TABLE II

2- AND 2,6-SUBSTITUTED PIPERIDINES

Piperidine substituent	B. p. °C.	Mm.	d^{25}_4	$n^{25}D$	M_D Calcd.	M_D Found	Acetyl value[a]
2-Methyl	117–119		0.8341	1.4426	31.32	31.47	..
2-Benzyl[b]	268–269	738	.9660	1.5272	55.65	55.76	1.00
2-Phenylethyl[c]	131–132	6	.9540	1.5213	60.25	60.41	..
2-Carbethoxy[d]	93–94	11	1.0065	1.4547	42.39	42.33	1.00
2,6-Dimethyl[e]	127–129	742	0.8158	1.4366	36.20	35.92	1.00
2,6-Diphenyl[f]	193–194	10	.9507	1.5168	75.38	75.45	0.97
2,6-Diphenylethyl[g]	238–239	11	1.0063	1.5587	93.79	93.82	1.01
2,6-Dicarbethoxy[h]	155–156	11	1.0748	1.4581	58.06	58.18	1.04
2-Methyl-6-phenyl[i]	112–114	12	0.9096	1.4882	55.64	55.50	0.98

[a] Crook and McElvain, THIS JOURNAL, **52**, 4010 (1930). [b] *Cf.* Bailey and McElvain, *ibid.*, **52**, 1637 (1930). [c] *Cf.* Ref. 8. [d] *Cf.* Willstätter, *Ber.*, **29**, 390 (1896). [e] *Cf.* Marcuse and Wolffenstein, *ibid.*, **32**, 2528 (1899). [f] *Cf.* Scholtz, *ibid.*, **34**, 1621 (1901). [g] Shaw, *J. Chem. Soc.*, **125**, 2364 (1923), reports the boiling point of this compound as 290–295° (20 mm.). The compound used in the present work gave the following analyses. Calcd. for $C_{17}H_{17}N$: C, 85.94; H, 9.28. Found: C, 85.87; H, 8.98. [h] This compound does not appear to have been described previously. *Anal.* Calcd. for $C_{11}H_{19}O_4N$: C, 57.60, H, 8.35. Found: 57.70; 8.22. [i] *Cf.* Ref. 7.

tion. The residue was cooled in an ice-bath, covered with a layer of ether, and sufficient of a solution of 20% sodium carbonate added to make the water layer alkaline. The water layer was separated and extracted twice with small portions of ether. The ether was removed from the combined extracts by distillation. The remaining residue on distillation yielded 36 g. (90%) of 2,6-dipicolinic ester which boiled at 188–188.5° (12 mm.) and melted at 42–43°. This compound does not appear to have been described previously in the literature.

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 59.17; H, 5.87. Found: C, 59.20; H, 6.05.

Substituted Piperidines.—With the exception of 2-carbethoxypiperidine the substituted piperidines used were prepared by catalytic reduction of the corresponding pyridines as described in a recent paper by Adkins, Kuick, Farlow and Wojcik.[8] 2-Carbethoxypiperidine was prepared from picolinic acid hydrochloride by the same procedure as that previously used for ethyl nipecotate.[9] The properties of these various piperidines are listed in Table II.

Summary

The relative rates at which a number of 2- and 2,6-substituted piperidines react with *n*-butyl bromide have been determined.

(8) Adkins, Kuick, Farlow and Wojcik, THIS JOURNAL, **56**, 2425 (1934).

(9) McElvain and Adams, *ibid.*, **45**, 2745 (1923).

MADISON, WISCONSIN RECEIVED MAY 1, 1935

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

Quaternary Ammonium Salts from Bromopropyldialkylamines. V. Conversion of Cyclic Ammonium Salts to Linear Polymers

BY C. F. GIBBS AND C. S. MARVEL

Previous work[1] has shown that when an amine of the type $Br—(CH_2)_3—NR_2$ condenses with itself the course of the reaction is determined by the nature of the R groups. If R is a methyl group, linear polymerization occurs. If R is ethyl, *n*-propyl or *n*-butyl a four-membered ring is formed.

In the present investigation it has been observed that in very dilute solution (approximately 0.01 molar) gamma-bromopropyldimethylamine will react intramolecularly to give a cyclic quaternary ammonium salt.[2] This cyclic salt is quite different in physical properties from the polymeric salt which is formed when bromopropyldimethylamine is allowed to stand without a solvent or in concentrated solution. This cyclic salt is much less stable than are those in which the alkyl groups on the nitrogen are larger than methyl. When the monomeric salt is heated to 200° for a short time it is transformed into a linear polymeric salt with a molecular weight of about 3600.

$$n\left[(CH_2)_3{>}N\begin{matrix}CH_3\\CH_3\end{matrix}\right]^+ Br^- \xrightarrow{\text{heat}}$$

$$\left[Br(CH_2)_3—\left\{\begin{matrix}CH_3\\|\\N—(CH_2)_3\\|\\CH_3\end{matrix}\right\}_{n-1}—N(CH_3)_2\right]^+ Br^-_{n-1}$$

(1) (a) Gibbs, Littmann and Marvel, THIS JOURNAL, **55** 753 (1933); (b) Gibbs and Marvel, *ibid.*, **56** 725 (1934).

(2) Ruzicka, Salomon and Meyer, *Helv. Chim. Acta*, **17**, 882 (1934), have used the high dilution method to obtain hexadecamethyleneimine

The same change from the cyclic structure to the polymeric form takes place slowly if the solid salt stands for several weeks at room temperature. It is evident that the cyclic salt must be under sufficient strain so that some of the free bromoamine is formed by a reversal of the ring closure and that this amine then reacts to give the more stable polymeric salt.

The pure cyclic salts in which R is greater than methyl do not show this tendency to change into polymeric products. One sample of bromopropyldiethylamine was allowed to stand, and the diethyltrimethyleneammonium bromide which first formed was not separated from the reaction mixture. After six months the quaternary ammonium salt was isolated. This product proved to be polymeric with a molecular weight of about 10,800. Pure diethyltrimethyleneammonium bromide did not rearrange on standing for six months and, when heated above its melting point (175–178°), it decomposed without the formation of any appreciable polymeric material. The cyclic salts with R groups higher than ethyl have shown no indication of changing into polymeric products under the conditions which have affected the methyl and ethyl derivatives.

In the experimental part of this paper diisoamyltrimethyleneammonium bromide is described. Several new tertiary amines which were prepared in the course of this work are also characterized.

Experimental

Dimethyltrimethyleneammonium Bromide.—A solution of 11.5 g. of gamma-bromopropyldimethylamine in 7 liters of absolute alcohol was allowed to stand at room temperature. At the end of about forty hours, titration of a sample of the solution showed that all of the halogen had changed to the ionic form. The solution was concentrated to about 25 cc. under reduced pressure on a steam-bath. The concentrated solution was filtered and then several volumes of anhydrous ether were added. A white, deliquescent, crystalline solid was precipitated. The yield was 10.7 g.

Anal. Calcd. for $C_5H_{12}NBr$: Br, 48.18; mol. wt., 166. Found: ionic Br, 48.23; total Br, 48.33; mol. wt. (cryoscopic in water) 0.3889 g. subs., 30 g. H_2O, Δt 0.285; mol. wt., 84.5.

The salt gave a neutral solution in water. It decomposed at 240–250°, but this figure is really the decomposition point of the polymeric form, since heat causes rearrangement of the cyclic monomer to the linear polymer.

Polymerization of Dimethyltrimethyleneammonium Bromide.—A sample of dimethyltrimethyleneammonium bromide weighing 0.08 g. was heated in an oil-bath at 200° for three minutes. During the process a slight amount of sublimation occurred. The residue and the sublimate, however, were identical. The residue was non-crystalline, basic, insoluble in alcohol and no longer deliquescent. The solid was suspended in 3 cc. of hot alcohol, and barely enough water added dropwise to effect solution. The solid was then precipitated from solution by the addition of an excess (12 cc.) of anhydrous ether. The mixture was poured into a weighed centrifuge tube and centrifuged. The yield was 0.04 g. of a solid which decomposed slowly at 240–250°. This substance appeared to be identical with the polymer previously obtained by the spontaneous condensation of bromopropyldimethylamine.[1a]

Anal. Calcd. for $(C_5H_{12}NBr)_x$: Br, 48.18. Found: total Br, 47.96; ionic Br, 46.34; mol. wt. (calcd. from ratio of total and ionic bromine), 4980.

A 1.5-g. sample of dimethyltrimethyleneammonium bromide which had stood for two weeks at room temperature in a vacuum desiccator was found to be partially insoluble in alcohol. The insoluble portion, after two washings with absolute alcohol, weighed 0.01 g. It decomposed at 240–250°, and the other physical properties resembled those of the polymeric salts previously described.

Anal. Calcd. for $(C_5H_{12}NBr)_x$: Br, 48.18. Found: total Br, 48.07; ionic Br, 45.94; mol. wt. (calcd. from ratio of total and ionic bromine), 3652.

Polymerization of Diethyltrimethyleneammonium Bromide.—A sample of gamma-bromopropyldiethylamine was allowed to stand. In a short time the crystals of cyclic quaternary salt separated. But after about six months these had changed to a non-crystalline product which gave

TABLE I

PROPERTIES AND ANALYSES OF AMINES

-Amine	B. p. or m. p., °C.	Mm.	d^{20}	$n^{20}D$	Formula	Analyses	Calcd.	Found
γ-Phenoxypropyldiisobutyl-	B 149–150	5	0.9107_4	1.4891	$C_{17}H_{29}ON$	N	5.42	5.69
Chloroplatinate[a]	M 119–120	...	.....	....	$(C_{17}H_{29}ON)_2 \cdot H_2PtCl_6$	Pt	20.85	20.79
γ-Phenoxypropyldiisoamyl-	B 159–160	5	$.9083_{20}$	1.4881	$C_{19}H_{33}ON$	N	4.81	4.60
γ-Phenoxypropyldiallyl-	B 129–130	5	$.9633_{20}$	1.5169	$C_{15}H_{21}ON$	N	6.06	6.44
γ-Phenoxypropyldibenzyl-	B 215–217	2	1.0636_{20}	1.5804	.....	.....		...
Hydrobromide[b]	M 163–164	...	.....	....	$C_{23}H_{25}ON \cdot HBr$	Br	19.42	19.29
γ-Phenoxydecyldiethyl-	B 165–167	1	0.9182_{20}	1.4932	$C_{18}H_{31}ON$	N	4.59	4.89
γ-Phenoxydecyldi-*n*-butyl-	B 171–173	0.5	$.9008_{20}$	1.4875	$C_{24}H_{43}ON$	N	3.88	4.23
γ-Bromopropyldiisoamyl-	B 109–111	3	1.0325_{20}	1.4621	.....	.....		...
Chloroplatinate	M 159–160	...	.....	....	$(C_{13}H_{29}NBr)_2 \cdot H_2PtCl_6$	Pt	19.74	20.21

[a] Crystallized from dilute alcohol. [b] Crystallized from 50% alcohol.

a basic solution in water. The new product was insoluble in absolute alcohol and decomposed at 258–260°.

Anal. Calcd. for $(C_7H_{16}NBr)_x$: Br, 41.24. Found: total Br, 41.17; ionic Br, 40.44; mol. wt. (calcd. from ratio of total to ionic bromine) 10,864.

The cyclic salt which had been purified did not show signs of changing to the polymeric form over a long period of time. Heating the cyclic salt to its melting point (175–178°) did not change it into the polymeric form.

Diisoamyltrimethyleneammonium Bromide.—This cyclic salt was prepared from bromopropyldiisoamylamine by the method previously described for similar salts.[1b] After standing for one week without solvent, 6 g. of amine gave 3.5 g. of cyclic salt; m. p. 71–73°.

Anal. Calcd. for $C_{13}H_{28}NBr$: Br, 28.78. Found: Br, 28.94.

Miscellaneous Amines.—A number of tertiary amines have been prepared by methods analogous to those described for related compounds.[1] Their properties are listed in Table I.

The phenoxyamines other than the diisoamyl derivative could not be satisfactorily cleaved by hydrogen bromide to give the corresponding bromoamines.

Summary

γ-Bromopropyldimethylamine in very dilute solution reacts intramolecularly to give the crystalline cyclic salt dimethyltrimethyleneammonium bromide. At room temperature this cyclic quaternary ammonium salt rearranges slowly to the linear polymer previously described. Heating accelerates this rearrangement.

Impure diethyltrimethyleneammonium bromide will also rearrange to a polymeric salt, but this rearrangement proceeds less readily. No similar rearrangement to give polymeric salts has been observed when propyl, *n*-butyl and isoamyl groups are attached to the nitrogen atom.

A number of phenoxyalkyldialkylamines have been characterized.

URBANA, ILLINOIS RECEIVED MAY 6, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

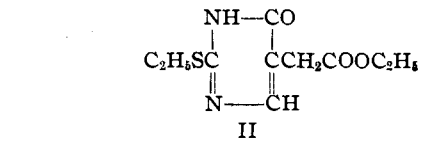
Researches on Pyrimidines. CXLVI. Synthesis of Uracil-5-methylamine

BY TREAT B. JOHNSON AND ANNE LITZINGER

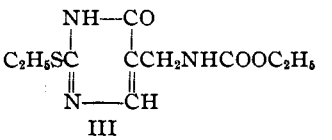
Of the different research programs now in progress in this Laboratory organized to develop the newer chemistry of purines and pyrimidines, our synthetic work dealing with the chemistry of thymine and its derivatives is of immediate interest on account of its bearing on the correct interpretation of the constitution of vitamin B_1. At the present time our knowledge of aliphatic chemistry as applied to the pyrimidine cycle is very limited. Side chain studies have thus far been restricted to very simple derivatives, and a research drive into this newer field promises to reveal information of immediate chemical and pharmacological interest.

We desire, therefore, to report in this preliminary paper, a successful application of a practical method for synthesizing the first aliphatic amine derivative of the uracil series to be described in the literature, namely, uracil-5-methylamine as represented by formula IV.[1] This is a true aliphatic amine, and bears a relationship to thymine corresponding to that existing between benzylamine and toluene. We believe that constructions of this type will prove to be of immediate interest in connection with the development of the newer chemistry of vitamin B_1. A pharmacological study of this new pyrimidine-amine and related compounds is now being carried on in the Department of Pharmacology of the Yale Medical School under the direction of Professor H. G. Barbour.[2]

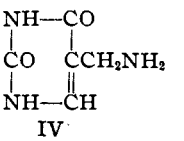
Our method of synthesizing this new amino derivative of thymine is based on the successful application of a Curtius reaction in the pyrimidine series. The starting point is the ethyl ester of 2-ethylmercapto-6-oxypyrimidine-5-acetic acid II,[3] which is easily converted into the corresponding urethan derivative represented by formula III.



II



III



IV

(1) A study of the chemistry of this interesting amine and its derivatives will be carried on in this Laboratory this coming year by Miss Anne Litzinger.

(2) This work will be partially supported by a special grant from the Research Committee of The American Medical Association.

(3) Johnson and Speh, *Am. Chem. J.*, **38**, 602 (1908).