Anal. Calcd. for C_3H_6ClNOS: S, 22.97. Found: S, 23.0.

2-Chloro-1,1-dimethyl-N-sulfinylethylamine (IV).—Starting with 45 g. (0.5 mole) of 2-amino-2-methyl-1-propanol, the above procedure gave 19 g. (25%) of IV, b.p. 42–43° (2 mm.).

Anal. Calcd. for C_4H_8ClNOS: S, 20.9. Found: S, 20.9.

Cyclic Sulfite Ester of 2-Methyl-2-sulfinylamino-1,3-propanediol (V).—Starting with 52.5 g. (0.5 mole) of 2-amino-2-methyl-1,3-propanediol, the above procedure gave after two distillations 25 g. (25%) of V, b.p. 65–70° (2 mm.).

Anal. Calcd. for $C_4H_7NO_4S_2$: S, 32.5. Found: S, 32.5.

Cyclic Sulfite Ester of 2-Ethyl-2-sulfinylamino-1,3-propanediol (VI).—Starting with 50 g. (0.42 mole) of 2-amino-2-ethyl-1,3-propanediol, the above procedure gave after two distillations 35 g. (39%) of VI, b.p. 82–85° (2 mm.).

Anal. Calcd. for $C_5H_9NO_4S_2$: S, 30.4. Found: S, 30.5.

Anticholinergic Agents. Esters of 4-Dialkyl- (or 4-Polymethylene-) amino-2-butynols

ROBERT F. MAJEWSKI, KENNETH N. CAMPBELL, STANLEY DYKSTRA, ROBERT COVINGTON, AND JACK C. SIMMS

Mead Johnson Research Center, Evansville, Indiana 47721

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During the study of a series of diphenylacetate, benzilate, and related esters of N,N-disubstituted 4-amino-2-butynyl alcohols[1] in this laboratory which were found to have potentially useful anticholinergic activities, the preparation and some biological properties of the diphenylacetates and some of the benzilates were reported elsewhere by Dahlbom, *et al.*[2,3] We wish to report the preparation of other novel acetylenic amino esters listed in Tables I and II.

Initially, the Mannich reaction was employed (method A) in our preparation of 4-amino-2-butynyl esters. The intermediate propargyl esters were readily obtained by the usual esterification procedures, and these esters were treated with paraformaldehyde and a secondary amine according to the procedure of Jones, *et al.*[4]

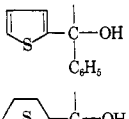
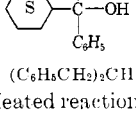
Most of the esters, however, were synthesized more conveniently (B) through a base-catalyzed ester–alcohol interchange involving the 4-amino-2-butynyl alcohols and various methyl esters. A few of them were also prepared (Ca) by the treatment of the aminobutynyl alcohols with the appropriate acid chlorides. Esterification of two of the aminobutynyl alcohols with α-chlorodiphenylacetyl chloride followed by treatment with ethanol furnished two α-ethoxydiphenylacetate esters (Cb).

Another procedure (D), employed specifically for the preparation of kilogram quantities of 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride (**19**) for clinical study, involved a base-catalyzed ester–ester transesterification of methyl phenylcyclohexylglycolate and 4-diethylamino-2-butynyl acetate.

The principle pharmacologic properties exhibited by the compounds listed in Tables I and II were smooth muscle depressant, local anesthetic, and/or anticholinergic actions. 4-Piperidino-2-butynyl α-methylmercaptodiphenylacetate hydrochloride (**23**) was found to have local anesthetic activity equivalent to lidocaine hydrochloride when tested by instillation in the rabbit eye and by infiltration in guinea pig skin. This compound was also similar to lidocaine hydrochloride in a well-known test[5] allowing quantitative appraisal of irritancy.

TABLE I

$R_1COOCH_2C{\equiv}CCH_2R_2 \cdot HCl$

No.	R_1	R_2	Method	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chloride, % Calcd.	Chloride, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	4-$ClH_3OC_6H_4$	$N(CH_3)_2$	A[a]	58	153–154[b]	$C_{14}H_{17}NO_3 \cdot HCl$	59.26	59.94	6.39	6.56	12.52	12.45	4.94	4.95
2	4-$CH_3OC_6H_4$	$C_5H_{10}N$[c]	A[d]	35	156.5–157.5[b]	$C_{17}H_{21}NO_3 \cdot HCl$	63.07	63.30	6.85	6.78	10.95	10.85	4.33	4.27
3	3,4,5-$(CH_3O)_3C_6H_2$	$N(CH_3)_2$	A[e]	43	152–153[b]	$C_{16}H_{21}NO_5 \cdot HCl$	55.89	55.94	6.46	6.86	10.31	10.50	4.07	4.10
4	3,4,5-$(CH_3O)_3C_6H_2$	C_4H_8N[f]	C(a)	11	171.5–173.5[g]	$C_{18}H_{23}NO_5 \cdot HCl$	58.46	58.60	6.54	6.65	9.59	9.94	3.79	3.56
5	3,4,5-$(CH_3O)_3C_6H_2$	$C_5H_{10}N$[c]	C(a)	35	185.5–187.5d.[g]	$C_{19}H_{25}NO_5 \cdot HCl$	59.44	59.71	6.84	6.84	9.24	9.21	3.65	3.46
6	4-ClC_6H_4	$C_5H_{10}N$[c]	C(a)	42	171–173[h]	$C_{16}H_{18}NO_2Cl \cdot HCl$	58.50	58.48	5.84	6.05			4.27	4.20
7	2-ClC_6H_4	$C_5H_{10}N$[c]	C(a)	31	171.5–173.5[h]	$C_{16}H_{18}NO_2Cl \cdot HCl$	58.50	58.30	5.84	6.01			4.27	4.29
8	4-$NH_2C_6H_4$	$C_5H_{10}N$[c]	B[i]	26	100.0–102.5[j]	$C_{16}H_{20}N_2O_2$	70.56	70.93	7.40	7.08			10.29	10.15
9	1-Naphthyl	$N(CH_3)_2$	B[k]	27	165.5–168.5[h]	$C_{17}H_{17}NO_2 \cdot HCl$	67.25	66.98	5.97	6.21			4.61	4.43
10	1-Naphthyl	$C_5H_{10}N$[c]	B[i]	57	189.5–191.5[h]	$C_{20}H_{21}NO_2 \cdot HCl$	69.86	70.36	6.46	6.57			4.07	3.84
11	1-Naphthyl	C_4H_8NO[l]	B[i]	39	194–197d.[m]	$C_{19}H_{19}NO_3 \cdot HCl$	66.00	65.70	5.83	5.82			4.05	3.64
12	2-Naphthyl	$C_5H_{10}N$[c]	B[k]	40	160–163[h]	$C_{20}N_{21}NO_2 \cdot HCl$	69.86	69.89	6.46	6.06	10.33	10.06	4.07	4.08
13	2-Naphthyl	C_4H_8NO[l]	B[i]	30	199–201.5[h]	$C_{19}H_{19}NO_3 \cdot HCl$	66.00	66.26	5.84	6.04	10.25	10.00	4.05	4.49
14	4,4'-Biphenyl	$C_5H_{10}N$[c]	B[i]	68	161.5–166.5[h]	$C_{22}H_{23}NO_2 \cdot HCl$	71.44	71.11	6.55	6.61			3.79	3.78
15	9-Fluorenyl	$C_5H_{10}N$[c]	B[i]	43	172–173[h]	$C_{23}H_{23}NO_2 \cdot HCl$	72.33	72.07	6.33	6.18			3.66	3.47
16	9-Fluorenyl	$N(C_2H_5)_2$	B[k]	21	143–144[h]	$C_{22}H_{23}NO_2 \cdot HCl$					9.58	9.10		
			D	0										
17	2-Phenyl-2-styryl	$C_5H_{10}N$[c]	B[i]	28	170–171.5[h]	$C_{24}H_{25}NO_2 \cdot HCl$	72.78	73.09	6.62	6.73			3.54	3.62
18		$N(C_2H_5)_2$	B[k]	59	81.5–83.5[h]	$C_{20}H_{23}NO_3S \cdot HCl$	60.98	61.39	6.14	6.86	9.00	8.69	3.56	3.70
19		$N(C_2H_5)_2$	D	60	125–128[h]	$C_{22}H_{31}NO_3 \cdot HCl$	67.06	66.88	8.19	8.25	9.00	8.68	3.56	3.50
20	$(C_6H_5CH_2)_2CH$	$C_5H_{10}N$[c]	C(a)	39	156.5–158.5[n]	$C_{25}H_{29}NO_2 \cdot HCl$	72.89	72.51	7.34	6.94			3.40	3.17

[a] Heated reaction mixture on steam bath 96 hr. [b] Recrystallized from propanol. [c] $C_5H_{10}N$ = piperidino. [d] Heated reaction mixture on steam bath 120 hr. [e] Heated reaction mixture on steam bath 85 hr. [f] C_4H_8N = pyrrolidino. [g] Recrystallized from ethyl acetate. [h] Recrystallized from ethyl acetate–ethanol. [i] Used sodium methoxide catalyst. [j] Free base melting point; recrystallized from ethanol–petroleum ether. [k] Used sodium metal catalyst. [l] C_4H_8NO = morpholino. [m] Recrystallized from ethanol. [n] Recrystallized from benzene.

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TABLE II

$(C_6H_5)C(R_1)COOCH_2C{\equiv}CCH_2R_2 \cdot HCl$

No.	R_1	R_2	Method	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
21	SCH_3	$N(C_2H_5)_2$	B[a]	30	146–148[b]	$C_{23}H_{27}NO_2S \cdot HCl$	66.07	66.45	6.75	6.72	3.35	3.30
22	SCH_3	C_4H_8N[c]	B[a]	37	154–156[d]	$C_{25}H_{25}NO_2S \cdot HCl$[e]	66.40	66.37	6.31	6.51	3.37	3.42
23	SCH_3	$C_5H_{10}N$[f]	B[a]	33	171.5–173[g]	$C_{24}H_{27}NO_2S \cdot HCl$	67.03	66.89	6.56	6.53	3.25	2.79
24	SCH_3	C_4H_8NO[h]	B[i]	15	171–173.5[b]	$C_{23}H_{25}NO_3S \cdot HCl$	63.93	63.99	6.07	6.02	3.24	3.03
25	OCH_3	$C_5H_{10}N$[f]	B[i]	58	170.5–172[b]	$C_{24}H_{27}NO_3 \cdot HCl$	69.61	69.71	6.81	6.90	3.39	3.22
26	OCH_2CH_3	$N(CH_3)_2$	C(b)	24	166.5–168.5[b]	$C_{22}H_{25}NO_3 \cdot HCl$	68.12	68.09	6.75	7.04	3.61	3.73
27	OCH_2CH_3	$C_5H_{10}N$[f]	C(b)	32	173.5–175[b]	$C_{25}H_{29}NO_3 \cdot HCl$	70.15	69.60	7.07	6.82	3.27	3.41

[a] Used sodium methoxide catalyst. [b] Recrystallized from ethyl acetate–ethanol. [c] C_4H_8N = pyrrolidino. [d] Recrystallized from isopropyl alcohol. [e] *Anal.* Calcd.: Cl, 8.52. Found: Cl, 8.43. [f] $C_5H_{10}N$ = piperidino. [g] Recrystallized from ethyl acetate–petroleum ether. [h] C_4H_8NO = morpholino. [i] Used sodium metal catalyst.

4-Diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride (**19**) was found to possess about 10% of the activity of atropine on several types of extravascular smooth muscle plus strong papaverine-like action. A comprehensive study of the pharmacological properties of this compound by Lish, *et al.*,[6] will be published shortly.

Experimental[7]

4-Dialkyl- (or 4-Polymethylene-) amino-2-butynols were prepared from 4-chloro-2-butynol and the corresponding secondary amines as previously described for 4-morpholino-2-butynol.[8] The following known 2-butynols were prepared: 4-dimethylamino-,[9,10] 4-diethylamino-,[11] 4-pyrrolidino-,[2] 4-piperidino-,[2] and 4-morpholino-.[8]

General Procedures for the Preparation of Esters of 4-Dialkyl- (or 4-Polymethylene-) amino-2-butynols. A. Mannich Reaction.—This procedure is analogous to that described by Jones, *et al.*[4] Various aromatic esters of propargyl alcohol were employed and the products were isolated as the hydrochloride salts. The solvents used for the recrystallization of the hydrochlorides obtained by this and the subsequent methods are available from Tables I and II.

B. Ester–Alcohol Interchange.—Equivalent amounts of the methyl ester (0.035 mole) and the appropriate 4-amino-2-butynol were dissolved in 50 ml. of heptane and about 0.2 g. of sodium methoxide (or 0.2 g. of sodium metal) catalyst was added. The reaction mixture was stirred and allowed to reflux, and the heptane–methanol azeotrope was collected and measured in a Dean–Stark trap to determine the extent of reaction. The reaction mixture was cooled in an ice bath and washed with water. The heptane solution was washed with 2 *N* HCl and the acidic extract was neutralized with 2 *N* NaOH. The oily free base was dissolved in ether, and the resultant solution was dried ($MgSO_4$) and treated with HCl to precipitate the hydrochloride salt.

C. Esterification with an Acid Chloride. (**a**).—To a stirred solution of acid chloride (0.074 mole), triethylamine (22.0 g., 0.37 mole), and 70 ml. of benzene was added, dropwise, the appropriate 4-amino-2-butynol (0.07 mole) dissolved in 25 ml. of benzene. The reaction mixture was heated on a steam bath for 3 hr. and poured onto crushed ice and water. The organic layer was separated, washed with water, and extracted with several 5-ml. portions of 2 *N* HCl to remove excess triethylamine (the extracts were made basic to determine if insoluble product was being extracted). Additional extractions with 2 *N* HCl were carried out and the extracts were combined, cooled in an ice bath, and neutralized with 2 *N* NaOH. The oil which separated was taken up in ether, and the ether solution was dried ($MgSO_4$). The solution was treated with dry HCl to precipitate the hydrochloride salt.

(**b**).—Equivalent amounts of 2,2-diphenyl-2-chloroacetyl chloride (0.043 mole) and the appropriate 4-amino-2-butynol were mixed and heated at 100–105° for 25 min., then at 70° for 30 min., and the resultant brown viscous oil was washed thoroughly with anhydrous ether and dissolved in 100 ml. of anhydrous ethanol. The ethanolic solution was allowed to reflux for 25 hr. with 5 g. of Na_2CO_3. The reaction mixture was cooled, filtered, and neutralized with 2 *N* NaOH, and most of the ethanol was removed under reduced pressure. The remaining aqueous mixture was extracted with ether and the extract was dried ($MgSO_4$). Hydrogen chloride was passed into the ether solution to precipitate the hydrochloride salt.

D. Ester–Ester Interchange.—Equivalent amounts (0.25 mole) of 4-diethylamino-2-butynyl acetate and the methyl ester of the appropriate carboxylic acid were dissolved in 400 ml. of heptane and 1.25 g. of sodium methoxide was added. The mixture was stirred and heated, and a solution of heptane and methyl acetate was slowly distilled from the reaction vessel over a period of about 1 hr. The reaction mixture was cooled, washed thoroughly with water, and extracted with 2 *N* NaOH, and the oily base was taken up in ether. The ether solution was dried ($MgSO_4$) and treated with HCl to precipitate an oily hydrochloride salt which solidified on cooling.

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New Antifertility Agents. 2,3-Diphenylbenzofurans[1a]

P. K. GROVER, H. P. S. CHAWLA, NITYA ANAND, V. P. KAMBOJ,[1b] AND AMIYA B. KAR[1b]

Division of Medicinal Chemistry and Division of Endocrinology, Central Drug Research Institute, Lucknow, India

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A number of organic compounds which possess the triarylethylene structure have been shown to possess marked effect on the reproductive system.[2,3] In a search for new antifertility agents, the 2,3-diphenyl-

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