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

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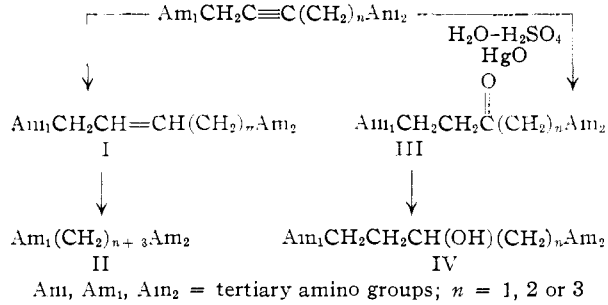
The availability of a series of acetylenic diamines made possible the convenient synthesis of symmetrical and unsymmetrical bis-aminoölefins (both *cis* and *trans*), unsymmetrical bis-aminoalkanes, bis-amino ketones and bis-amino alcohols. The hydration of the 2-alkynes produced the corresponding 3-alkanones 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).



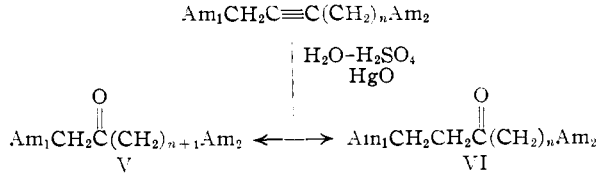
Am, Am_1, Am_2 = tertiary amino groups; n = 1, 2 or 3

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 (1941).

TABLE I

$Am_1(CH_2)_mCH{=}CH(CH_2)_nAm_2$

Am_1	Am_2	m	n	Isomer	B.p. °C.	B.p. Mm.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Salt	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, %[c] Calcd.	Halogen, %[c] Found	M.p., °C.
$(CH_3)_2N$	$(CH_3)_2N$	1	3	*cis*	58–60	1.0	$C_{10}H_{22}N_2$	16.47	16.37	CH_3Br	7.77	7.63	44.44	43.92	218–219
$(CH_3)_2N$	$(CH_3)_2N$	1	2	*cis*						CH_3Br[a]	8.09	8.00	46.24	46.70	233–235
$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	2	*cis*	68–71	0.2	$C_{18}H_{38}N_2$	13.20	13.13	CH_3Br	6.96	6.80	39.80	39.58	225–227
$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	2							CH_3Br[a]	6.96	6.95	39.80	39.77	225–227
$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	2	*trans*	70–72	0.2	$C_{18}H_{38}N_2$	13.20	12.87	CH_3Br	6.96	6.78	39.80	39.65	220–222
Morpholino	Morpholino	1	2	*cis*	115–118	.03	$C_{18}H_{34}N_2O_2$	11.66	11.62	CH_3Br	6.51	6.40	37.20	37.69	224–225
Morpholino	Morpholino	1	2	*trans*	115–118	.03	$C_{18}H_{34}N_2O_2$	11.66	11.55	CH_3Br	6.51	6.35	37.20	37.42	214–216
Pyrrolidino	Pyrrolidino	1	3	*cis*	95–97	.01	$C_{14}H_{26}N_2$	12.61	12.34	CH_3Br	6.79	6.64	38.83	38.12	145–147
Pyrrolidino	Pyrrolidino	1	3	*trans*	102–105	.02	$C_{14}H_{26}N_2$	12.61	12.32	CH_3Br	6.79	6.57	38.83	38.86	138–141
Pyrrolidino	$(CH_3)_2N$	1	2	*cis*	64–66	.01	$C_{11}H_{22}N_2$	15.38	15.20	CH_3Br	7.52	7.34	43.01	43.74	265–266
Pyrrolidino	$(CH_3)_2N$	1	2	*trans*	65–67	.01	$C_{11}H_{22}N_2$	15.38	15.18	CH_3Br	7.52	7.51	43.01	43.23	255–257
Pyrrolidino	$(CH_3)_2N$	1	3	*cis*	73–75	.1	$C_{12}H_{24}N_2$	14.28	14.25	CH_3Br	7.25	7.26	41.45	41.39	247–249
Pyrrolidino	$(CH_3)_2N$	1	3	*trans*	63–65	.05	$C_{12}H_{24}N_2$	14.28	14.35	CH_3Br	7.25	7.25	41.45	41.95	236–237
Morpholino	$(CH_3)_2N$	1	3	*cis*	74–77	.01	$C_{12}H_{24}N_2O$	13.20	13.09	CH_3Br	6.96	6.83	39.80	39.57	185–187
Morpholino	Morpholino	1	3	*cis*	123–126	.03	$C_{14}H_{26}N_2O_2$	11.02	10.75	CH_3Br[a]	6.23	6.13	36.03	36.65	227–229
Morpholino	Morpholino	1	3	*trans*	123–126	.03	$C_{14}H_{26}N_2O_2$	11.02	10.76	CH_3Br	6.23	6.11	36.03	35.79	213–215
1,2,3,4-THIQ[b]	$(CH_3)_2N$	1	2	*cis*	129–132	.15	$C_{16}H_{24}N_2$	11.47	11.43	CH_3Br[a]	6.45	6.31	36.86	36.54	222–224
1,2,3,4-THIQ	$(CH_3)_2N$	1	2	*trans*	133–135	.2	$C_{16}H_{24}N_2$	11.47	10.92	CH_3Br	6.45	6.26	36.86	36.58	217–219
Pyrrolidino	Pyrrolidino	2	2	*cis*						CH_3Br[a]	6.79	6.77	38.83	38.80	254–256
$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2	*cis*						CH_3Br[a]	6.73	6.63	38.46	38.71	256–258
Pyrrolidino	Pyrrolidino	1	1	*cis*						CH_3Br[a]	7.29	7.10	41.66	41.38	268–270
$(CH_3)_2N$	$(CH_3)_2N$	1	1	*cis*						CH_3Br[a]	8.43	8.31	48.19	48.10	278–280
$(CH_3)_2N$	$(CH_3)_2N$	2	2	*cis*						CH_3Br[a]	7.77	7.73	44.44	44.26	253–256

[a] Prepared by reduction of the bis-amino acetylenic dimethobromides. [b] THIQ = tetrahydroisoquinolino. [c] Accuracy of halogen assay, ±1%.

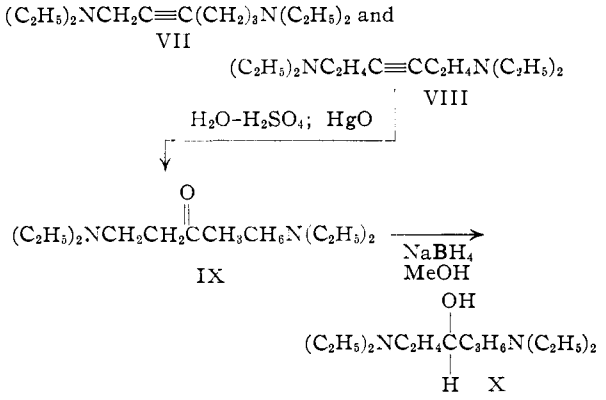
TABLE II

$Am_1(CH_2)_nAm_2$

Am_1	Am_2	n	B.p. °C.	B.p. Mm.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Salt	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found	M.p., °C.
$(CH_3)_2N$	$(CH_3)_2N$	6	58–61	1.0	$C_{10}H_{24}N_2$	16.27	16.25	CH_3Br	7.73	7.80	44.19	44.07	274–276
$(C_2H_5)_2N$	$(C_2H_5)_2N$	5	68–71	0.2	$C_{13}H_{30}N_2$	13.08	12.75	CH_3Br	6.93	6.91	39.60	39.67	259–261
Morpholino	Morpholino	5	114–117	.03	$C_{13}H_{26}N_2O_2$	11.57	11.36	CH_3Br	6.48	6.48	37.03	37.35	239–241
Morpholino	Morpholino	6	125–127	.03	$C_{14}H_{28}N_2O_2$	10.93	10.75						
Pyrrolidino	Pyrrolidino	6	103–105	.02	$C_{14}H_{28}N_2$	12.50	12.40						
Pyrrolidino	$(CH_3)_2N$	5	64–66	.01	$C_{11}H_{24}N_2$	15.21	14.87	CH_3Br	7.48	7.35	42.78	43.45	264–265
Pyrrolidino	$(CH_3)_2N$	6	79–82	.2	$C_{12}H_{26}N_2$	14.14	14.16	CH_3Br	7.21	7.10	41.23	42.20	231–233
Morpholino	$(CH_3)_2N$	6	74–76	.01	$C_{13}H_{26}N_2O$	13.08	12.68	CH_3Br	6.93	6.75	39.60	39.17	243–245
1,2,3,4-THIQ[a]	$(CH_3)_2N$	5	140–142	.5	$C_{16}H_{26}N_2$	11.38	11.24	CH_3Br	6.42	6.20	36.69	36.38	227–230

[a] THIQ = tetrahydroisoquinolino.

pointed to the formation of the Mannich base VI in which β-elimination of the amino group would be expected. This assumption appeared to be justified in view of the fact that both the 1,6-bis-diethylamino-2-hexyne (VII) and 1,6-bis-diethylamino-3-hexyne (VIII) yielded the identical bis-diethylamino hexanone (IX) and bis-diethylamino hexanol (X) on hydration followed by reduction of the respective ketones with sodium borohydride in methanol.



In the light of the above evidence we conclude that the hydration of the bis-amino-2-alkynes, prepared by us, presumably leads to the formation of the 3-keto derivatives. The synthesis of tertiary 1-amino-3-heptanones *via* the hydration of the 1-amino-2-heptynes has been reported by Koulkes[6] who similarly concluded that the amino group directs the incoming hydroxyl ion into the 3-position of the carbon chain.

It should be mentioned here that the diamino ketones were quite resistant to low pressure, catalytic reduction with platinum oxide or palladium-on-charcoal. However, the hydrogenation of these ketones proceeded smoothly with sodium borohydride in methanol.

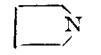
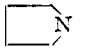
Structure–Activity Relationships.—The bis-amino derivatives of the above alkenes, alkanes, alkanones and alkanols were submitted in the form of their bis-quaternary ammonium bromides for pharmacologic testing. The compounds were administered intravenously and intraduodenally to the nembutalized, normotensive dog. The structure–activity data are summarized in Table IV.

The bis-aminoölefins were generally inferior to their bis-aminoacetylene precursors[1] as hypotensive agents. Of the two geometric isomers, the *cis* forms were usually quite weak in their ability to lower blood pressure, whereas the *trans* forms in several instances approached the hypotensive activity of the acetylenic parent compounds (*cf.* no. 6, 10, 33). This is in line with the conclusions reached in our previous paper,[1] that the greater

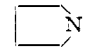
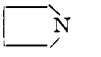
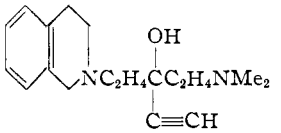
(6) M. Koulkes, *Bull. soc. chim. France*, 39 (1954).

TABLE III

$$Am_1(CH_2)_mC(=O)(CH_2)_nAm_2$$

Am_1	Am_2	m	n	B.p. °C.	Mm.	Formula	Nitrogen, % Calcd.	Found	Salt	Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	M.p., °C.
$(CH_3)_2N$	$(CH_3)_2N$	2	3	68–70	0.3	$C_{10}H_{22}N_2O$	15.04	14.84	CH_3Br	7.45	7.32	42.59	42.58	167–169
$(C_2H_5)_2N$	$(C_2H_5)_2N$[a]	2	3	95–98	.3	$C_{14}H_{30}N_2O$	11.57	11.66	HCl	8.88	8.53	22.53	22.40	168–169
$(C_2H_5)_2N$	$(C_2H_5)_2N$[b]	2	3	95–97	.3	$C_{14}H_{30}N_2O$	11.57	11.53	HCl	8.88	8.66	22.53	22.32	168–169
		2	3	107–108	.25	$C_{14}H_{26}N_2O$	11.76	11.76	HCl	9.00	8.82	22.82	22.32	176–177

$$Am_1(CH_2)_mCH(OH)(CH_2)_nAm_2$$

Am_1	Am_2	m	n	B.p. °C.	Mm.	Formula	Nitrogen, % Calcd.	Found	Salt	Nitrogen, % Calcd.	Found	Halogen, % Calcd.	Found	M.p., °C.
$(CH_3)_2N$	$(CH_3)_2N$	2	3	65–67	0.3	$C_{10}H_{24}N_2O$	14.89	14.60	CH_3Br	7.41	7.57	42.34	42.53	270–271
$(C_2H_5)_2N$	$(C_2H_5)_2N$[c]	2	3	102–104	.3	$C_{14}H_{32}N_2O$	11.47	11.26	CH_3Br	6.45	6.40	37.82	37.42	226–228
$(C_2H_5)_2N$	$(C_2H_5)_2N$[c]	2	3						HCl	8.83	8.79	22.39	22.09	176–177
$(C_2H_5)_2N$	$(C_2H_5)_2N$[d]	2	3	102–104	.3	$C_{14}H_{32}N_2O$	11.47	11.16	CH_3Br	6.45	6.39	37.82	37.81	226–228
$(C_2H_5)_2N$	$(C_2H_5)_2N$[d]	2	3						HCl	8.83	8.90	22.39	22.09	176–178
		2	3	131–133	.1	$C_{14}H_{28}N_2O$	11.66	11.41	CH_3Br	6.51	6.41	37.20	36.94	182–184
$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2	123–125	10.0	$C_{13}H_{30}N_2O$	12.17	11.85	HCl	9.24	9.26	23.43	23.19	199–200
$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2						CH_3Br	6.66	6.72	38.09	37.97	253–254
				110–112	.05	$C_{18}H_{26}N_2O$	9.79	9.68	CH_3Br	5.69	5.46	32.52	32.18	210–212

[a] Obtained from the hydration of 1,6-diethylamino-2-hexyne. [b] Obtained from the hydration of 1,6-diethylamino-3-hexyne. [c] Original starting material 1,6-bis-diethylamino-2-hexyne. [d] Original starting material 1,6-bis-diethylamino-3-hexyne.

rigidity conferred on the carbon chain by the insertion of an unsaturated linkage will allow the molecule to act in its more extended form. This increased inter-nitrogen distance appeared to be favorable to optimal blood pressure lowering properties. On the other hand, when this distance was reduced to its minimum value, as in the case of the diamino *cis*-alkenes, hypotensive activity was substantially lowered (no. 1 *vs.* 2; 5 *vs.* 6; 9 *vs.* 10).

Among the bis-aminoalkanes, only the unsymmetrically substituted N,N′-derivatives (no. 23 and 24) showed increased hypotensive potency over hexamethonium (no. 26) and pentolinium (no. 27).

The introduction of a carbonyl or hydroxyl function into the alkane chain to yield bis-amino alkanones and bis-aminoalkanols proved detrimental to hypotensive potency as well as the duration of the blood pressure lowering effect. Only one compound, 1,5-bis-diethylamino-3-pentanol dimethobromide (no. 33), showed a fair blood pressure reduction on intravenous as well as intraduodenal administration.

Ethinylation of the keto-diamines derived from two of the more potent acetylenic precursors yielded an inactive compound in one case (no. 34) and a potent and long-acting hypotensor in another (no. 35).

Conclusion.—Partial as well as complete reduction of some hypotensively potent acetylenic bis-ammonium derivatives resulted in compounds with reduced hypotensive properties. The *trans* isomers were, in most instances, superior to the corresponding *cis* forms. The introduction of "ketonic" or "hydroxyl" function proved detrimental to the blood pressure lowering effect.

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. We are indebted to Mr. P. A. Nuhfer of the Pharmacology Department for the hypotensive data.

Experimental

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

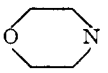
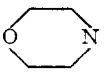
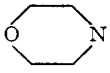
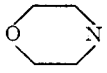
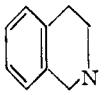
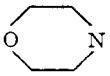
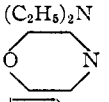
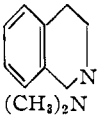
Diamino-*cis*-olefins. (1) ***cis*-1,5-Bis-diethylamino-2-pentene.**—An ethanolic solution containing 21.0 g. (0.10 mole) of the acetylene derivative and two drops of synthetic quinoline was subjected to hydrogenation at room temperature and 60 p.s.i. of hydrogen in the presence of 0.10 g. of 5% palladium-on-barium carbonate catalyst. The uptake of hydrogen ended abruptly after 0.10 mole of gas had been absorbed. The catalyst was removed by filtration and the product isolated by fractional distillation; b.p. 68–71° (0.20 mm.), yield 20 g. (94%).

1,5-Bis-diethylamino-2-pentene Dimethobromide.—To 10 g. (0.047 mole) of the olefin base in 50 cc. of isopropyl alcohol was added 8.9 g. (0.094 mole) of methyl bromide gas. The solid was isolated by filtration and recrystallized from ethanol, yield 18.2 g. (96%). This compound could also be obtained in identical yield and purity by the reduction of 1,5-bis-diethylamino-2-pentyne dimethobromide using the procedure outlined for the hydrogenation of the basic 2-alkyne compound.

Diamino-*trans*-olefins. (2) ***trans*-1,5-Bis-diethylamino-2-pentene.**—To 150 cc. of liquid ammonia was added 4.0 g. (0.16 mole) of sodium followed by the addition of 21 g. (0.10 mole) of 1,5-bis-diethylamino-2-pentyne. The mixture was stirred at room temperature for two hours. Ammonium nitrate was added to the disappearance of the blue color. After the addition of 50 cc. of concentrated ammonium hydroxide, the reaction mixture was extracted repeatedly with ether. The ethereal extracts were dried with potassium carbonate and the product collected by distillation, b.p. 70–71° (0.20 mm.), yield 20.8 g. (98%). **The dimethobromide** salt was prepared as described in the previous example.

Bis-aminoalkanes. (3) **1,5-Bis-diethylaminopentane.**—An ethanolic solution containing 21 g. (0.10 mole) of 1,5-bis-diethylamino-2-pentyne and 0.5 g. of Raney nickel catalyst was reduced at 60 p.s.i. of hydrogen and room

TABLE IV

No.	Am_1	Am_2	m	n	Isomer	B.p. lowering % I.v. dose 1.0 mg./kg.	I.d. dose 10.0 mg./kg.	Duration[b] min. I.v.	I.d.[a]
			$Am_1(CH_2)_mCH{=}CH(CH_2)_nAm_2 \cdot 2CH_3Br$						
1	$(C_2H_5)_2N$	$(C_2H_5)_2N$	1	2	*cis*	−19	− 8	105	100
2					*trans*		−24		120
3			1	3	*cis*	−21	−25	110	100
4					*trans*		−24		215
5		$(CH_3)_2N$	1	2	*cis*	−25	− 5	10	75
6					*trans*		−38		136
7		$(CH_3)_2N$	1	3	*cis*	− 9	− 6	60	85
8					*trans*	−15	−10	70	85
9			1	2	*cis*	− 8	− 9	60	90
10					*trans*	−20	−30	100	120
11			1	3	*cis*	−15	−12	25	70
12					*trans*		−33		300
13		$(CH_3)_2N$	1	2	*cis*	−15	−18	80	140
14					*trans*		−18		45
15	$(CH_3)_2N$	$(CH_3)_2N$	2	2	*cis*	0			
16	$(CH_3)_2N$	$(CH_3)_2N$	1	2	*cis*	0			
17			1	1	*cis*	−20	0	6	
18			2	2	*cis*	−12	−24	50	40
19	$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2	*cis*	−15	0	120	
20		$(CH_3)_2N$	1	3	*cis*	−16	0	110	
			$Am_1(CH_2)_mAm_2 \cdot 2CH_3Br$						
21	$(C_2H_5)_2N$	$(C_2H_5)_2N$	5			−22	−11	150	105
22		$(CH_3)_2N$	6			−23	−13	20	90
23		$(CH_3)_2N$	5			−61	−23	100	120
24		$(CH_3)_2N$	6			−28	−28	50	140
25		$(CH_3)_2N$	5			−25	−22	80	100
26	$(CH_3)_2N$ (Hexamethonium)	$N(CH_3)_2$	6			−34	−15	13	60
27	 (Pentolinium)		5			−20	− 6	75	65
28	$(C_2H_5)_2NCH_2C{\equiv}CC_2H_4N(C_2H_5)_2$					−66	−54	80	110
						−40[c]		120[c]	
29	$(CH_3)_2N$	$(CH_3)_2N$	2	3		−13		15	
			$Am_1(CH_2)_mCH(OH)(CH_2)_nAm_2 \cdot 2CH_3Br$						
30	$(CH_3)_2N$	$(CH_3)_2N$	2	3		−31		30	
31	$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	3		−15		10	
32			2	3		−28		45	
33	$(C_2H_5)_2N$	$(C_2H_5)_2N$	2	2		−26	−20	75	120

temperature until hydrogen uptake had stopped. The catalyst was removed by filtration and the product collected by fractional distillation, b.p. 68–71° (0.20 mm.), yield 20 g. (91%).

Bis-amino-ketones. (4) 1,6-Bis-diethylamino-3-hexanone.—To 60 cc. of a 1:1 aqueous sulfuric acid solution was added 3.0 g. of mercuric oxide. The mixture was heated to 60° and 22 g. (0.10 mole) of 1,6-bis-diethylamino-2-

TABLE IV (*continued*)

No.	Am_1	Am_2	m	n	Isomer	B.p. lowering, % I.v. dose 1.0 mg./kg.	I.d dose 10.0 mg./kg.	Duration[b], min. I.v.	I.d.[a]
					$Am_1(CH_2)_mC(OH)(C{\equiv}CH)(CH_2)_nAm_2 \cdot 2CH_3Br$				
34		$(CH_3)_2N$	2	3		0		0	
35		$(CH_3)_2N$	2	2		−28	−34	165	120

[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] I.v. dose = 0.30 mg./kg [d] Bis-maleate.

hexyne added dropwise with stirring. The temperature was held at 60° for 3 hours and the solution then poured onto crushed ice. After the addition of sufficient solid potassium hydroxide to produce two distinct layers, the alkaline mixture was extracted repeatedly with ether. The combined ether extracts were dried with potassium carbonate and the product collected by distillation, b.p. 95–100° (0.30 mm.), yield 15 g. (63%).

The hydrochloride salt was prepared in acetone with ethereal hydrochloric acid, m.p. 168–169°. The hydrochloride salt obtained from the hydration of the 1,6-bis-diethylamino-3-hexyne melted also at 168–169°; a mixed melting of the two hydrochlorides showed no depression, indicating that the hydration of either 1,6-diethylamino-2-hexyne or 1,6-diethylamino-3-hexyne yields the same ketone: 1,6-diethylamino-3-hexanone.

Bis-aminoalcohols. (5) 1,6-Bis-diethylamino-3-hexanol.—To 38 g. (1.0 mole) of sodium borohydride in 100 cc. of methanol was added dropwise 47 g. (0.20 mole) of the ketone described above. The mixture was heated on the steam-bath for one hour, poured on ice and acidified with dilute aqueous hydrochloric acid. The solution was concentrated, the residue dissolved in water and the solution treated with solid KOH until two layers appeared. The alkaline mixture was extracted with ether and the combined ether extracts dried with potassium carbonate. The product was collected by distillation, b.p. 102–104° (0.30 mm.), yield 32 g. (70%).

The dimethobromide salt was prepared in isopropyl alcohol, m.p. 226–228°. The sodium borohydride reduction of the ketone obtained from the hydration of the 3-hexyne derivative yielded the identical dimethobromide, m.p. 226–228°. A mixed m.p. of the two salts showed no depression. The two hydrochloride salts melted at 176–177° and 176–178°, respectively. A mixed m.p. showed no depression. This is additional proof for the identity of the 1,6-diethylamino-3-hexanone obtained from the two isomeric 2- and 3-alkynes.

Bis-amino-ethinylalcohols. (6) 1-Pyrrolidino-6-dimethylamino-3-ethinylhexan-3-ol.—In a 500-cc. 3-necked flask equipped with stirrer, Dry Ice condenser, gas inlet tube and dropping funnel was placed 200 cc. of liquid ammonia, 0.1 g. of ferric nitrate and 3.4 g. (0.15) of sodium. Tank acetylene, scrubbed with sulfuric acid and dried, was admitted until the theoretical amount had been added (color change: milky white solutions turn gray). To the sodium acetylide thus formed was added dropwise 30 g. (0.14 mole) of 1-pyrrolidino-6-dimethylamino-3-hexanone, the solution allowed to reflux for 2.5 hours at room temperature and then hydrolyzed with 100 cc. of ammonium hydroxide. The mixture was extracted with ether, the ether extracts dried with potassium carbonate and the product collected by distillation at 83–86° (0.1 mm.), yield 14 g. (50%). *Anal.* Calcd. for $C_{14}H_{26}N_2O$: N, 11.76. Found: N, 12.00.

MILWAUKEE 1, WISC.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Reaction of 2-Aminopyridine with α-Halo Ketones

BY ROGER ADAMS AND J. S. DIX[1]

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Unequivocal syntheses of 2-phenylimidazo[1,2-a]pyridine and 3-phenylimidazo[1,2-a]pyridine and their methyl analogs have been achieved. These results confirm structures previously assigned products of the reaction of 2-aminopyridine with α-halo ketones.

2-Aminopyridine is reported to react with an alkyl halide in two ways dependent upon whether the free base or a metallic salt of the aminopyridine is used. 2-Aminopyridine generally leads preponderantly to substitution on the ring nitrogen while sodium 2-aminopyridine leads only to amino group substitution.[2,3] The reaction of 2-aminopyridine with α-halo ketones generally has been assumed to follow a similar course and to proceed with substitution on the ring nitrogen. In the case of phenacyl bromide, the primary reaction product loses water with formation of a compound of structure III, 2-phenylimidazo[1,2-a]pyridine[4] (R = C_6H_5). However, the 2-substituted imidazo[1,2-a]pyridine structures previously assigned to this and analogous products were made questionable by the disclosure that the reaction of phenacyl bromide with either 2-aminopyridine or its lithium salt[5] resulted in the same compound. With the lithium salt the amino nitrogen would be expected to react, and thus upon cyclization 3-phenylimidazo[1,2-a]pyridine (VIII, R = C_6H_5) would be formed. The main product resulting from either procedure was

(1) University of Illinois Fellow, 1954–1955; Standard Oil of California Fellow, 1955–1957.

(2) T. M. Sharp, *J. Chem. Soc.*, 1855 (1939).

(3) I. A. Kaye, I. C. Kogon and C. L. Parris, THIS JOURNAL, **74**, 403 (1952).

(4) A. E. Chichibabin, *Ber.*, **59**, 2048 (1926).

(5) C. Djerassi and G. Pettit, THIS JOURNAL, **76**, 4470 (1954).