TABLE II
CATALYST EVALUATION

$$C_6H_5C{\equiv}CH + HC(OEt)_3 \xrightarrow[\Delta]{\text{cat.}} C_6H_5C{\equiv}CC(OEt)_2 + EtOH$$
(H)

Catalyst, g.	Time, hr.	Ethyl alcohol, g.	Yield of acetal, %
None	2.0	None	None
2, ZnI_2	0.4	15.5	71
2, $ZnCl_2$[b] (coml.)	1.7	17.0	64.0
1.5, $ZnCl_2$ (coml.)	3.5	12.4	53.5
10, $ZnCl_2$[a,b]	3.2	..	28.3
2, $ZnBr_2$	3.0	28.9	11.8
2, $Zn(NO_3)_2$	0.4	15.5	71
2, $ZnSO_4$	5.7	8.0	29.4
2, $Zn(OAc)_2 \cdot 2H_2O$	3.5	8.8	37.1
2, $(C_{17}H_{35}COO)_2Zn$	5.5	29.5	6.3
2, Zn formate	5.0	8.7	31
2, Zn molybdite	4.7	10.0	7.4
2, CdI_2	3.0	16.0	72.3
2, CdI_2	1.5	7.4	45.5
2, $CdCl_2$	9.0	5.0	22.5
2, $HgBr_2$	7.0	10.5	20.6
2, HgI_2	2.5	3.5	Not isolated
2, $MgCl_2$	3.0	14	8.1

[a] Freshly fused. [b] Slightly larger charge of reactants used in this run.

55 g. of malonaldehyde bis-(diethyl acetal), b.p. 108° (20 mm.), $n^{25}D$ 1.4099. *Anal.* Calcd. for $C_{11}H_{24}O_4$: C, 60.0; H, 11.0; OEt, 81.8. Found: C, 61.5; H, 11.1; OEt, 81.1.

The infrared spectrum of III was identical to that of a commercial sample of malonaldehyde bis-(diethyl acetal) (b.p. 115° (25 mm.), $n^{25}D$ 1.4088). The infrared spectrum showed absorption at 3.35 and 3.45 μ for saturated CH, as well as broad, strong absorption in the 9 μ region for ether -C-O-.

Identification of Propiolaldehyde Diethyl Acetal (II).—Since the boiling point of II is so close to that of recovered triethyl orthoformate, II was isolated only as its 2,4-dinitrophenylhydrazone derivative. The amount of II present was undetermined but small. The infrared spectra of the dinitrophenylhydrazone of II and of the same derivative prepared from an authentic sample of propiolaldehyde were identical. Bands in the spectra were obtained at 4.75 μ for -C≡C-; 3.25 μ for aromatic CH; 6.15, 6.25 and 6.45 μ for aromatic >C=C<; 6.6 and 7.5 μ for $-NO_2$; and 3.05 μ for HC≡ and -NH-.

Acetylene reacted very slowly with higher orthoesters. Very low yields of products believed to be acetylenic ketals were obtained, and these materials were not fully characterized.

Study of Catalysts.—For catalyst evaluation, the reaction between phenylacetylene and triethyl orthoformate was employed. Unless otherwise specified, one-third molar amounts of the two reactants were charged into a still-flask, the candidate catalyst added, and the reaction mixture heated while removing ethyl alcohol. Generally, the distillation of ethyl alcohol started at an initial flask temperature of 130–140°. Near the end of the reaction, the flask temperature frequently reached 200° or slightly higher. Of the catalysts evaluated, zinc iodide, zinc chloride, zinc nitrate and cadmium iodide were most effective. A variety of other zinc salts, as well as certain cadmium, mercury or magnesium halides, were less effective. These results are summarized more fully in Table II.

WILMINGTON, DEL.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, LAKESIDE LABORATORIES, INC.]

Hypotensive Agents. I. Acetylenic Diamines

BY JOHN H. BIEL AND FRANK DIPIERRO

RECEIVED MARCH 24, 1958

The introduction of a triple bond into a number of active blood pressure lowering agents has yielded compounds which were effective hypotensors in the dog, being superior to the saturated parent compounds in regard to potency, duration of action and ease of absorption from the gastro-intestinal tract. Four series of derivatives were prepared: (1) bis-*t*-amino-alkynes, (2) N-(ω-*t*-aminoalkynyl)-1,2,3,4-tetrahydroisoquinolines, (3) α-(4-*t*-amino-2-butynyl)-N-methylpyrrolidines, (4) β-(4-*t*-amino-2-butynyl)-N-methylpiperidines. Only the bis-quaternary ammonium salts displayed hypotensive properties. A general method of synthesis was developed for the aminoalkylation of acetylene and N,N-disubstituted propargylamines which afforded the desired compounds in high yields and did not necessitate the use of pressure equipment. This process also represents a facile synthetic route for the preparation of "mixed" acetylenic, olefinic and alkylenic diamines, as well as "mixed" diaminoketones (Mannich bases) and diaminoalcohols.

Acetylene derivatives have found limited usefulness as therapeutic agents. Some of the more outstanding applications have been in the fields of steroids and non-barbiturate sedatives. Estrone which is poorly absorbed from the gastro-intestinal tract can be converted to a potent, orally highly effective preparation, 17-ethynylestradiol[1]; 17α-ethynyl-19-nortestosterone is an orally active progestational hormone and ovulation inhibitor.[1] In these instances the acetylenic group imparts apparently greater stability to the compound in the gastro-intestinal tract.

The introduction of a triple bond into a variety of tertiary alcohols[2–5] has yielded several clinically effective non-barbiturate sedatives.[6–8] The presence of an acetylenic moiety greatly enhanced the sedative properties of the saturated parent compounds.[9]

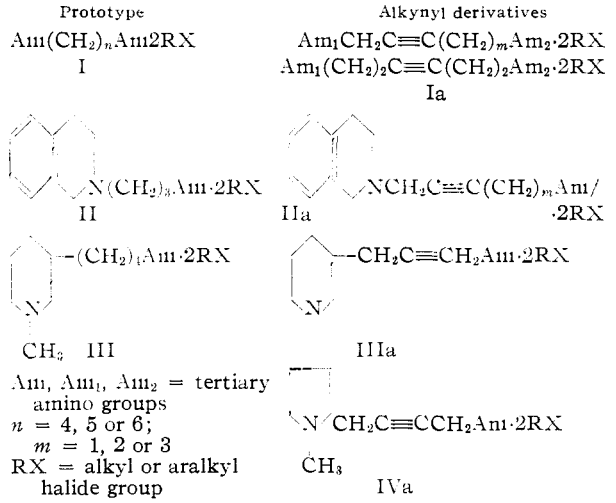
While this work was in progress, Marszak[10] and his co-workers reported that the acetylenic function increased the parasympathomimetic activity in a series of aliphatic aminoethers.

We became interested in exploring the effect of a triple bond in a variety of hypotensively active bis-ammonium alkanes for several reasons: (1) The "methonium" hypotensive drugs are notorious for

(1) F. Hartley, *J. Pharm. and Pharmacol.*, **9**, 10 (1957).
(2) D. Papa, F. J. Villani and H. F. Ginsberg, THIS JOURNAL, **76**, 4446 (1954).
(3) G. Franke, *Med. Klin.*, **49**, 891 (1954).
(4) K. E. Hamlin, U. S. Patent 2,779,799 (1957).
(5) W. M. McLamore, S. Y. P'An and A. Bavley, *J. Org. Chem.*, **20**, 109 (1955).
(6) S. Y. P'An, L. Markarian and W. M. McLamore, *J. Pharmacol. Exptl. Therap.*, **109**, 268 (1953).
(7) H. H. Hirsch and W. H. Orsinger, *Am. Practitioner*, **3**, 23 (1952).
(8) G. M. Gruber, K. G. Kohlstaedt, R. B. Moore and F. B. Peck, *J. Pharmacol. Exptl. Therap.*, **112**, 480 (1954).
(9) W. Longemann, D. Artini and A. Meli, *Arzneimittel-Forsch.*, **6**, 136 (1956).
(10) J. Jacob, I. Marszak, S. Cruik and J. P. Guermont, *Compt. rend.*, **239**, 1561 (1954).

being poorly absorbed from the gastrointestinal tract. It was hoped that the replacement of an ethylene ($-CH_2CH_2-$) by an ethynyl ($C\equiv C$) group might enhance the absorbability of the parent compounds.[2] Since the distance between the two quaternary nitrogens is critical to hypotensive activity in a given series,[11-14] it was of interest to study the effect of the greater rigidity of the alkyne chain on the hypotensive properties of these substances (the introduction of a triple bond forces the bis-ammonium compound to act in its more extended form).[3] The availability of acetylenic diamines made possible the convenient synthesis of hitherto difficultly available bis-aminoölefins, unsymmetrically substituted bis-aminoalkanes, as well as bis-aminoketones and bis-aminoalcohols (*via* the hydration of the triple bond).[4] It was also our hope that an acetylenic moiety might produce a more favorable ratio of central hypotension *vs.* ganglionic blockade in these substances and thus reduce the incidence of disagreeable side effects resulting from parasympathetic ganglionic blockade.

The acetylenic moiety was introduced into three structural prototypes known to produce a definite hypotensive effect in animals: the bis-ammonium alkanes (I),[11-13] 3-(4′-aminobutyl)-piperidines[15] (III), N-(ω-ammonium alkyl)-1,2,3,4-tetrahydroisoquinolinium halides (II.)[16] Incidentally, there was obtained a fourth type, N-methyl-2-(4-*t*-amino-2-butynyl)-pyrrolidines (IVa).



Monoamine alkynes previously had been prepared by Campbell[17] *via* the reaction of a monoalkyl sodium acetylide with an alkyl halide in liquid ammonia. However, this method did not lend itself to the production of the bis-aminoalkynes and a new synthetic approach had to be considered.

To avoid the necessity of working with acetylenic compounds under high pressure and elevated temperatures, an operation which is both hazardous and expensive, we devised the general synthetic scheme

$$BrCH_2C\equiv CH + Am_1H \longrightarrow$$

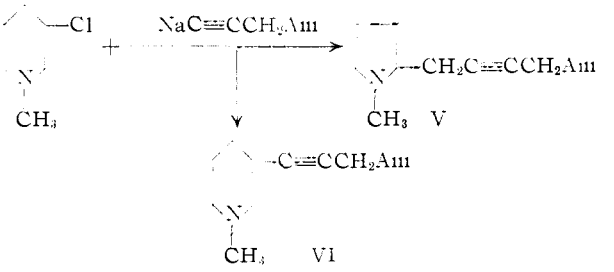
$$Am_1CH_2C\equiv CH \xrightarrow[2,\ ClYAm_2]{1,\ NaNH_2} Am_1CH_2C\equiv CYAm_2$$

70–95% toluene 50–90%

Y = alkylene chain, N-methyl-3-piperidyl, N-methyl-3-piperidylmethyl

The propargylamines were formed readily by treating propargyl bromide with a 100% molar excess of the appropriate secondary amine in ethyl ether, isopropyl ether or toluene. Care had to be taken to prevent the formation of quaternary propargyl halide salts by adding the propargyl bromide slowly to the amine. Once the proper reaction conditions had been established, ether was substituted by toluene as a solvent and the toluene solution of the propargylamine used in the next step without isolating the acetylenic amine. The sodium salt of the propargylamine was then prepared with sodium amide in refluxing toluene, followed by the addition of the appropriate aminoalkyl halide. The resulting bis-amino-2-alkynes were obtained in 50–90% yield.

The ring contraction of N-alkyl-3-piperidyl to N-alkyl-2-pyrrolidylmethyl which occurs during the reaction of N-methyl-3-chloropiperidine with basic reagents was first shown by Reitsema[18] and confirmed by us[19] for a variety of basic reactants. Based on this experimental precedent, we felt that the reaction of N-methyl-3-chloropiperidine with sodium (*t*-aminomethyl)-acetylide yielded presumably the N-methyl-2-(4′-*t*-amino-2-butynyl)-pyrrolidine (V) rather than the isomeric N-methyl-3-(3′-*t*-amino-1-propynyl)-piperidine (VI).



Since the infrared spectra of some known 3-piperidyl and 2-pyrrolidyl compounds did not reveal any striking differences between these two ring systems, the structure of V will have to be determined by chemical degradation studies. On a preliminary basis we wish to assign structure V to the compound obtained from N-methyl-3-chloropiperidine with the aminoalkyne derivative.

The synthesis of the quaternary salts of the N-(4-amino-2-butynyl)-1,2,3,4-tetrahydroisoquinolines was accomplished by treating N-methyl-1,2,3,4-tetrahydroisoquinoline with 1-bromo-4-ammonium-2-butynyl bromide according to the procedure described by Gray, *et al.*[20] The symmet-

(11) W. D. M. Paton and E. J. Zaimis, *Brit. J. Pharmacol.*, **6**, 155 (1951).
(12) R. Wien, *J. Pharmacol. Exptl. Therap.*, **110**, 53 (1954).
(13) R. Wien, D. F. J. Mason, N. D. Edge and G. T. Langston, *Brit. J. Pharmacol.*, **7**, 534 (1952).
(14) C. J. Cavallito, A. P. Gray and T. B. O'Dell, *Arch. Intern. Pharmacodyn.*, **101**, 38 (1955).
(15) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).
(16) T. B. O'Dell, C. Luna and M. D. Napoli, *J. Pharmacol. Exptl. Therap.*, **114**, 317 (1955).
(17) K. N. Campbell, F. C. Patora and B. K. Campbell, *J. Org. Chem.*, **17**, 1141 (1952).
(18) R. R. Reitsema, THIS JOURNAL, **71**, 2041 (1949).
(19) Unpublished data.
(20) A. P. Gray, W. L. Archer, D. C. Seldlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3536 (1955).

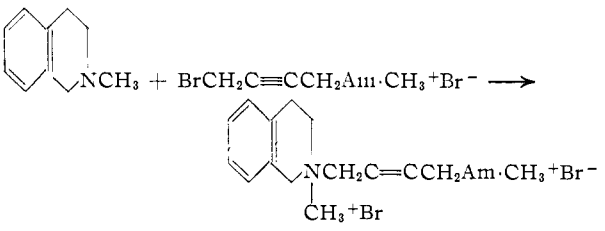
TABLE I

$Am_1(CH_2)_mC{\equiv}C(CH_2)_nAm_2$

				Bases					Salts				
				B.p.			Nitrogen, %			Nitrogen, %		Halogen, %		M.p.,
Am_1	Am_2	m	n	°C.	Mm.	Formula	Calcd.	Found	Salt[a]	Calcd.	Found	Calcd.	Found	°C.
$(CH_3)_2N$	$(CH_3)_2N$	1	1	95–98	0.4	$C_8H_{16}N_2$	20.00	19.43	CH_3Br	8.48	8.60	48.48	48.48	260
Pyrrolidino	Pyrrolidino	1	1	93–95	0.1	$C_{12}H_{20}N_2$	14.57	14.70	CH_3I	5.88	5.62	53.36	53.59	239–240
$(CH_3)_2N$	$(CH_3)_2N$	1	2	87–90	8.0	$C_9H_{18}N_2$	18.18	17.70	CH_3Br	8.13	8.03	46.51	46.34	238–240
$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	2	85–90	1.5	$C_{13}H_{26}N_2$	13.33	13.23	CH_3Br	7.00	6.90	40.00	40.12	197–198
$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	2						C_2H_5Br	6.25	6.23	35.71	35.88	210–211
$[(CH_3)_2CH]_2N$	$[(CH_3)_2CH]_2N$	1	2	100–105	0.3	$C_{17}H_{34}N_2$	10.53	10.73	CH_3Br	6.14	6.19	35.09	34.84	217–218
Pyrrolidino	Pyrrolidino	1	2	95–98	.3	$C_{13}H_{24}N_2$	13.46	13.37	CH_3Br	7.42	7.21	40.40	40.78	230–213
Morphilino	Morpholino	1	2	125–127	.05	$C_{13}H_{22}N_2O_2$	11.76	11.65	CH_3Br	6.54	6.64	37.38	37.04	200–201
Pyrrolidino	$(CH_3)_2$–N	1	2	64–66	.01	$C_{11}H_{20}N_2$	15.55	15.35	CH_3I	6.03	5.90	54.74	54.52	238–240
$OClCH_2N(CH_3)$–	$(C_2H_5)_2N$	1	2						CH_3I	4.63	4.71	44.05[f]	44.40[f]	160–161
$(CH_3)_2N$	$(CH_3)_2N$	1	3	60–61	1.0	$C_{10}H_{20}N_2$	16.66	16.60	CH_3Br	7.82	7.78	44.69	44.32	229- 230
$(CH_3)_2N$	$(CH_3)_2N$	1	3						HCl	11.41	11.86	28.99	28.63	152–154
$(CH_3)_2N$	$(CH_3)_2N$	2	2	59–60	1.0	$C_{10}H_{20}N_2$	16.66	16.65	CH_3Br	7.82	7.96	44.69	44.52	245–247
$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	3	95–98	0.5	$C_{14}H_{28}N_2$	12.50	12.34	CH_3Br	6.76	6.56	38.64	38.70	225–228
$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	3						HCl	9.42	9.40	23.61	23.57	245–246
$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2	80–85	0.5	$C_{14}H_{28}N_2$	12.50	12.40	CH_3Br	6.76	6.82	38.64	38.91	234–236
$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2				0		HCl	9.42	9.48	23.61	23.57	235–237
Pyrrolidino	Pyrrolidino	1	3	150–151	3.0	$C_{14}H_{24}N_2$	12.72	12.67	CH_3I	5.75	5.45	50.19	49.96	132–134
Pyrrolidino	Pyrrolidino	1	3						CH_3Br	6.82	6.78	39.02	39.41	120–122
Pyrrolidino	Pyrrolidino	1	3						C_2H_5Br	6.11	5.94	34.93	34.72	158–160
Pyrrolidino	Pyrrolidino	2	2	146–150	2.0	$C_{14}H_{24}N_2$	12.72	12.71	CH_3Br	6.82	6.74	39.02	39.09	234–235
Pyrrolidino	$(CH_3)_2N$	1	3	80–82	0.2	$C_{12}H_{22}N_2$	14.43	14.51	CH_3Br	7.29	7.11	41.66	42.06	172–173
Pyrrolidino	$(C_2H_5)_2N$	1	3	89–91	0.15	$C_{14}H_{26}N_2$	12.61	12.50	CH_3Br	6.79	6.66	38.83	39.08	183–185
Morpholino	Morpholino	1	3	163–164		$C_{14}H_{24}N_2O$	11.11	11.06	CH_3Br[e]	6.33	6.09	36.19	35.91	227–229[d]
Morpholino	Morpholino	1	3						HCl	8.61	8.50	21.85	21.64	213–215
Morpholino	$(CH_3)_2N$	1	3	74–77	0.01	$C_{12}H_{22}N_2O$	13.33	13.25	CH_3Br	7.00	6.91	40.00	40.12	218–219
Morpholino	Morpholino	2	2	110–112	0.03	$C_{14}H_{24}N_2O_2$	11.11	11.28						
Piperidine	Piperidine	1	3	160–162	1.1	$C_{16}H_{28}N_2$	11.29	10.99	CH_3Br	6.39	6.30	36.53	36.24	248–250
Piperidine	Piperidine	1	3						HCl	8.72	8.48	22.12	22.27	240–241
$[(CH_3)_2CH]_2N$	$[(CH_3)_2CH]_2N$	1	3	108–110	0.2	$C_{18}H_{36}N_2$	10.00	10.12	CH_3Br	5.95	5.89	34.40	34.69	198–199
3-$CH_3NC_5H_9$–[b]	$(CH_3)_2N$	0	1	70–73	1.5	$C_{11}H_{20}N_2$	15.55	15.37	CH_3Br	7.56	7.22	43.24	43.10	207–209
3-$CH_3NC_5H_9$[b]	$(CH_3)_2N$	0	1						HCl	11.06	10.95	28.06	27.81	201–203
$3CH_3NC_5H_9$[b]	$(C_2H_5)_2N$	0	1	86–88	0.05	$C_{13}H_{24}N_2$	13.46	13.16	CH_3Br	7.04	6.80	40.20	40.58	214–216
$3CH_3NC_5H_9$[b]	$(C_2H_5)_2N$	0	1						C_2H_5Br	6.28	6.15	35.87	35.48	80–85[g]
$3CH_3NC_5H_9$[b]	Morpholino	0	1	105–107	0.04	$C_{13}H_{22}N_2O$	12.61	12.51	CH_3Br	6.79	6.67	38.83	38.74	212–213
$3CH_3NC_5H_9$[b]	Pyrrolidino	0	1	95–98	.5	$C_{14}H_{24}N_2$	12.72	12.52	CH_3Br	7.07	6.85	40.40	40.96	229–230
$3CH_3NC_5H_9$[b]	Morpholino	1	1	107–110	.07	$C_{14}H_{24}N_2O$	11.86	11.81	CH_3Br	6.57	6.36	36.68	36.32	232–233
$3CH_3NC_5H_9$[b]	$(C_2H_5)_2N$	1	1	88–90	.3	$C_{14}H_{26}N_2$	12.61	12.42	CH_3Br	6.79	6.53	38.83	38.44	155–159[g]
$3CH_3NC_5H_9$[b]	Pyrrolidino	1	1	95–98	.5	$C_{14}H_{24}N_2$	12.72	12.32	CH_3Br	6.82	6.55	39.02	39.41	100–102[g]
$CH_3NC_5H_9$-3-O[i]	$(C_2H_5)_2N$	1	1	118–120	2.0	$C_{14}H_{26}N_2O$	11.76	11.50	CH_3Br	6.66	6.66	37.38	37.13	120–182
THIQ[c]	$(CH_3)_2N$	1	1						CH_3Br	6.71	6.56	38.30	38.25	206–207
THIQ[c]	Pyrrolidino	1	1						CH_3Br	6.31	6.21	36.07	36.24	203–204
THIQ[c]	Piperidino	1	1						CH_3Br	6.13	6.07	34.98	34.71	224–225
THIQ[c]	Morpholino	1	1						CH_3Br	6.08	6.02	34.80	34.60	219–220
THIQ[c]	$(CH_3)_2N$	1	2	140–142	0.4	$C_{16}H_{22}N_2$	11.57	11.36	CH_3Br	6.48	6.45	37.03	36.81	213–215
THIQ[c]	Pyrrolidino	1	2	145–147	.01	$C_{18}H_{24}N_2$	10.45	10.49	CH_3Br	6.11	6.15	34.93	35.21	205–208
THIQ[c]	$(CH_3)_2N$	1	3	153–155	.4	$C_{17}H_{24}N_2$	10.93	10.90	CH_3Br	6.27	6.23	35.87	36.03	204–205

[a] Bis-quaternary ammonium or bis-acid addition salts. [b] N-Methyl-3-piperidyl. [c] 1,2,3,4-Tetrahydroisoquinolino. [d] Sealed tube. [e] Very hygroscopic. [f] Iodide, %. [g] Hygroscopic. [h] N-Methyl-2-pyrrolidylmethyl. [i] N-Methyl-3-piperidyloxy.

rically substituted bis-amino-3-hexynes were produced in high yield by the condensation of disodium acetylide—previously formed in liquid ammonia—with an aminoalkyl halide in refluxing toluene.



Structure–Activity Relationships.—The acetylenic diamines were submitted in the form of their salts for pharmacologic testing. The compounds were administered intravenously and intraduodenally to the nembutalized, normotensive dog. The structure–activity data are summarized in Table II.

In the 2-pentyne series, the bis-pyrrolidino, bis-diethylamino and 1-pyrrolidino-5-dimethylamino derivatives (nos. 6, 3 and 8) provided the most potent derivatives. Compound 3 was the most effective and longest-acting hypotensor of the entire series and its favorable activity was confirmed by Buckley and his co-workers.[21] In the hexyne series, maximum potency and duration of action was displayed by those compounds which bore the dimethylamino, diethylamino and pyrrolidino substituents (nos. 10, 12, 13, 17, 20, 21 and 25). In certain instances, the position of the triple bond had a marked influence on the hypotensive properties of the two isomers (nos. 10 *vs.* 12, 13 *vs.* 15). Many of the compounds were more active and longer-acting than the two parent substances, pentolinium and hexamethonium, especially when compared by the intraduodenal route. The acid addition and propargyl halide salts were devoid of activity.

(21) F. M. Schalit, J. P. Buckley, W. S. Hudak, J. J. DeFeo and E. C. Reif, *J. Am. Pharm. Assoc.*, **46**, 598 (1957).

TABLE II

$Am_1(CH_2)_mC{\equiv}C(CH_2)_nAm_2 \cdot 2RX$

No.	Am_1	Am_2	m	n	RX	Blood p. lowering, % I.v. dose 1.0 mg./k.	Blood p. lowering, % I.d. dose[a] 10 mg./kg.	Duration,[b] min. Iv.	Duration,[b] min. I.d.
1	$(CH_3)_2N$	$(CH_3)_2N$	1	1	CH_3Br	−94[c]	..	4	..
2	Pyrrolidino	Pyrrolidino	1	1	CH_3I	− 9	0	6	..
3	$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	2	CH_3Br	−66		80	
						−40[d]	54	120[d]	110
4	$(C_2H_5)_2N$	$(C_2H_5)_2N$[f]	1	2	C_2C_3Br	−19	..	30	..
5	$[(CH_3)_2CH]_2N$	$[(CH_3)_2CH]_2N$	1	2	CH_3Br	− 4	..	10	..
6	Pyrrolidino	Pyrrolidino	1	2	CH_3Br	−23	−30	100	200
7	Morpholino	Morpholino	1	2	CH_3Br	−15	−12	40	90
8	Pyrrolidino	$(CH_3)_2N$	1	2	CH_3I	−59	−50	240	105
9	$OClCH_2N(CH_3)$-	$(C_2H_5)_2N$	1	2	CH_3I	−22	−21	140	120
10	$(CH_3)_2N$	$(CH_3)_2N$	1	3	CH_3Br	−26	−18	30	120
11	$(CH_3)_2N$	$(CH_3)_2N$	1	3	HCl	0	−25	0	210
12	$(CH_3)_2N$	$(CH_3)_2N$	2	2	CH_3Br	−47	..	100	..
13	$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	3	CH_3Br	−31	−23	75	90
14	$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	3	HCl	0	..	0	..
15	$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2	CH_3Br	−13	..	45	..
16	$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2	HCl	0	..	0	..
17	Pyrrolidino	Pyrrolidino	1	3	CH_3I	−52	−16	120	150
18	Pyrrolidino	Pyrrolidino	1	3	CH_3Br	−17	..	100	..
19	Pyrrolidino	Pyrrolidino	1	3	C_2H_3Br	−18	..	15	..
20	Pyrrilidino	Pyrrolidino	2	2	CH_3Br	−39	−24	160	60
21	Pyrrolidino	$(CH_3)_2N$	1	3	CH_3Br	−38	−32	30	205
22	Pyrrolidino	$(C_2H_5)_2N$	1	3	CH_3Br	−11	..	10	..
23	Morpholino	Morpholino	1	3	CH_3Br	−26	−17	100	200
24	Morpholino	Morpholino	1	3	HCl	0	..	0	..
25	Morpholino	$(CH_3)_2N$	1	3	CH_3Br	−30	−26	90	105
26	Piperidine	Piperidine	1	3	CH_3Br	−20	− 9	70	60
27	$[(CH_3)_2CH]_2N$	$[(CH_3)_2CH]_2N$	1	3	CH_3Br	−45[e]	..	40	..
	Hexamethonium					−34	−15	13	60
	Pentolinium					−20	− 6	75	65
28	3-$CH_3NC_5H_9$-[f]	$(CH_3)_2N$	0	1	CH_3Br	−11	..	12	..
29	3-$CH_3NC_5H_9$-[f]	$(CH_3)_2N$	0	1	HCl	0	..	0	..
30	3-$CH_3NC_5H_9$-[f]	$(C_2H_5)_2N$	0	1	CH_3Br	−34	−22	30	180
31	3-$CH_3NC_5H_9$-[f]	$(C_2H_5)_2N$[f]	0	1	C_2H_3Br	− 8	..	30	..
32	3-$CH_3NC_5H_9$[f]	Morpholino	0	1	CH_3Br	−30	−22	100	180
33	3-$CH_3NC_5H_9$[f]	Pyrrolidino	0	1	CH_3Br	−42	−23	30	210
34	3-$CH_3NC_5H_9$[g]	Morpholino	1	1	CH_3Br	−17	..	4	..
35	3-$CH_3NC_5H_9$[g]	$(C_2H_5)_2N$	1	1	CH_3Br	−15	0	2	0
36	3-$CH_3NC_5H_9$[g]	Pyrrolidino	1	1	CH_3Br	0	0	0	0
37	$CH_3NC_5H_9$-3-O[h]	$(C_2H_5)_2N$	1	1	CH_3Br	−19	..	1	..
38	THIQ[i]	$(CH_3)_2N$	1	1	CH_3Br	−18	..	15	..
39	THIQ[i]	Pyrrolidino	1	1	CH_3Br	−34	..	30	..
40	THIQ[i]	Piperidino	1	1	CH_3Br	−18	..	10	..
41	THIQ[i]	Morpholino	1	1	CH_3Br	−14	..	15	..
42	THIQ[i]	$(CH_3)_2N$	1	2	CH_3Br	−50	−45	270	112
43	THIQ[i]	Pyrrolidino	1	2	CH_3Br	..	−28	..	105
44	THIQ[i]	$(CH_3)_2N$	1	3	CH_3Br	−29	−32	30	120
45	IN-243[j]					−44	−24	110	90
						−11[d]		100	

[a] Intraduodenal. [b] The "duration" of action figures cannot be taken as absolute values. In some instances the b.p. had come back to normal, in other cases the experiment had to be discontinued with the b.p. still at its lowest point because additional anesthesia would have had to be administered. Usually, with the longer-acting (>60 minutes) hypotensives b.p. was still reduced substantially at the end of the experiment. [c] Precipitous, acetylcholine-like blood pressure drop which could be prevented by the prior administration of 1.0 mg./kg. of atropine. [d] I.v. dose = 0.3 mg./kg. [e] I.v. dose = 2.0 mg./kg. [f] N-Methyl-2-pyrrolidylmethyl. [g] N-Methyl-3-piperidyl. [h] N-Methyl-3-piperidyloxy. [i] 1,2,3,4-Tetrahydroisoquinolino. [j] N-(3'-Dimethylaminopropyl)-1,2,3,4-tetrahydroisoquinoline dimethobromide (Irwin, Neisler and Co.).[20]

To test the effect of chain length on the hypotensive activity, some diamino-butyne derivatives were synthesized. Compound 1, 1,4-dimethylamino-2-butyne dimethobromide, was of particular pharmacologic interest, since it elicited a profound but fleeting acetylcholine-like hypotensive response which could be blocked by the prior administration of atropine. This compound also produced copious salivation in the dog and thus appears to be a potent parasympathetic stimulant. Hence, a dramatic reversal in pharmacologic behavior is observed in going from the four to the five-carbon bis-

aminoalkynes. Everett, *et al.*,[22] have described the potent parasympathomimetic properties of 1,4-bis-pyrrolidino-2-butyne (Tremorine) which also produced Parkinson-like symptoms in animals.

To test the effect of two triple bonds on hypotensive activity, we prepared the dimethiodide of 1,6-bis-morpholino-2,4-hexadiyne. This compound was devoid of any hypotensor effect in the doses tested. Since the corresponding 2-hexyne derivative (no. 23) produced a fair blood pressure lowering response, it would appear that total rigidity or maximum extension of the carbon chain is detrimental to hypotensive activity.

Since the more potent hypotensors were found in the pentyne series (nos. 3 and 8) the five-carbon chain apparently represents the optimum inter-nitrogen distance for maximum blood pressure lowering activity.

Phillips[15] published an interesting paper on a series of 3-(4′-aminobutyl)-piperidines (III) which displayed potent ganglionic blocking and hypotensive properties in anesthetized cats both in the forms of their quaternary ammonium and tertiary or secondary amine acid addition salts. The introduction of an acetylenic bond into several of these derivatives (IIIa) (nos. 34–36) produces a weak and fleeting hypotensive response in the dog at the doses tested. The hydrochloride salts were inactive. However, the related 2-(4′-amino-2-butynyl)-pyrrolidine series (IVa) yielded three potent and long-acting hypotensive agents (nos. 30, 32 and 33).

In a series of N-(ω-ammonium alkyl)-1,2,3,4-tetrahydroisoquinolines,[22] the three-carbon chain was reported to be critical for optimum hypotensive activity.[16] This evidence appeared to be borne out by the weak hypotensive properties of the corresponding butynyl derivatives (nos. 38–41), but was reversed sharply for the next higher homologs, the pentynyl and hexynyl compounds (nos. 42–44), which were among the most potent hypotensors described in this paper. Compound 42 elicited a biphasic blood pressure drop which is said to be indicative of a prolonged central hypotensive effect.[16]

Conclusion.—The introduction of an acetylenic function into three types of "bis-onium" hypotensive agents produced derivatives which were superior, in many instances, to the saturated parent substances with respect to (1) potency, (2) duration of action and (3) ease of absorption from the gastrointestinal tract when tested in the anesthetized, normotensive dog. Like the saturated analogs they owe their hypotensive effect, at least in part, to their ganglionic blocking properties.

Acknowledgment.—We wish to thank Dr. H. L. Friedman for his many helpful suggestions and Dr. H. L. Daiell for his continued interest throughout the course of this project. We are indebted to Mr. Elmer F. Kluchesky for supplying the analytical data and to Mr. P. A. Nuhfer of the Pharmacology Division for the hypotensive data.

Experimental

The synthetic procedures used for the preparation of the various derivatives are illustrated by the following examples:

(22) G. M. Everett, L. E. Blockus, I. M. Sheppard and J. E. P. Toman, *Federation Proc.*, **15**, Pt. I, 420 (1956).

(1) **3-Amino-1-propynes. 3-Pyrrolidino-1-propyne.**—To 46.0 g. (0.60 mole) of pyrrolidine in 100 cc. of anhydrous ethyl ether was added with stirring 35.0 g. (0.30 mole) of propargyl bromide. The mixture was stirred at reflux for 12 hours. The ether solution was decanted from the oily pyrrolidine hydrobromide and the latter extracted three times with ether. The combined ether extracts were dried with potassium carbonate. The product was collected by distillation at 74–77° (85 mm.), yield 35.8 g. (95%). *Anal.* Calcd. for $C_7H_{11}N$: N, 12.84. Found: N, 12.52.

(2) **1,4-Bis-amino-2-butynes. 1,4-Bis-pyrrolidino-2-butyne.**—To 56 g. (0.80 mole) of pyrrolidine was added slowly with cooling 25 g. (0.20 mole) of 1,4-dichloro-2-butyne. The mixture was allowed to stand at room temperature for one hour and then diluted with 250 cc. of water. The aqueous solution was saturated with potassium hydroxide, extracted with ether and the ether extracts dried with potassium carbonate. The product was collected by fractional distillation *in vacuo*, b.p. 93–95° (0.1 mm.), yield 27 g. (72%).

(3) **Bis-amino-2-alkynes. 1,5-Bis-(N,N-diethylamino)-2-pentyne.**—To 31 g. (0.80 mole) of sodium amide in 100 cc. of toluene was added 100 g. (0.90 mole) of 3-diethylamino-1-propyne. The reaction mixture was brought gradually to the reflux temperature and refluxing continued until the copious evolution of ammonia had ceased. To the hot mixture was added 135 g. (1.0 mole) of β-diethylaminoethyl chloride; stirring and refluxing were continued for 16 hours. The reaction mixture was cooled to room temperature and the salts dissolved by the addition of 250 cc. of water. The toluene layer was separated and extracted repeatedly with dilute aqueous hydrochloric acid. The acid extracts were washed with ether and then treated with solid potassium hydroxide until two well-defined layers appeared. The alkaline mixture was extracted with ether, the ether extracts dried with potassium carbonate and the product collected by fractional distillation, b.p. 85–90° (1.5 mm.), yield 122 g. (73%).

1-Pyrrolidino-6-dimethylamino-2-hexyne.—To 117 g. (3.0 moles) of sodium amide was added 327 g. (3 moles) of 3-pyrrolidino-1-propyne. The mixture was stirred and refluxed for two hours and then treated with 430 g. (3.5 moles) of 3-dimethylaminopropyl chloride; stirring and refluxing were continued for 16 hours. The product was worked up as described in the foregoing example, b.p. 93–95° (0.30 mm.), yield 420 g. (70%); $n^{20}D$ 1.4746.

(4) **Bis-amino-3-hexynes. 1,6-Bis-(N,N-diethylamino)-hexyne.**—To 39 g. of sodium amide in 2 liters of liquid ammonia was added acetylene until the color of the reaction mixture changed. Stirring was continued for another half-hour and 136.5 g. (1.0 mole) of diethylaminoethyl chloride in 150 cc. of toluene added. The mixture was allowed to reflux with stirring for one hour, and the ammonia allowed to evaporate. When all the ammonia had evaporated, the mixture was stirred with reflux for 20 hours. To the cooled reaction mixture was then added 250 cc. of water to dissolve the solids. The toluene layer was extracted with three 150-cc. portions of dilute aqueous hydrochloric acid. The aqueous acid solution was washed with ether and the ether washings discarded. The aqueous phase was saturated with solid potassium hydroxide and extracted with ether. The ether extracts were dried with potassium carbonate and the product collected at 80–85° (0.5 mm.), yield 100 g. (88%), $n^{20}D$ 1.4591.

(5) **2-(Aminobutynyl)-pyrrolidines. N-Methyl-2-(4′-diethylamino-2′-butynyl)-pyrrolidine.**—To 12 g. (0.3 mole) of sodium amide in 50 cc. of xylene was added 33 g. (0.3 mole) of 3-diethylamino-1-propyne. The mixture was refluxed for 1 hour and 70 g. (0.50 mole) of N-methyl-3-chloropiperidine added. Stirring and refluxing were continued for 20 hours. The reaction mixture was collected and 100 cc. of water added to dissolve the solids. The water layer was separated and the xylene extracted repeatedly with dilute hydrochloric acid. The aqueous acid extracts were washed with ether and saturated with solid potassium hydroxide. The alkylene mixture was extracted with ether, the ether extracts dried with potassium carbonate and the product collected at 86–88° (0.05 mm.), 80 g. (77%).

(6) **3-(Aminobutynyl)-piperidines. N-Methyl-3-(4′-morpholino-2-butynyl)-piperidine.**—To 12 g. (0.30 mole) of sodium amide in 75 cc. of toluene was added 38 g. (0.30 mole) of 3-morpholino-1-propyne. The mixture was refluxed for one hour and 89 g. of N-methyl-3-bromomethylpiperidine added. Stirring and refluxing were continued

for 16 hours. The product was worked up as described in the previous examples and collected by fractional distillation *in vacuo*, b.p. 107–110° (0.07 mm.), yield 17 g. (34%).

1,6-Bis-morpholino-2,4-hexadiyne Dimethiodide.—To 6.0 g. (0.025 mole) of 1,6-bis-morpholino-2,4-hexadiyne[23] in 50 cc. of acetone was added 7.0 g. (0.05 mole) of methyl iodide. The mixture was stirred and refluxed for 3 hours, cooled and the product separated by filtration; yield 12 g. (98%), m.p. 202–203°. Recrystallization from isopropyl alcohol did not alter the m.p. *Anal.* Calcd. for $C_{16}H_{26}I_2N_2O_2$: I, 47.68; N, 5.26. Found: I, 47.32; N, 5.08.

(7) Ammonium-2-butynyltetrahydroisoquinolinium Derivatives. N-(4-Diethylamino-2-butynyl)-1,2,3,4-tetrahydroisoquinoline Dimethobromide.—To 26.5 g. (0.125 mole) of 1,4-dibromo-2-butyne in 60 cc. of anhydrous benzene was added 6.1 g. (0.070 mole) of diethylmethylamine. An exothermic reaction took place with the formation of an insoluble oil. The benzene layer was decanted and the oil dissolved in 60 cc. of acetonitrile. To this solution was added 10.3 g. (0.070 mole) of N-methyl-1,2,3,4-tetrahydroisoquinoline. A brown oil precipitated which crystallized on further stirring. The crude precipitate was isolated by filtration and recrystallized from 450 cc. of isopropyl alcohol, yield 12 g., m.p. 200–201° dec.

(8) Aminoalkynyltetrahydroisoquinolines (THIQ). N-Propargyl-1,2,3,4-tetrahydroisoquinoline.—To 142 g. (1.42 moles) of 1,2,3,4-THIQ in 600 cc. of isopropyl alcohol was added 85 g. (0.80 mole) of propargyl bromide. The reaction mixture was refluxed with stirring for 2 hours, the precipitate removed by filtration and the filtrate subjected to fractional distillation. The product was collected at 85–86° (0.4 mm.), yield 102 g. (93%), $n^{25}D$ 1.5585. *Anal.* Calcd. for $C_{12}H_{13}N$: N, 8.18. Found: N, 8.07.

N-(5'-Dimethylamino-2-pentynyl)-1,2,3,4-tetrahydroisoquinoline.—To 0.50 mole of sodium amide in 100 cc. of xylene was added 86 g. (0.50 mole) of N-propargyl-1,2,3,4-THIQ and the mixture refluxed with stirring for one hour. To the refluxing solution was then added 1.0 mole of 2-dimethylaminoethyl chloride. Stirring and refluxing were continued for 16 hours. The product was isolated in the usual manner, b.p. 140–143° (0.6 mm.), yield 190 g. (79%).

(23) The Aldrich Co., Milwaukee, Wisc.

MILWAUKEE, WISC.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, LAKESIDE LABORATORIES, INC.]

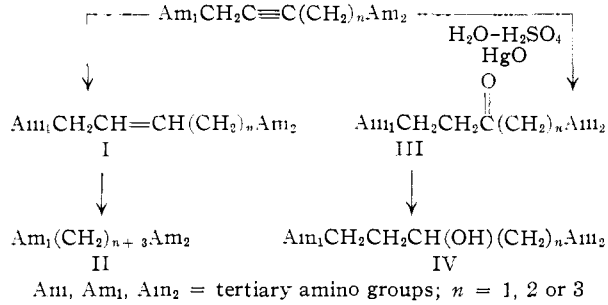
Hypotensives. III. Reaction Products of Acetylenic Diamines

BY JOHN H. BIEL AND FRANK DIPIERRO

RECEIVED APRIL 8, 1958

The availability of a series of acetylenic diamines made possible the convenient synthesis of symmetrical and unsymmetrical bis-aminoölefins (both *cis* and *trans*), unsymmetrical bis-aminoalkanes, bis-amino ketones and bis-amino alcohols. The hydration of the 2-alkynes produced the corresponding 3-alkanones which, as Mannich bases, often underwent partial elimination of one of the tertiary amino groups. The ketones were quite resistant to low pressure catalytic hydrogenation, but were smoothly reduced with sodium borohydride to the bis-amino alcohols. The influence of these structural characteristics on the hypotensive effect of the parent bis-aminoalkynes was studied. Partial as well as complete reduction of the triple bond markedly reduced hypotensive potency. The *trans*-bis-aminoölefins provided the more effective hypotensors, being distinctly superior to their *cis* isomers with regard to potency and duration of action. The introduction of a "keto" or "hydroxyl" function into the alkane chain decreased the hypotensive effect of the parent compounds.

In a previous paper[1] we described the synthesis and hypotensive properties of several series of acetylenic diamines. These compounds were not only potent pharmacologic agents in themselves, but also provided convenient starting materials for the facile preparation of difficultly available symmetrical and unsymmetrical diaminoölefins (I) (both *cis* and *trans*), unsymmetrical bis-aminoalkanes (II), bis-amino ketones (III) (Mannich bases) and bis-aminoalcohols (IV).



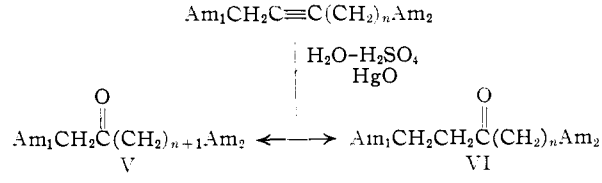
Am, Am_1, Am_2 = tertiary amino groups; n = 1, 2 or 3

The bis-aminoölefins were produced either by catalytic reduction of the corresponding acetylenes with a poisoned palladium catalyst[2] or by a chemical reduction with sodium in liquid ammonia. While the former method is said to yield the *cis* forms,[3] the latter one will produce the *trans* forms exclusively.[3-5] In each instance, the dimethobromide salts of the geometric isomers obtained from these two procedures had different melting points; the mixed melting points of the two isomers were depressed.

The bis-aminoalkanes were prepared readily by a Raney nickel reduction of the bis-aminoacetylenes at low pressures of hydrogen and room temperature.

Hydration of the acetylenic diamines with dilute aqueous sulfuric acid in the presence of a mercuric sulfate catalyst yielded the desired bis-amino-ketones. In most instances, it was undesirable to distil these ketones, since they partially deaminated at higher temperatures.

The hydration of the 2-alkyne derivatives could produce either the bis-amino-2-alkanones (V), or the isomeric bis-amino-3-alkanones (VI)



The partial elimination of one of the amino groups

(1) J. H. Biel and F. DiPierro, THIS JOURNAL, **80**, 4609 (1958).
(2) D. J. Cram and N. L. Allinger, *ibid.*, **78**, 2518 (1956).
(3) K. N. Campbell and B. K. Campbell, *Chem. Revs.*, **31**, 77 (1931).
(4) A. L. Henne and K. W. Greenlee, THIS JOURNAL, **65**, 2020 (1943).
(5) K. N. Campbell and L. T. Eby, *ibid.*, **63**, 216, 2683 (1911).