Anal. Calcd. for C₃H₆CINOS: 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. $42-43^{\circ}$ (2 mm.).

September 1965

Anal. Calcd. for C₄H₈ClNOS: 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-propaned iol, the above procedure gave after two distillations 25 g. (25%) of V, b.p. 65–70° (2 mm.).

Anal. Calcd. for C₄H₇NO₄S₂: 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-1,3propanediol, the above procedure gave after two distillations $35 \text{ g.} (39\%) \text{ of VI, b.p. } 82-85^{\circ} (2 \text{ mm.}).$

Anal. Calcd. for C₅H₉NO₄S₂: 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

Received April 5, 1965

During the study of a series of diphenylacetate, benzilate, and related esters of N,N-disubstituted 4-amino-2-butynyl alcohols¹ 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 re-

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-2butynyl phenylcyclohexylglycolate hydrochloride (19) for clinical study, involved a base-catalyzed esterester 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 hydro-

Table I $R_1COOCH_2C \equiv CCH_2R_2 \cdot HCl$

Yield,					Carbon, % Hydrogen, % Chloride, % Nitro						Nitroge	en, %	
R_1	R_2	Method	%	M.p., °C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4-CH ₃ OC ₆ H ₄	$N(CH_3)_2$	A^a	58	$153-154^{b}$	C14H17NO3 • HCl	59.26	59.94	6.39	6.56	12.52	12.45	4.94	4.95
4-CH ₃ OC ₆ H ₄	$C_bH_{10}N^c$	Λ^{d}	35	$156.5 - 157.5^{b}$	$C_{17}H_{21}NO_3 \cdot HC1$	63.07	63.30	6.85	6.78	10.95	10.85	4.33	4.27
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	$N(CH_8)_2$	$\Lambda^{m{e}}$	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
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	$C_4H_8N^f$	C(a)	11	$171.5 - 173.5^g$	$C_{18}H_{28}NO_{5}\cdot HCl$	58.46	58.60	6.54	6.65	9.59	9.94	3.79	3.56
3,4,5-(CH ₃ O) ₃ C ₆ H ₂	$C_bH_{10}N^c$	C(a)	35	185.5-187.5d.g	C19H25NO5 · HCl	59.44	59.71	6.84	6.84	9.24	9.21	3.65	3.46
4-ClC ₆ H ₄	$C_bH_{19}N^c$	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
2-ClC ₆ H ₄	$C_{\delta}H_{10}N^{c}$	C(a)	31	$171.5 - 173.5^h$	$\mathrm{C}_{16}\mathrm{H}_{18}\mathrm{NO}_{2}\mathrm{Cl}\cdot\mathrm{HCl}$	58.50	58.30	5.84	6.01			4.27	4.29
4-NH ₂ C ₆ H ₄	$C_{\delta}H_{10}N^{c}$	\mathbf{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
1-Naphthyl	$N(CH_3)_2$	\mathbf{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
1-Naphthyl	$C_5H_{10}N^c$	\mathbf{B}^{i}	57	$189.5 – 191.5^h$	$C_{20}H_{21}NO_2 \cdot HC1$	69.86	70.36	6.46	6.57			4.07	3.84
1-Naphthyl	$C_4H_8NO^t$	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
2-Naphthyl	$C_6H_{10}N^c$	\mathbb{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
2-Naphthyl	$C_4H_8NO^l$	\mathbf{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
4,4'-Biphenyl	$C_5H_{10}N^c$	\mathbf{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
9-Fluorenyl	$C_bH_{10}N^c$	\mathbf{B}^{i}	43	$172 - 173^h$	$C_{28}H_{28}NO_2 \cdot HCl$	72.33	72.07	6.33	6.18			3.66	3.47
9-Fluorenyl	$N(C_2H_5)_2$	\mathbf{B}^{k}	21	$143 - 144^h$	$C_{22}H_{23}NO_2 \cdot HCl$					9.58	9.10		
		D	0										
2-Phenyl-2-styryl	C6H10Nc	\mathbf{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
LC-OH	N(C2H4)2	\mathbf{B}^{k}	59	$81.5 - 83.5^{h}$	C20H23NO3S·HCl	60.98	61.39	6.14	6.86	9.00	8.69	3.56	3.70
\$	•,-												
C_6H_5													
⟨ S ⟩—¢—он	$N(C_2H_5)_2$	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
C6115													
(C6H5CH2)2CH	C5H10N°	C(a)	39	$156.5 - 158.5^n$	C25H29NO2.HCl		72.51						3.17
	4-CH ₃ OC ₆ H ₄ 4-CH ₃ OC ₆ H ₄ 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ 4-ClC ₆ H ₄ 4-ClC ₆ H ₄ 4-NH ₂ C ₆ H ₄ 1-Naphthyl 1-Naphthyl 1-Naphthyl 2-Naphthyl 2-Naphthyl 2-Naphthyl 9-Fluorenyl 9-Fluorenyl 9-Fluorenyl	4-CH ₃ OC ₆ H ₄ 4-CH ₃ OC ₆ H ₄ C ₆ H ₁₀ N ^c 3.4.5-(CH ₃ O) ₃ C ₆ H ₂ N(CH ₃) 3.4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₅ H ₁₀ N ^c 4-ClC ₆ H ₄ C ₅ H ₁₀ N ^c 4-ClC ₆ H ₄ C ₅ H ₁₀ N ^c 4-NH ₂ C ₆ H ₄ C ₅ H ₁₀ N ^c 1-Naphthyl N(CH ₃) 1-Naphthyl C ₅ H ₁₀ N ^c 1-Naphthyl C ₅ H ₁₀ N ^c 2-Naphthyl C ₅ H ₁₀ N ^c 2-Naphthyl C ₅ H ₁₀ N ^c C ₆ H ₁₀ N ^c C ₆ H ₁₀ N ^c C ₇ C ₆ H ₅ C—OH N(C ₂ H ₅) ₂ N(C ₂ H ₅) ₂	R1 R2 Method 4-CH ₃ OC ₅ H ₄ N(CH ₃) ₂ A ^a 4-CH ₃ OC ₆ H ₄ C ₅ H ₁₀ N ^c A ^d 3,4.5-(CH ₂ O) ₃ C ₆ H ₂ N(CH ₃) ₂ A ^e 3,4.5-(CH ₃ O) ₅ C ₆ H ₂ C ₄ H ₃ N ^c C(a) 3,4.5-(CH ₃ O) ₅ C ₆ H ₂ C ₅ H ₁₀ N ^c C(a) 4-ClC ₆ H ₄ C ₅ H ₁₀ N ^c C(a) 4-ClC ₆ H ₄ C ₅ H ₁₀ N ^c C(a) 4-NH ₂ C ₆ H ₄ C ₅ H ₁₀ N ^c B ⁱ 1-Naphthyl N(CH ₃) ₂ B ^k 1-Naphthyl C ₅ H ₁₀ N ^c B ⁱ 1-Naphthyl C ₅ H ₁₀ N ^c B ⁱ 2-Naphthyl C ₅ H ₁₀ N ^c B ⁱ 2-Naphthyl C ₅ H ₁₀ N ^c B ⁱ 4-4'-Biphenyl C ₅ H ₁₀ N ^c B ⁱ 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 2-Phenyl-2-styryl C ₅ H ₁₀ N ^c B ⁱ C ₅ H ₅ D S-C-OH N(C ₂ H ₅) ₂ B ^k	R ₁ R ₂ Method % 4-CH ₃ OC ₅ H ₄ N(CH ₃) ₂ A ^a 58 4-CH ₃ OC ₅ H ₄ C ₅ H ₁₀ N° A ^d 35 3,4,5-(CH ₃ O) ₃ C ₅ H ₂ N(CH ₂) ₂ A ^e 43 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₅ N' C(a) 11 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₅ H ₁₀ N° C(a) 35 4-ClC ₆ H ₄ C ₅ H ₁₀ N° C(a) 42 2-ClC ₆ H ₄ C ₅ H ₁₀ N° C(a) 31 4-NH ₂ C ₆ H ₄ C ₅ H ₁₀ N° B ⁱ 26 1-Naphthyl N(CH ₃) ₂ B ^k 27 1-Naphthyl C ₅ H ₁₀ N° B ⁱ 57 1-Naphthyl C ₅ H ₁₀ N° B ⁱ 39 2-Naphthyl C ₅ H ₁₀ N° B ⁱ 39 2-Naphthyl C ₅ H ₁₀ N° B ⁱ 30 4,4'-Biphenyl C ₅ H ₁₀ N° B ⁱ 30 4,4'-Biphenyl C ₅ H ₁₀ N° B ⁱ 43 9-Fluorenyl N(C ₂ H ₅) ₂ B ^k 21 D 2-Phenyl-2-styryl C ₅ H ₁₀ N° B ⁱ 28 S C OH N(C ₂ H ₅) ₂ B ^k 59 S C OH N(C ₂ H ₅) ₂ B ^k 59	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	R ₁ R ₂ Method % M.p., °C. Formula 4-CH ₃ OC ₈ H ₄ N(CH ₃) ₂ A ^a 58 153-154 ^b C ₁₄ H ₁₇ NO ₅ · HCl 4-CH ₃ OC ₈ H ₄ N(CH ₃) ₂ A ^a 35 156.5-157.5 ^b C ₁₇ H ₂₁ NO ₅ · HCl 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ N(CH ₃) ₂ A ^e 43 152-153 ^b C ₁₆ H ₂₁ NO ₅ · HCl 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₈ N' C(a) 11 171.5-173.5 ^g C ₁₈ H ₂₃ NO ₅ · HCl 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₈ H ₁₀ N° C(a) 35 185.5-187.5d. ^g C ₁₉ H ₂₃ NO ₅ · HCl 4-Cl ₆ H ₄ C ₈ H ₁₀ N° C(a) 42 171-173 ^h C ₁₆ H ₁₃ NO ₂ Cl· HCl 4-Cl ₆ H ₄ C ₈ H ₁₀ N° C(a) 31 171.5-173.5 ^f C ₁₆ H ₁₃ NO ₂ Cl· HCl 4-NH ₂ C ₆ H ₄ C ₈ H ₁₀ N° B ^f 26 100.0-102.5 ^f C ₁₆ H ₂₀ N ₂ O ₂ 1-Naphthyl N(CH ₃) ₂ B ^k 27 165.5-168.5 ^h C ₁₇ H ₁₇ NO ₂ · HCl 1-Naphthyl C ₄ H ₁₀ N° B ^f 57 189.5-191.5 ^h C ₂₀ H ₂₁ NO ₂ · HCl 1-Naphthyl C ₄ H ₃ NO ^f B ³ 39 194-197d. ^m C ₁₈ H ₁₈ NO ₂ · HCl 2-Naphthyl C ₄ H ₃ NO ^f B ³ 40 160-163 ^h C ₂₀ N ₂₁ NO ₂ · HCl 2-Naphthyl C ₄ H ₃ NO ^f B ³ 40 160-163 ^h C ₂₀ N ₂₁ NO ₂ · HCl 2-Naphthyl C ₄ H ₃ NO ^f B ³ 40 160-163 ^h C ₂₀ N ₂₁ NO ₂ · HCl 2-Naphthyl C ₄ H ₃ NO ^f B ³ 41 160-163 ^h C ₂₂ H ₂₃ NO ₂ · HCl 9-Fluorenyl C ₈ H ₁₀ N° B ³ 43 172-173 ^h C ₂₂ H ₂₃ NO ₂ · HCl 9-Fluorenyl C ₈ H ₁₀ N° B ³ 43 172-173 ^h C ₂₂ H ₂₃ NO ₂ · HCl 9-Fluorenyl N(C ₂ H ₈) ₂ B ^k 21 143-144 ^h C ₂₂ H ₂₃ NO ₂ · HCl D 0 2-Phenyl-2-styryl C ₆ H ₁₀ N° B ³ 28 170-171.5 ^h C ₂₄ H ₂₅ NO ₂ · HCl C ₆ H ₅	R ₁ R ₂ Method % M.p., °C. Formula Calcd. 4-CH ₃ OC ₆ H ₄ N(CH ₃) ₂ A ^a 58 153-154 ^b C ₁₄ H ₁₇ NO ₅ · HCl 59.26 4-CH ₃ OC ₆ H ₄ N(CH ₃) ₂ A ^a 35 156.5-157.5 ^b C ₁₇ H ₂₁ NO ₅ · HCl 63.07 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ N(CH ₃) ₂ A ^a 43 152-153 ^b C ₁₆ H ₂₁ NO ₅ · HCl 55.89 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₅ N ^f C(a) 11 171.5-173.5 ^b C ₁₆ H ₂₁ NO ₅ · HCl 58.46 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₁₀ N ^c C(a) 35 185.5-187.5d. ^a C ₁₉ H ₂₂ NO ₅ · HCl 58.46 3,4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₅ H ₁₀ N ^c C(a) 42 171-173 ^h C ₁₆ H ₁₈ NO ₂ Cl· HCl 58.50 4-ClC ₆ H ₄ C ₅ H ₁₀ N ^c C(a) 31 171.5-173.5 ^h C ₁₆ H ₁₈ NO ₂ Cl· HCl 58.50 4-NH ₂ C ₆ H ₄ C ₅ H ₁₀ N ^c B ⁱ 26 100.0-102.5 ^j C ₁₆ H ₂₂ NO ₂ C 70.56 1-Naphthyl N(CH ₃) ₂ B ^k 27 165.5-168.5 ^h C ₁₆ H ₁₈ NO ₂ Cl· HCl 69.86 1-Naphthyl C ₅ H ₁₀ N ^c B ⁱ 39 194-197d. ^m C ₁₈ H ₁₈ NO ₂ · HCl 69.86 1-Naphthyl C ₄ H ₅ NO ^b B ⁱ 39 194-197d. ^m C ₁₈ H ₁₈ NO ₂ · HCl 66.00 2-Naphthyl C ₄ H ₅ NO ^b B ⁱ 39 199-201.5 ^h C ₂₀ H ₂₁ NO ₂ · HCl 66.00 2-Naphthyl C ₄ H ₅ NO ^b B ⁱ 30 199-201.5 ^h C ₂₀ H ₂₁ NO ₂ · HCl 66.00 4.4'-Biphenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^h C ₂₂ H ₂₂ NO ₂ · HCl 72.33 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^h C ₂₂ H ₂₂ NO ₂ · HCl 72.33 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^h C ₂₂ H ₂₂ NO ₂ · HCl 72.33 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^h C ₂₂ H ₂₂ NO ₂ · HCl 72.33 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^h C ₂₂ H ₂₂ NO ₂ · HCl 72.33 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^h C ₂₂ H ₂₂ NO ₂ · HCl 72.33 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^h C ₂₄ H ₂₅ NO ₂ · HCl 72.78	R ₁ R ₂ Method % M.p., °C. Formula Calcd. Found 4-CH ₃ OC ₆ H ₄ N(CH ₃) ₂ A ^a 58 153-154 ^b C ₁₄ H ₁₇ NO ₃ ·HCl 59.26 59.94 4-CH ₃ OC ₆ H ₄ C ₅ H ₁₀ N° A ^d 35 156.5-157.5 ^b C ₁₇ H ₂₁ NO ₃ ·HCl 63.07 63.30 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ N(CH ₃) ₂ A ^e 43 152-153 ^b C ₁₆ H ₂₁ NO ₅ ·HCl 55.89 55.94 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₅ N′ C(a) 11 171.5-173.5 ^b C ₁₈ H ₂₃ NO ₅ ·HCl 58.46 58.60 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₅ H ₁₀ N° C(a) 35 185.5-187.5d. ^g C ₁₉ H ₂₅ NO ₅ ·HCl 58.46 58.60 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₅ H ₁₀ N° C(a) 35 185.5-187.5d. ^g C ₁₉ H ₂₅ NO ₅ ·HCl 58.50 58.48 2-ClC ₆ H ₄ C ₅ H ₁₀ N° C(a) 31 171.5-173.5 ^b C ₁₆ H ₁₈ NO ₂ Cl·HCl 58.50 58.48 2-ClC ₆ H ₄ C ₅ H ₁₀ N° C(a) 31 171.5-173.5 ^b C ₁₆ H ₁₈ NO ₂ Cl·HCl 58.50 58.30 4-NH ₂ C ₆ H ₄ C ₅ H ₁₀ N° B ⁱ 26 100.0-102.5 ^j C ₁₆ H ₂₅ NO ₂ C ₁ 70.56 70.93 1-Naphthyl N(CH ₃) ₂ B ^b 27 165.5-168.5 ^b C ₁₇ H ₁₇ NO ₂ ·HCl 67.25 66.98 1-Naphthyl C ₅ H ₁₀ N° B ⁱ 57 189.5-191.5 ^b C ₂₆ H ₂₁ NO ₂ ·HCl 69.86 70.36 1-Naphthyl C ₄ H ₈ NO ^l B ³ 39 194-197d. ^m C ₁₉ H ₁₉ NO ₂ ·HCl 69.86 70.36 1-Naphthyl C ₄ H ₈ NO ^l B ³ 39 194-197d. ^m C ₁₉ H ₁₉ NO ₂ ·HCl 66.00 65.70 2-Naphthyl C ₄ H ₈ NO ^l B ³ 30 199-201.5 ^b C ₂₉ H ₂₁ NO ₂ ·HCl 66.00 65.70 2-Naphthyl C ₄ H ₁₀ N° B ⁱ 43 172-173. ^b C ₂₉ H ₂₁ NO ₂ ·HCl 72.33 72.07 9-Fluorenyl C ₅ H ₁₀ N° B ⁱ 43 172-173. ^b C ₂₉ H ₂₃ NO ₂ ·HCl 71.44 71.11 9-Fluorenyl C ₅ H ₁₀ N° B ⁱ 43 172-173. ^b C ₂₉ H ₂₃ NO ₂ ·HCl 72.33 72.07 9-Fluorenyl N(C ₂ H ₆) ₂ B ^k 21 143-144 ^h C ₂₉ H ₂₃ NO ₂ ·HCl 72.78 73.09 1-1 11 11 11 11 11 11 11 11 11 11 11 11	R ₁ R ₂ Method % M.p., °C. Formula Calcd. Found Calcd. 4-CH ₃ OC ₆ H ₄ N(CH ₃) ₂ A ^a 58 153-154 ^b C ₁₄ H ₁₇ NO ₃ ·HCl 59.26 59.94 6.39 4-CH ₃ OC ₆ H ₄ N(CH ₃) ₂ A ^a 35 156.5-157.5 ^b C ₁₇ H ₂₁ NO ₃ ·HCl 63.07 63.30 6.85 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ N(CH ₃) ₂ A ^a 43 152-153 ^b C ₁₆ H ₂₁ NO ₅ ·HCl 55.89 55.94 6.46 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₅ N ⁷ C(a) 11 171.5-173.5 ^b C ₁₈ H ₂₃ NO ₅ ·HCl 55.89 55.94 6.46 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₅ N ⁷ C(a) 11 171.5-173.5 ^b C ₁₈ H ₂₃ NO ₅ ·HCl 58.46 58.60 6.54 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₁₀ N ^c C(a) 35 185.5-187.5d. ^a C ₁₉ H ₂₃ NO ₅ ·HCl 59.44 59.71 6.84 4-ClC ₆ H ₄ C ₄ H ₁₀ N ^c C(a) 42 171-173 ^b C ₁₆ H ₁₃ NO ₂ Cl·HCl 58.50 58.48 5.84 2-ClC ₆ H ₄ C ₅ H ₁₀ N ^c C(a) 31 171.5-173.5 ^b C ₁₆ H ₂₃ NO ₂ Cl·HCl 58.50 58.30 5.84 4-NH ₂ C ₆ H ₄ C ₅ H ₁₀ N ^c B ⁱ 26 100.0-102.5 ^j C ₁₈ H ₂₂ NO ₂ O ₂ 70.56 70.93 7.40 1-Naphthyl N(CH ₃) ₂ B ^b 27 165.5-168.5 ^b C ₁₇ H ₁₇ NO ₂ ·HCl 67.25 66.98 5.97 1-Naphthyl C ₅ H ₁₀ N ^c B ⁱ 30 194-197d. ^m C ₁₉ H ₁₃ NO ₃ ·HCl 66.00 65.70 5.83 2-Naphthyl C ₅ H ₁₀ N ^c B ^b 30 199-201.5 ^b C ₁₉ H ₁₉ NO ₃ ·HCl 66.00 65.70 5.83 2-Naphthyl C ₅ H ₁₀ N ^c B ⁱ 68 161.5-166.5 ^b C ₂₂ H ₂₃ NO ₂ ·HCl 69.86 70.36 6.46 2-Naphthyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^b C ₂₂ H ₂₃ NO ₂ ·HCl 71.44 71.11 6.55 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^b C ₂₂ H ₂₃ NO ₂ ·HCl 72.33 72.07 6.33 9-Fluorenyl C ₅ H ₁₀ N ^c B ⁱ 43 172-173 ^b C ₂₂ H ₂₃ NO ₂ ·HCl 72.33 72.07 6.33	R ₁ R ₂ Method % M.p., °C. Formula Caled. Found Caled. Found 4-CH ₃ OC ₅ H ₄ N(CH ₃) ₂ A ^a 58 153-154 ^b C ₁₄ H ₁₇ NO ₅ ·HCl 59.26 59.94 6.39 6.56 4-CH ₃ OC ₅ H ₄ C ₅ H ₁₀ N° A ^d 35 156.5-157.5 ^b C ₁₇ H ₂₁ NO ₅ ·HCl 63.07 63.30 6.85 6.78 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ N(CH ₂) ₂ A ^e 43 152-153 ^b C ₁₆ H ₂₁ NO ₅ ·HCl 55.89 55.94 6.46 6.86 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₅ N ^f C(a) 11 171.5-173.5 ^g C ₁₈ H ₂₈ NO ₅ ·HCl 58.46 58.60 6.54 6.65 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₅ H ₁₀ N° C(a) 35 185.5-187.5d. ^g C ₁₉ H ₂₈ NO ₅ ·HCl 59.44 59.71 6.84 6.84 4-ClC ₆ H ₄ C ₅ H ₁₀ N° C(a) 42 171-173 ^h C ₁₆ H ₁₈ NO ₂ Cl·HCl 58.50 58.48 5.84 6.05 2-ClC ₆ H ₄ C ₅ H ₁₀ N° C(a) 31 171.5-173.5 ^h C ₁₆ H ₁₈ NO ₂ Cl·HCl 58.50 58.48 5.84 6.05 2-ClC ₆ H ₄ C ₅ H ₁₀ N° B ⁱ 26 100.0-102.5 ^j C ₁₈ H ₂₈ NO ₂ Cl·HCl 58.50 58.48 5.84 6.05 1.84 N·H ₂ CcH ₄ C ₅ H ₁₀ N° B ⁱ 26 100.0-102.5 ^j C ₁₆ H ₂₀ N ₁ O ₂ Cl·HCl 58.50 58.48 5.84 6.01 1.Naphthyl N(CH ₃) ₂ B ^k 27 165.5-168.5 ^h C ₁₇ H ₁₇ NO ₂ ·HCl 67.25 66.98 5.97 6.21 1.Naphthyl C ₅ H ₁₀ N° B ⁱ 57 189.5-191.5 ^h C ₂₀ H ₂₁ NO ₂ ·HCl 69.86 70.36 6.46 6.57 1.Naphthyl C ₅ H ₁₀ N° B ⁱ 39 194-197d. ^m C ₁₈ H ₁₅ NO ₂ ·HCl 69.86 70.36 6.46 6.57 1.Naphthyl C ₅ H ₁₀ N° B ^k 40 160-163 ^h C ₂₀ N ₂₁ NO ₂ ·HCl 69.86 69.89 6.46 6.66 2.Naphthyl C ₅ H ₁₀ N° B ⁱ 30 199-201.5 ^h C ₁₉ H ₁₉ NO ₃ ·HCl 66.00 65.70 5.83 5.82 2.Naphthyl C ₅ H ₁₀ N° B ⁱ 43 172-173 ^h C ₂₂ H ₂₃ NO ₂ ·HCl 71.44 71.11 6.55 6.61 9-Fluorenyl C ₅ H ₁₀ N° B ⁱ 43 172-173 ^h C ₂₂ H ₂₃ NO ₂ ·HCl 72.33 72.07 6.33 6.18 9-Fluorenyl N(C ₂ H ₆) ₂ B ^k 21 143-144 ^h C ₂₂ H ₂₃ NO ₂ ·HCl 72.78 73.09 6.62 6.73 4.14 C ₄ H ₆	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	R ₁ R ₂ Method % M.p., °C. Formula Calcd. Found Calcd. Found 4-CH ₃ OC ₆ H ₄ N(CH ₃) ₂ A ^a 58 153-154 ^b C ₁₄ H ₁₇ NO ₅ ·HCl 59.26 59.94 6.39 6.56 12.52 12.45 4-CH ₂ OC ₆ H ₄ N(CH ₃) ₂ A ^a 43 152-153 ^b C ₁₇ H ₂₁ NO ₅ ·HCl 63.07 63.30 6.85 6.78 10.95 10.85 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ N(CH ₃) ₂ A ^a 43 152-153 ^b C ₁₈ H ₂₁ NO ₅ ·HCl 55.89 55.94 6.46 6.86 10.31 10.50 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₅ N/ C(a) 11 171.5-173.5 ^c C ₁₈ H ₂₁ NO ₅ ·HCl 58.46 58.60 6.54 6.65 9.59 9.94 3,4.5-(CH ₃ O) ₃ C ₆ H ₂ C ₅ H ₁₀ N ^c C(a) 35 185.5-187.5d. C ₁₈ H ₂₁ NO ₅ ·HCl 58.46 58.60 6.54 6.65 9.59 9.94 4-ClC ₆ H ₄ C ₅ H ₁₀ N ^c C(a) 42 171-173.5 ^c C ₁₈ H ₂₁ NO ₅ ·HCl 58.46 58.60 6.54 6.65 9.59 9.94 4-ClC ₆ H ₄ C ₅ H ₁₀ N ^c C(a) 31 171.5-173.5 ^c C ₁₈ H ₂₁ NO ₅ ·HCl 58.50 58.48 5.84 6.05 1.2-ClC ₆ H ₄ C ₅ H ₁₀ N ^c C(a) 31 171.5-173.5 ^c C ₁₈ H ₂₁ NO ₅ ·HCl 58.50 58.48 5.84 6.05 1.2-ClC ₆ H ₄ C ₅ H ₁₀ N ^c C(a) 31 171.5-173.5 ^c C ₁₈ H ₂₁ NO ₅ ·HCl 58.50 58.48 5.84 6.05 1.2-ClC ₆ H ₄ C ₅ H ₁₀ N ^c B ⁱ 26 100.0-102.5 ^j C ₁₈ H ₂₂ NO ₅ ·HCl 58.50 58.30 5.84 6.01 1.Naphthyl N(CH ₃) ₂ B ^b 27 165.5-166.5 ^b C ₂₈ H ₂₁ NO ₅ ·HCl 67.25 66.98 5.97 6.21 1.Naphthyl N(CH ₃) ₂ B ^b 27 165.5-166.5 ^b C ₂₈ H ₂₁ NO ₅ ·HCl 67.25 66.98 5.97 6.21 1.Naphthyl C ₅ H ₁₀ N ^c B ⁱ 57 189.5-191.5 ^b C ₂₈ H ₁₁ NO ₅ ·HCl 67.25 66.98 5.97 6.21 1.Naphthyl C ₆ H ₁₀ N ^c B ⁱ 57 189.5-191.5 ^b C ₂₈ H ₁₁ NO ₅ ·HCl 66.00 65.70 5.83 5.82 1.Naphthyl C ₆ H ₁₀ N ^c B ⁱ 68 161.5-166.5 ^b C ₂₈ H ₂₁ NO ₅ ·HCl 66.00 65.70 5.83 5.82 1.Naphthyl C ₆ H ₁₀ N ^c B ⁱ 68 161.5-166.5 ^b C ₂₈ H ₂₁ NO ₅ ·HCl 66.00 66.26 5.84 6.04 10.25 10.00 4.4 ^c -Biphenyl C ₆ H ₁₀ N ^c B ⁱ 68 161.5-166.5 ^b C ₂₈ H ₂₁ NO ₅ ·HCl 72.33 72.07 6.33 6.18 10.06 10.33 10.06 10.00 1	R ₁ R ₂ Method % M.p., °C. Formula Calcd. Found Calcd. Found Calcd. Found Calcd. 4-CH ₃ OC ₆ H ₄ N ₁ (CH ₃) ₂ A ^a 58 153-154 ^b C ₄ H ₁₁ NO ₃ ·HCl 59.26 59.94 6.39 6.56 12.52 12.45 4.94 4-CH ₄ OC ₆ H ₄ N ₆ CH ₂ C ₄ H ₁₀ N° A ^d 35 156.5-157.5 ^b C ₁₇ H ₂ NO ₃ ·HCl 55.89 55.94 6.36 6.85 6.78 10.95 10.85 4.94 3.45-(CH ₃ O) ₃ C ₆ H ₂ N ₁ (CH ₃) ₂ A ^e 43 152-153 ^b C ₁₈ H ₂ NO ₃ ·HCl 55.89 55.94 6.46 6.86 10.31 10.50 4.07 3.4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₁₀ N° C(a) 11 171.5-173.5 ^g C ₁₈ H ₂ NO ₅ ·HCl 58.46 58.60 6.54 6.65 9.59 9.59 9.44 3.79 3.4,5-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₁₀ N° C(a) 35 185.5-187.5d.g C ₁₈ H ₂ NO ₅ ·HCl 58.46 58.60 6.54 6.65 9.59 9.59 9.44 3.79 3.45-(CH ₃ O) ₃ C ₆ H ₂ C ₄ H ₁₀ N° C(a) 42 171-173 ^b C ₁₈ H ₂ NO ₅ ·HCl 58.50 58.30 58.48 5.84 6.05 4.27 4.27 4.NH ₂ C ₈ H ₄ C ₅ H ₁₀ N° C(a) 42 171-173 ^b C ₁₈ H ₂ NO ₅ Cl·HCl 58.50 58.30 5.84 6.81 6.81 0.31 10.20 4.27 4.NH ₂ C ₈ H ₄ C ₅ H ₁₀ N° B ^c 26 100.0-102.5 ^c C ₁₈ H ₂ N ₂ O ₂ 70.56 70.93 7.40 7.08 110.29 10.

^a Heated reaction mixture on steam bath 96 hr. ^b Recrystallized from propanol. ^c C_bH₁₀N = piperidino. ^d Heated reaction mixture on steam bath 120 hr. ^e Heated reaction mixture on steam bath 85 hr. ^f C₄H₈N = pyrrolidino. ^e Recrystallized from ethyl acetate. ^h Recrystallized from ethyl acetate-ethanol. ^e Used sodium methoxide catalyst. ^e Free base melting point; recrystallized from ethanol-petroleum ether. * Used sodium metal catalyst. 1 C4H8NO = morpholino. ** Recrystallized from ethanol. ** Recrystallized from ethanol. ** Recrystallized from ethanol. ** lized from benzene.

ported 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.

chloride 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 wellknown test⁵ allowing quantitative appraisal of irritancy.

⁽¹⁾ K. N. Campbell and R. F. Majewski, U. S. Patent 3,176,019 (1965).

 ⁽²⁾ R. Dahlbom and R. Mollberg, Acta Chem. Scand., 17, 916 (1963).
 (3) R. Dahlbom, B. Hansson, and R. Mollberg, ibid., 17, 2354 (1963).

TABLE II

1	C^*A	1.	YC:	ďΩ	.) (4	M	CT-	Lí	اعتعال	C)	CS	T.	D.,.	116	4
, i	1 a c 1	14	11 /	tΙλ	111	-28	,,,,	1 / 1		,		LΙF	10	100	111	

		Yield,					Carb	on, %	Hydrogen, 🖓		Nitrogen, Sa	
No.	\mathbf{R}_1	R_2	Method	26	M.p., °C.	Formula	Caled.	Found	Caled.	Found	Caled.	Found
21	SCH_3	$N(C_2H_5)_2$	\mathbf{B}^{a}	30	$146 - 148^b$	$\mathrm{C}_{23}\mathrm{H}_{27}\mathrm{NO}_2\mathrm{S}\cdot\mathrm{HCl}$	66.07	66.45	6.75	6.72	3.35	3,30
22	SCH_3	$\mathrm{C_4H_8N^c}$	\mathbf{B}^{a}	37	$154 - 156^d$	$\mathrm{C}_{23}\mathrm{H}_{25}\mathrm{NO}_2\mathrm{S}\cdot\mathrm{HCl}^e$	66.40	66.37	6.31	6.51	3.37	3.42
23	SCH_3	$\mathrm{C_5H_{10}N}^f$	\mathbf{B}^{u}	33	171.5 - 173''	$\mathrm{C}_{24}\mathrm{H}_{27}\mathrm{NO}_2\mathrm{S}\cdot\mathrm{HCl}$	67.03	66.89	6.56	6.53	3.25	2.79
24	SCH_3	$\mathrm{C_4H_8NO}^h$	\mathbf{B}^{i}	15	$171 173.5^b$	$\mathrm{C}_{23}\mathrm{H}_{25}\mathrm{NO}_3\mathrm{S}\cdot\mathrm{HCl}$	63.93	63.99	6.07	6.02	3.24	3.03
25	OCH_3	$\mathrm{C_5H_{10}N^f}$	\mathbf{B}^i	58	$170.5 - 172^b$	$\mathrm{C}_{24}\mathrm{H}_{27}\mathrm{NO}_3\cdot\mathrm{HCl}$	69.61	69.71	6.81	6.90	3.39	3.22
26	$\mathrm{OCH_2CH_3}$	$\mathrm{N}(\mathrm{CH_3})_2$	C(b)	24	$166.5 – 168.5^{\circ}$	$\mathrm{C}_{22}\mathrm{H}_{25}\mathrm{NO}_{8}\cdot\mathrm{HCl}$	68.12	68.09	6.75	7.04	3.61	3.73
27	OCH_2CH_3	$\mathrm{C_5H_{10}N^f}$	C(b)	-32	$173.5 - 175^b$	$\mathrm{C}_{25}\mathrm{H}_{29}\mathrm{NO}_3\!\cdot\!\mathrm{HCl}$	70.15	69.60	7.07	6.82	3.27	3.41

" Used sodium methoxide catalyst. "Recrystallized from ethyl acetate-ethanol. " C_4H_5N = pyrrolidino. "Recrystallized from isopropyl alcohol. ".1 nal. Calcd.: Cl, 8.52. Found: Cl, 8.43. " $C_5H_{10}N$ = piperidino. "Recrystallized from ethyl acetate-petroleum ether. " C_4H_5NO = morpholino." 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.*, will be published shortly.

Experimental⁷

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-,⁸, 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 (MgSO₄) 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 (MgSO₄). The solution was treated with dry HCl to precipitate the hydrochloride salt.

- (b).—Equivalent amounts of 2,2-diphenyi-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 Na₂CO₃. 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 (MgSO₄). 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 (MgSO₄) and treated with HCl to precipitate an oily hydrochloride salt which solidified on cooling.

Acknowledgment.—The biological screening of these compounds was carried out by various staff members of the Pharmacology Department, Mead Johnson Research Center. The authors wish to thank Mrs. Nancy Eisley Dunn for her technical assistance.

New Antifertility Agents. 2.3-Diphenylbenzofurans^{1a}

P. K. Grover, H. P. S. Chawla, Nitya Anand, V. P. Kamboj, th and Amiya B. Kar^{1b}

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

Received April 26, 1965

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-

⁽⁵⁾ J. O. Hoppe, E. B. Alexander, and L. C. Miller, J. Am. Pharm. Assoc. Sci. Ed., 39, 147 (1950).

⁽⁶⁾ P. M. Lish, J. A. LaBudde, E. L. Peters, and S. I. Robbins, Arch, intern. pharmacodynam., in press.

⁽⁷⁾ Melting points are uncorrected.

⁽⁸⁾ J. H. Biel, E. P. Sprengeler, and H. L. Friedman, J. Am. Chem. Soc., 79, 6184 (1957).

⁽⁹⁾ M. Olomucki, Compt. rend., 237, 192 (1953).

⁽¹⁰⁾ I. Marszak, A. Marszak-Fleury, R. Epsztein, J. P. Guermont, J. Jacob, and G. Montezin, Mem. serv. chim. état (Paris), 36, 411 (1951).

⁽¹¹⁾ J. Colonge and G. Poilane, Bull. soc. chim. France, 502 (1955).

 ⁽a) This investigation was supported by a grant from the Ford Foundation.
 (b) Division of Endocrinology.

 ^{(2) (}a) L. J. Lerner, F. J. Holthaus, Jr., and C. R. Thompson, Endocrinology, 63, 295 (1958);
 (b) J. F. Miquel, Tetrahedron, 8, 205 (1960);
 (c) H. H. Fox, J. T. Ghas, H. L. Lee, and A. Boris, J. Med. Chem., 7, 696, 790 (1964)

⁽³⁾ D. Lednieer, J. C. Babcock, S. C. Lyster, J. C. Stucki, and G. W. Duncan, Chem. Ind. (London), 2098 (1961).