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Acetylene Compounds of Potential Pharmacological Value

I. 4-Amino-2-butynyl Esters of Diphenylacetic Acid, 1-Phenylcyclopentane-1-carboxylic Acid and Phenothiazine-10-carboxylic Acid

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A number of 4-amino-2-butynyl esters of diphenylacetic acid, 1-phenylcyclopentane-1-carboxylic acid and phenothiazine-10-carboxylic acid have been prepared for pharmacological tests on anticholinergic activity and ability to inhibit tremors induced by 1,4-dipyrrolidino-2-butyne (Tremorine).

The introduction of large substituents into the acyl groups of the parasymphatomimetic stimulant agents acetylcholine (I) and carbaminoylcholine (II) often gives rise to compounds having an antagonistic *i.e.* parasymphatolytic effect.

$$R{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{N}(CH_3)_3Cl^-$$

I. R = CH_3

II. R = NH_2

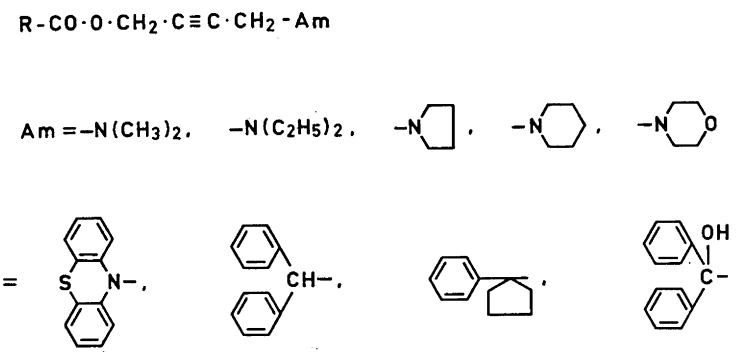
The parasymphatolytic effect can often be enhanced by the exchange of higher alkyl groups for the methyl groups in the trimethylammonium group or by replacement of the quaternary head by a tertiary amino group. In fact, most synthetic parasymphatolytic drugs in clinical use are esters of β-diethylaminoethanol or quaternary salts of these esters.

It has been shown that 4-acetoxy-2-butynyltrimethylammonium iodide

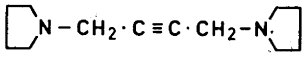
$$CH_3{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}\overset{+}{N}(CH_3)_3I^-$$

has an extremely strong parasymphatomimetic activity [1]. We found it of interest to ascertain if the introduction of large substituents in the acyl group of this compound also would afford compounds with parasymphatolytic pro-

perties in analogy with acetylcholine and carbaminoylcholine. We therefore prepared a number of compounds of the general formula



Acetylene derivatives of this type may be of interest also from another point of view. Some years ago Everett showed that an acetylene compound, 1,4-dipyrrolidino-2-butyne (Tremorine), was able to induce tremor and spasticity in several species of small animals [2]. These effects were antagonised by drugs useful in Parkinson's disease, and Tremorine has therefore found extensive use as a pharmacological tool for the screening of compounds of possible value in the treatment of Parkinson's disease.



Tremorine

As the β-diethylaminoethyl esters of phenothiazine-10-carboxylic acid and 1-phenylcyclopentane-1-carboxylic acid have found use clinically in the treatment of Parkinson's disease, we found it of great interest to determine if the 4-amino-2-butynyl esters of these acids, which are structurally more related to Tremorine than the β-diethylaminoethyl esters, were able to inhibit the symptoms produced by Tremorine.

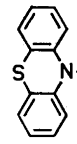
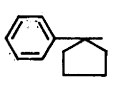
The present paper describes the syntheses of the 4-amino-2-butynyl esters of diphenylacetic acid, 1-phenylcyclopentane-1-carboxylic acid and phenothiazine-10-carboxylic acid and quaternary salts of the esters of phenothiazine-10-carboxylic acid. The corresponding esters of benzilic acid will be dealt with in a subsequent communication.

The results of the pharmacological evaluation of the new compounds will be reported elsewhere.

EXPERIMENTAL

4-Amino-2-butyn-1-ols. The 4-amino-2-butyn-1-ols used as starting materials were prepared from 4-chloro-2-butyn-1-ol and the appropriate amine as described by Biel *et al.*[3] for 4-morpholine-2-butyn-1-ol. The 4-diethylamino- and 4-dimethylamino compounds have also been described in the literature [4,5].

Table 1. R—COO—CH_2—C≡CH_2—Am · RX

No.	R	Am	RX	Yield %	M.p. °C	Formula	Calc. %			Found %		
							C	H	N	C	H	N
1		$-N(CH_3)_2$	HCl	48	185—186 (dec.)	$C_{19}H_{18}N_2O_2S \cdot HCl$	60.87	5.11	7.47	60.45	5.19	7.41
2	”	”	C_2H_5Br	83	158—159 (dec.)	$C_{19}H_{18}N_2O_2S \cdot C_2H_5Br$	56.37	5.18	6.26	56.34	5.28	6.11
3	”	$-N(C_2H_5)_2$	HCl	61	181—182 (dec.)	$C_{21}H_{22}N_2O_2S \cdot HCl$	62.59	5.75	6.95	62.43	6.00	6.93
4	”	”	CH_3Br	91	141—142 (dec.)	$C_{21}H_{22}N_2O_2S \cdot CH_3Br$	57.26	5.46	6.07	56.95	5.65	5.76
5	”		HCl	69	155.5—156.5 (dec.)	$C_{21}H_{20}N_2O_2S \cdot HCl$	62.91	5.28	6.99	62.61	5.40	6.72
6	”	”	CH_3Br	89	163—164 (dec.)	$C_{21}H_{20}N_2O_2S \cdot CH_3Br$	57.51	5.05	6.10	56.68	5.19	5.84
7	”		HCl	72	176—177 (dec.)	$C_{22}H_{22}N_2O_2S \cdot HCl$	63.69	5.59	6.75	63.30	5.69	6.46
8	”	”	CH_3Br	98	170—171 (dec.)	$C_{22}H_{22}N_2O_2S \cdot CH_3Br$	58.35	5.32	5.92	57.96	5.65	5.62
9	”		HCl	64	188—189 (dec.)	$C_{21}H_{20}N_2O_3S \cdot HCl$	60.49	5.08	6.72	60.29	5.24	6.44
10		$-N(CH_3)_2$	HCl	86	144—146	$C_{18}H_{23}NO_2 \cdot HCl$	67.17	7.52	4.36	67.04	7.48	4.33
11	”	$-N(C_2H_5)_2$	”	57	92.5—94	$C_{20}H_{27}NO_2 \cdot HCl$	68.65	8.06	4.00	68.10	8.06	4.17
12	”		”	65	124—126	$C_{21}H_{27}NO_2 \cdot HCl$	69.69	7.64	3.87	69.30	7.47	3.78
13	”		”	71	167—169	$C_{20}H_{25}NO_3 \cdot HCl$	66.01	7.20	3.85	65.97	7.25	4.02

No.	R	Am	RX	Yield %	M.p. °C	Formula	Calc. %			Found %		
							C	H	N	C	H	N
14		$-N(C_2H_5)_2$	HCl	79	128—130	$C_{22}H_{25}NO_2$·HCl	71.05	7.05	3.77	70.64	7.07	3.89
15	"		"	83	142—144	$C_{22}H_{23}NO_2$·HCl	71.44	6.54	3.79	71.32	6.47	3.91
16	"		"	78	158—160	$C_{23}H_{25}NO_2$·HCl	71.95	6.83	3.65	71.80	6.96	3.80
17	"		"	80	160—161.5	$C_{22}H_{23}NO_3$·HCl	68.47	6.27	3.63	68.23	6.33	3.72

4-Piperidino-2-butyn-1-ol. Yield 85 %. B.p. 112–113°/0.9 mm; n_D^{22} 1.5092. (Found: C 70.0; H 9.68; N 9.29. Calc. for $C_9H_{15}NO$: C 70.55; H 9.87; N 9.14).

4-Pyrrolidino-2-butyn-1-ol. Yield 71 %. B.p. 101–102°/0.4 mm; n_D^{22} 1.5043. (Found: C 68.9; H 9.38; N 10.1. Calc. for $C_8H_{13}NO$: C 69.0; H 9.41; N 10.1).

4-Amino-2-butynyl esters of diphenylacetic acid, 1-phenylcyclopentane-1-carboxylic acid and phenothiazine-10-carboxylic acid. A solution of the appropriate acid chloride (0.055 mole), a 4-amino-2-butyn-1-ol (0.05 mole), and triethylamine (0.06 mole) in benzene (50 ml) was refluxed. The reflux time was usually 3 h, but in the preparation of the esters of phenothiazine-10-carboxylic acid, the reaction time was prolonged to 20 h. After cooling the triethylamine hydrochloride was removed by filtration and the benzene was removed under reduced pressure. The residue was dissolved in ether (50 ml) and converted to hydrochloride by the addition of ethereal hydrogen chloride. The product was recrystallised from ethanol-ether.

Quaternary salts. Quaternary salts were prepared from the esters of phenothiazine-10-carboxylic acid by the same method as described for quaternary salts of β-diethylaminoethyl phenothiazine-10-carboxylate [6]. They were recrystallised from ethanol-ether.

Physical constants and analytical data are collected in Table 1. Before analysis the compounds were dried at 50° and 0.05 mm. The elemental analyses were performed by Dr. A. Bernhardt, Mülheim, Germany.

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