pyridinemethanols have been prepared. The antihistaminic activity of their dimethylaminoethyl ethers has been evaluated.

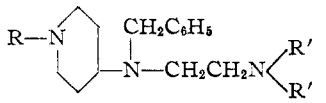
CINCINNATI, OHIO RECEIVED APRIL 23, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

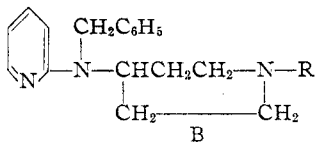
Histamine Antagonists. III. Derivatives of 4-Aminopiperidine

BY ROBERT H. REITSEMA AND JAMES H. HUNTER

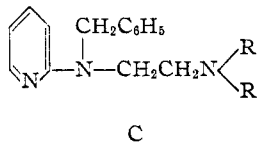
Certain 4-aminopiperidines have been prepared as potential antihistaminic agents based on their structural analogy to N,N-dialkyl-N'-benzyl-N'-(α-pyridyl)-ethylenediamines (C) which are known to have antihistaminic activity.[1] The 4-aminopiperidine group has been substituted for the α-aminopyridine group in type A and for the ethylenediamine group in type B.



A



B

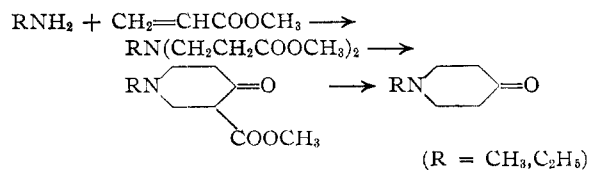


C

All of these new piperidine derivatives were shown to exhibit some activity against histamine-induced spasms in the isolated gut. The most effective member of this series, 1-ethyl-4-(N-benzyl-N-α-pyridylamino)-piperidine (VII), was three-fourths as active as β-dimethylaminoethyl benzohydryl ether hydrochloride.[2]

The majority of 4-aminopiperidines reported in the literature had been made from chelidonic acid derivatives.[3,4] Utilizing 1-ethyl-4-piperidone, Fuson, Parham and Reed[5] were able to prepare 1-ethyl-4-aminopiperidine by reductive amination. This latter method now has been extended to indicate its generality in the synthesis of secondary aminopiperidines.

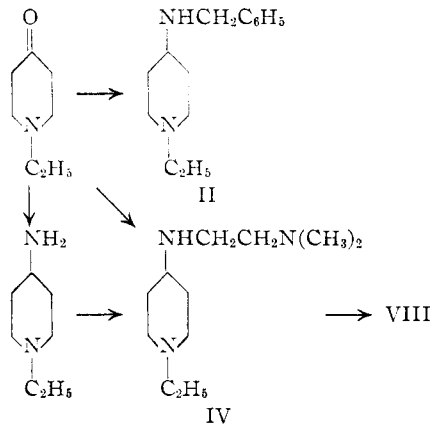
The condensation of methyl- and ethylamine with the methyl acrylate proceeded smoothly. Subsequent cyclization gave 1-methyl- and 1-ethyl-4-piperidone hydrochloride in high yields.



(R = CH_3,C_2H_5)

Reductive alkylation of primary amines with the piperidones yielded the substituted 4-aminopiperidines indicated in Table I.

These secondary amines were alkylated with benzyl bromide or α-bromopyridine to give tertiary amines of types A and B. Unsuccessful attempts were made to prepare 1-ethyl-4-(N-benzyl - N - dimethylaminoethylamino) - piperidine (VIII) by alkylation of the sodium salt or the Grignard derivative of II with β-dimethylaminoethyl chloride. Apparently the alkylation of the secondary amine proceeded so slowly that the halide was decomposed first. Condensation of IV with benzyl bromide proceeded satisfactorily. It was also possible to alkylate 1-ethyl-4-aminopiperidine with dimethylaminoethyl chloride to provide an alternate, though inferior, synthesis of the secondary amine, IV.



II

IV

The pyrrolidylethylamine required in the synthesis of V was obtained by reduction of pyrrolidylacetonitrile. It had been found that higher yields of N,N-dimethylethylenediamine were obtained by rapid reduction of the nitrile without solvent than were possible in the presence of methanolic ammonia. Consequently this method was also used for pyrrolidylacetonitrile although the use of ammonia with this more stable amine probably would have reduced the amount of the secondary amine and improved the yield.

Experimental[6]

bis-(β-Carbomethoxyethyl)-ethylamine.—By a procedure analogous to that used earlier,[5,7] from 135 g. (3.0

(1) Huttrer, *et al.*, THIS JOURNAL, **68**, 1999 (1946).

(2) We are indebted to Dr. Milton J. VanderBrook of our Pharmacology Department for carrying out these preliminary assays.

(3) Hahn, Cerkovnikov and Prelog, *Helv. Chim. Acta*, **26**, 1132 (1943).

(4) Cerkovnikov and Prelog, *Ber.*, **74B**, 1648, 1658 (1941).

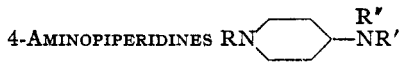
(5) Fuson, Parham and Reed, THIS JOURNAL, **68**, 1239 (1946).

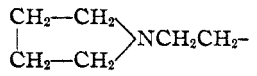
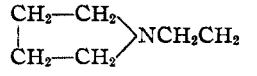
(6) Microanalyses by Mr. Harold Emerson and staff of these Laboratories.

(7) Mozingo and McCracken, "Organic Syntheses," **20**, 35 (1940).

TABLE I

4-AMINOPIPERIDINES



Compound	R	R′	R″	Yield,[a] %	B. p., °C.	Mm.	$n^{25}D$
I	CH_3–	$C_6H_5CH_2$–	H	56	168–172	17	1.5367
II	C_2H_5–	$C_6H_5CH_2$–	H	59	113–115	0.2	1.5263
III	C_2H_5–	$HOCH_2CH_2$–	H	50	117–119	17	1.4905
IV	C_2H_5–	$(CH_3)_2NCH_2CH_2$	H	58	136–139	17–18	1.4723
V	C_2H_5–		H	46	101–104	0.05	1.4883
VI	CH_3–	$C_6H_5CH_2$–	α-Pyridyl	54	185–187	0.4–0.5	
VII[b]	C_2H_5–	$C_6H_5CH_2$–	α-Pyridyl	34	188–194	0.3–0.6	
VIII	C_2H_5–	$(CH_3)_2NCH_2CH_2$–	$C_6H_5CH_2$	24	185–188	0.7	
IX[c]	C_2H_5–		$C_6H_5CH_2$	21	167–189	0.8	

[a] Yields are based upon crude piperidone hydrochloride. [b] Prepared as described for VI. [c] Prepared as described for VIII.

moles) of ethylamine and 550 g. (7.34 moles) of methyl acrylate there was obtained 606.9 g. (94%) of amine, b. p. 82° (0.4 mm.), $n^{20}D$ 1.4434.

Anal. Calcd. for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81. Found: C, 55.58; H, 8.92.

Amination of 1-Alkyl-4-piperidones.—1-Methyl- and 1-ethyl-4-piperidones, prepared from bis-(β-carbomethoxyethyl)-methyl- and ethylamine by the procedure of Fuson, Parham and Reed,[6] were treated with equimolecular amounts of the alkylamine while the solution was shaken and cooled below 25°. The solution then was diluted with absolute alcohol and reduced at room temperature in the presence of platinum oxide catalyst. About two hours were required for the usual 0.3 mole run. The catalyst was removed by filtration and the products indicated in Table I were obtained by distillation of the residue after removal of the solvent. Dissolving the residue in ether after removal of ethanol and drying before distillation was of little advantage. Redistillation was regularly performed on the products.

1-Ethyl-4-(β-dimethylaminoethylamino)-piperidine, IV.—To sodamide prepared from 13.8 g. (0.6 mole) of sodium was added 300 ml. of dry toluene and 38.4 g. (0.3 mole) of 1-ethyl-4-aminopiperidine.[5] The suspension was heated for one and one-half hours and allowed to cool. Then 43.2 g. (0.3 mole) of β-dimethylaminoethyl chloride hydrochloride was added with cooling. The black color changed rapidly to a light yellow. The mixture was boiled under reflux for eighteen hours. Excess sodamide was decomposed with ammonium chloride, then water, and an oily layer was salted out. The solution was extracted with ether and the combined ethereal extracts dried. After removal of solvent, the residue was fractionated to give 23.3 g. of crude 1-ethyl-4-aminopiperidine, b. p. 77–80° (16 mm.), and 7.7 g. of IV, b. p. 126–133° (15 mm.).

The melting point of the tripicrate of this product, m. p. 236–237° (dec.), was not depressed in admixture with the tripicrate of IV prepared by reductive amination of 1-ethyl-4-piperidone.

1-Methyl-4-(N-benzyl-N-α-pyridylamino)-piperidine (VI).—A mixture of 23.5 g. (0.115 mole) of 1-methyl-4-benzylaminopiperidine (I), 18.2 g. (0.115 mole) of α-bromopyridine, 15 g. of anhydrous potassium carbonate and 0.2 g. of copper bronze was heated with stirring at 170 ± 10° for forty-five hours. The mixture was cooled and 25 ml. of water was added. The copper was removed by filtration and the organic layer of the filtrate was separated. The aqueous layer was extracted with ether. The combined organic layers were dried and, after removal of ether, distilled at reduced pressure to give 18.4 g. (54%) of light yellow oil, b. p. 188–198° (0.3–0.5 mm.). In addition, 4.4. g. of starting amine was recovered. Redistillation of a sample of the product gave a fraction which boiled at 185–187° (0.4–0.5 mm.).

1-Ethyl-4-(N-benzyl-N-dimethylaminoethylamino)-piperidine (VIII).—To a mixture of 58.0 g. (0.291 mole) of

TABLE II

ANALYSES OF 4-AMINOPIPERIDINES

Compound	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	.....	$C_{13}H_{20}N_2$	76.42	76.74	9.87	9.49		
I Dipicrate	225.5–227 (dec.)	$C_{25}H_{26}N_8O_{14}$	45.32	45.27	3.96	4.08	16.91	16.56
II	.....	$C_{14}H_{22}N_2$	77.01	76.85	10.16	10.23	12.83	13.02
II Dipicrate	227–228 (dec.)	$C_{26}H_{28}N_8O_{14}$	46.16	46.17	4.17	4.14	16.56	16.47
II Dihydrochloride	303–304.5 (dec.)	$C_{14}H_{24}N_2Cl_2$[a]	57.73	57.71	8.31	8.22		
III Dipicrate	217–219 (dec.)	$C_{21}H_{26}N_8O_{14}$	40.00	40.01	4.16	4.02	17.77	17.98
III Benzoate·2HCl	235 (dec.)	$C_{16}H_{24}N_2O_2Cl_2$	55.01	55.06	7.50	7.58	8.02	7.66
IV Tripicrate	238.5–239 (dec.)	$C_{29}H_{34}N_{12}O_{21}$	39.28	39.75	3.86	3.95	18.96	18.57
V	.....	$C_{13}H_{27}N_3$	69.28	69.19	12.08	11.26	18.64	17.49
V Dipicrate	255 (dec.)	$C_{25}H_{33}N_9O_{14}$	40.79	41.06	3.98	3.99	18.42	17.26
VI	.....	$C_{18}H_{23}N_3$	76.83	76.86	8.26	7.66	14.93	14.84
VII Dipicrate	223–224.5 (dec.)	$C_{31}H_{31}N_9O_{14}$	49.40	49.71	4.15	3.96	16.73	16.59
VIII Tripicrate	193–195 (dec.)	$C_{35}H_{40}N_{12}O_{21}$	44.26	44.25	4.13	3.91	17.21	16.49
IX Tripicrate	198.6–200 (dec.)	$C_{38}H_{42}N_{12}O_{21}$	45.60	45.20	4.23	4.31	16.80	16.46

[a] Calcd.: Cl, 24.35. Found: Cl, 24.30, 24.65.

1-ethyl-4-(β-dimethylaminoethylamino)-piperidine (IV) in 500 ml. of xylene, 40.2 g. (0.291 mole) of potassium carbonate and 0.5 g. of copper powder was added 49.8 g. (0.291 mole) of benzyl bromide during thirty minutes. The suspension was stirred then for forty hours at 160 ± 10°. The mixture was worked up as above to give, in addition to 27 g. of a water and ether-insoluble oil, a fraction which boiled mainly at 185–188° (0.7 mm.) and solidified in the receiver. Attempts to obtain an analytically pure sample of this compound which recrystallized from ether, m. p. 99–100°, or of its hygroscopic hydrochloride were unsuccessful. The picrate prepared in ethanol was only very slightly soluble in ethanol or acetic acid but could be recrystallized from ethyl acetate. The tripicrate, m. p. 193–195° (dec.), was prepared in ethanol and recrystallized from ethyl acetate.

Pyrrolidylacetonitrile.—A solution of 208 g. (2.0 moles) of sodium bisulfite in 200 ml. of water was added to 142 g. (2.0 moles) of pyrrolidine at 25°. Then 162 g. (2.0 moles) of 37% aqueous formaldehyde was added with stirring and cooling below 30°. The temperature was raised to 60°, and 130 g. (2.0 moles) of potassium cyanide in 200 ml. of water was added with stirring during one-half to three-quarters hours. The milky solution was stirred at steam-bath temperature for six hours. After the solution was cooled the liquid was decanted and the wet organic layer of about 210 g. was separated. The aqueous layer was extracted four times with 200 ml. portions of ether and the combined organic layers dried over magnesium sulfate. By distillation 170.7 g. (77%) of pyrrolidylacetonitrile, b. p. 83° (17 mm.), was obtained. Redistillation of a sample gave a product which boiled at 86° (22 mm.), $n^{22.6}D$ 1.4558. The analysis of this material varied about 0.7% from the calculated value for carbon and hydrogen. The picrate, m. p. 153–154° (dec.), prepared from it analyzed for the picrate of pyrrolidylacetonitrile after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{13}N_5O_7$: C, 42.48; H, 3.86; N, 20.65. Found: C, 42.58; H, 3.80; N, 19.87.

β-Pyrrolidylethylamine.—Pyrrolidylacetonitrile, 165 g. (1.5 moles), was shaken in a bomb under hydrogen at 85° in the presence of 10 g. of Raney nickel catalyst. After five hours 81% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the residue was distilled at atmospheric pressure to give a forerun of 18.0 g., b. p. 158–161°, and 63.5 g. of the primary amine, b. p. 161° ± 2°. The dipicrate prepared from either fraction melted at 218–220° (dec.).[8]

Anal. Calcd. for $C_{18}H_{20}N_8O_{14}$: C, 37.77; H, 3.52; N, 19.58. Found: C, 38.02; H, 3.51; N, 18.67.

In addition to the primary amine the corresponding secondary amine, *bis*-pyrrolidylethylamine, was obtained, which upon redistillation boiled at 161° (17 mm.) and weighed 36.2 g.

Anal. Calcd. for $C_{12}H_{25}N_3$: C, 68.19; H, 11.92; N, 19.88. Found: C, 68.16; H, 11.28; N, 18.88.

Summary

1. The preparation of five 4-aminopiperidines by reductive alkylation is described.

2. The alkylation of these secondary amines with benzyl bromide or α-bromopyridine gave potential antihistamine agents.

3. 1-Ethyl-4-(N-benzyl-N-α-pyridylamino)-piperidine proved to be the most active of the compounds toward histamine induced spasms in the isolated gut.

4. An improved synthesis of pyrrolidylethylamine is given.

(8) Van Alphen (*Rec. trav. chim.*, **58**, 1105 (1939)) reported that pyrrolidylethylamine boiled at 166–167° and that its picrate melted at 219°.

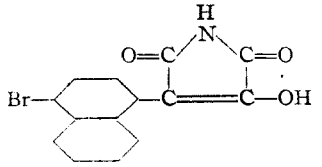
KALAMAZOO, MICHIGAN RECEIVED JUNE 21, 1948

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

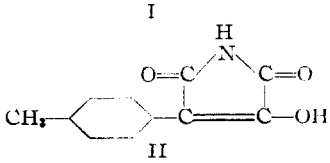
The Reaction of Bromine with Arylcyanopyruvic Esters

BY GLENN S. SKINNER, WILSON MCA. KLEIBACKER, RONALD ROSENBERG, JULES A. GLADNER AND STANLEY L. REED

In a previous report[1] it was shown that ethyl cyanophenylpyruvate reacts with bromine to yield *p*-bromophenylhydroxymaleimide. This work has been continued with the object of determining the result of the reaction when the α-naphthyl radical is substituted for the phenyl radical and also when ortho and para positions in the benzene nucleus are blocked. Typical products obtained are represented by the formulas

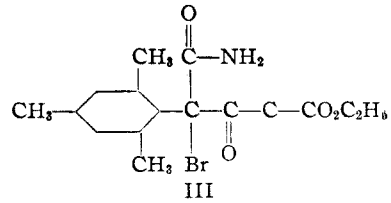


I



II

(1) Skinner, Coghlan and Berlin, THIS JOURNAL, **64**, 2600 (1942).



III

Ethyl cyano-α-naphthylpyruvate reacts similarly to yield 4-bromo-α-naphthylhydroxymaleimide (I). The ease with which this substance is purified indicates that it is the essential product of the reaction. Its identity was established by oxidation to 4-bromo-1-naphthoic acid. This result adds weight to the idea that the bromine first adds to the enol form and then rearranges to the ring. If substitution were the first step the purification should have been complicated by the formation of isomers due to the entry of bromine also in positions 5 and 8.

Although no *o*-bromophenylhydroxymaleimide was isolated from the reaction of bromine on ethyl cyanophenylpyruvate, one might predict that the