2	6.52	8.63	59.4	6.79	8.61
18	CH_3	CH_3		73	225—226 (decomp.)	$C_{17}H_{22}N_2O_3 \cdot HCl$	60.3	6.84	8.27	60.2	6.82	8.18
19	CH_3	Cl		75	212—213 (decomp.)	$C_{16}H_{19}ClN_2O_3 \cdot HCl$	53.5	5.61	7.80	53.5	5.82	7.87