

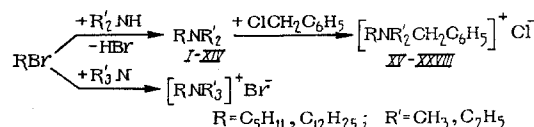
SYNTHESIS OF VARIOUS SALTS OF QUATERNARY
AMMONIUM BASES

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Because of their surface and biological activities, the salts of quaternary ammonium bases with a long aliphatic chain are widely used in biology, medicine, chemistry, and pharmacy.

During the course of work on the expansion of their use (in particular, in the study of the possibility of their use to separate neutral polysaccharides) a series of salts has been synthesized from the corresponding alkylbromides:



Aklylation of secondary amines with alkylbromides has been carried out by two methods. In the case of dimethylamine the method developed previously [1] was used with the difference that the reaction time was considerably shortened. With a 100% excess of dimethylamine the following reactions occur:

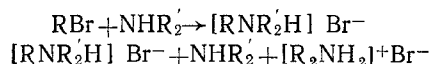


TABLE 1. Yield and Physical Constants of Tertiary Amines*

Com- pound	R	R'	Yield (%)		Boiling point (°C)	n _D
			methods [1-2]†	modified method		
I	C ₅ H ₁₁	CH ₃	—	32.4	121—2 (750 mm)	1.4092 (15°)
II	C ₆ H ₁₃	CH ₃	32.7	53.7	143—5 (755 mm)	1.4135 (21°)
III	C ₇ H ₁₅	CH ₃	41.9	85.7	167—8 (758 mm)	1.4191 (20°)
IV	C ₈ H ₁₇	CH ₃	61.3	87.4	193 (758 mm)	1.4242 (20°)
V	C ₉ H ₁₉	CH ₃	—	74.4	63—5 (5 mm)	1.4275 (22°)
VI	C ₁₁ H ₂₃	CH ₃	—	72.5	89—92 (3 mm)	1.4331 (20°)
VII	C ₁₂ H ₂₅	CH ₃	43.8	78.9	132—3 (8 mm)	1.4390 (20°)
VIII	C ₉ H ₁₁	C ₂ H ₅	55.2	92.0	156—7 (750 mm)	1.4188 (21°)
IX	C ₈ H ₁₃	C ₂ H ₅	—	68.8	177—8 (750 mm)	1.4247 (21°)
X	C ₇ H ₁₅	C ₂ H ₅	—	73.4	198—9 (760 mm)	1.4291 (18°)
XI	C ₈ H ₁₇	C ₂ H ₅	61.4	78.6	107—8 (17 mm)	1.4320 (20°)
XII	C ₉ H ₁₉	C ₂ H ₅	51.8	86.4	88—90 (5 mm)	1.4365 (17°)
XIII	C ₁₁ H ₂₃	C ₂ H ₅	—	99.0	111—3 (3 mm)	1.4387 (22°)
XIV	C ₁₂ H ₂₅	C ₂ H ₅	56.3	81.2	146—8 (7 mm)	1.4420 (20°)

*The physical constants of the tertiary amines prepared correspond to those presented in literature. No information on the synthesis of XIII could be found. Found, %: C 78.12; H 14.45; N 6.73. $C_{13}H_{29}N$. Calculated, %: C 78.31; H 14.66; N 7.02.

† The authors indicate yields of 47% [1] and 56% [2] for II and XIV, respectively.

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According to previously published methods [1-2] the precipitate (the salt of the secondary amine) is thrown away, and the tertiary amine is isolated from the solution. We have assumed that the relatively low yield of tertiary amine is explained by the fact that the second reaction does not proceed to a conclusion, and that the residue contains the tertiary amine salt as well as that of the secondary amine. In fact, treatment of the precipitate with alkali enabled us, after appropriate purification, to isolate an additional quantity of tertiary amine and to substantially increase the total yield.

For alkylation of diethylamine we used the method described in [2], with additional treatment of the residue as described above, and this also lead to an increase in the yield of tertiary amine (Table 1).

Reaction of alkylbromides with lower tertiary amines was carried out by the methods described in the literature [3-4]. The yield of quaternary ammonium salts was 46-81%.

In contrast to previous descriptions [1], the conversion of II-IV and VII to quaternary salts was carried out in an aqueous medium [5].

For conversion of I, V, VI, and VIII-XIV to quaternary salts, the method proposed for VII (in a benzene medium) was used [6]. The changes which we have introduced relate to the method of isolation of the salts. The organic solvent is driven off from the reaction mixture and the residue dissolved in water; the aqueous solution was washed several times with ether and evaporated to a thick syrup which, on cooling, was converted to a crystalline mass. With this method of purification the material losses are minimal and, besides this, it is possible to obtain a series of quaternary ammonium salts which were previously unknown in the crystalline form (Table 2).

Investigation of the compounds obtained in the I. M. Sechenov No. 1 Moscow Medical Institute has shown that compound XXI may be recommended for use in pharmacy as a preservative for eye drops [11] and grease bases [12, 13] (the Pharmacological Committee has decided in favor of the use of XXI as a preservative for ointments and this preservative has been provisionally entered in the pharmacopoeia), in surgery as an antimicrobial and antithrombogenic coating for artificial heart valves [1, 14], and in biochemistry for precipitation of neutral polysaccharides and separation of their mixtures [15, 16]. The recently published simple method of fractionation of starch to amylose and amylopectin using trimethylolctylammonium bromide [17, 18] is of great practical significance.

EXPERIMENTAL

Dimethylheptylamine (III)

In 20 g absolute ethanol we dissolved 17.9 g 1-bromoheptane. The quantity of absolute ethanol is determined by calculation so that saturation with dimethylamine gives a 45% solution. The solution obtained is cooled to 3-5°C and saturated at this temperature with dry dimethylamine to give an increase in weight of 9 g. The reaction mixture is kept in a closed flask at room temperature where spontaneous heating of the solution occurs and a white crystalline precipitate is formed. After 7 h a sample is taken (the supernatant liquid

TABLE 2. Quaternary Ammonium Salts

Compound	R	R'	Melting point (°C)	Found (%)		Empirical formula	Calculated (%)	
				N	Cl		N	Cl
XV*	C ₈ H ₁₁	CH ₃	119,0-20,0	14,64	5,54	C ₁₁ H ₂₄ ClN	15,07	5,79
XVI*	C ₆ H ₁₃	CH ₃	152,0-3,5	14,12	5,24	C ₁₃ H ₂₆ ClN	13,86	5,47
XVII	C ₇ H ₁₅	CH ₃	113,0-4,0	13,18	5,07	C ₁₆ H ₂₈ ClN	13,13	5,19
XVIII	C ₈ H ₁₇	CH ₃	69-70	—	—	—	—	—
XIX	C ₉ H ₁₉	CH ₃	61,5-2,5	11,49	4,59	C ₁₈ H ₃₂ ClN	11,90	4,70
XX	C ₁₁ H ₂₃	CH ₃	47,0-7,5	9,94	4,07	C ₂₀ H ₃₆ ClN · H ₂ O	10,31	4,07
XXI	C ₁₂ H ₂₅	CH ₃	44,5-45,0	9,76	4,16	C ₂₁ H ₃₈ ClN · H ₂ O	9,94	3,92
XXII	C ₉ H ₁₉	C ₂ H ₅	118,0-9,0	13,08	5,20	C ₁₆ H ₂₈ ClN	13,13	5,19
XXIII	C ₆ H ₁₃	C ₂ H ₅	110,0-2,0	12,51	4,93	C ₁₇ H ₃₀ ClN	12,48	4,93
XXIV	C ₇ H ₁₅	C ₂ H ₅	113,0-4,0	12,37	4,63	C ₁₈ H ₃₂ ClN	11,90	4,70
XXV*	C ₈ H ₁₇	C ₂ H ₅	61,5-62,0	11,18	4,42	C ₁₉ H ₃₄ ClN	11,37	4,49
XXVI**	C ₉ H ₁₉	C ₂ H ₅	52,0-52,5	10,97	4,21	C ₂₀ H ₃₆ ClN	10,87	4,29
XXVII	C ₁₁ H ₂₃	C ₂ H ₅	58,0-58,5	10,22	3,95	C ₂₂ H ₄₀ ClN	10,85	3,77
XXVIII	C ₁₂ H ₂₅	C ₂ H ₅	58,5-59,0	—	—	—	—	—

*The compound is mentioned in [7-9], but there are no data on its isolation in the crystalline form.

†The iodide has been obtained previously [10].

must dissolve completely in 5% hydrochloric acid). The liquid is removed from the residue, mixed with ether, washed several times with water, and then acidified with 5% hydrochloric acid. The aqueous solution of tertiary amine hydrochloride is separated from the ether and made alkaline with a concentrated solution of sodium hydroxide. Compound II floats to the surface in the form of a yellow oil. This is removed, dried over sodium hydroxide, and distilled for final purification. The yield is 41.9%.

The residue is made alkaline with a concentrated solution of sodium hydroxide, and the lower layer, which is a solution of dimethylamine in alkali, separated from the upper tertiary amine which is only sparingly soluble in alkali. The tertiary amine is dissolved in ether and the ethereal solution treated as described above. The yield of the second portion of III is 43.8%. The overall yield is 85.7%.

Dimethylalkylamines with longer radicals are obtained similarly except that they are held for a longer period at room temperature.

Dimethylheptylbenzylammonium Chloride (XVII)

A mixture of 13.3 g III, 11.55 g benzyl chloride, and 0.26 g XVII* is emulsified in water (the quantity of which is equal to the theoretical yield of XVII) and heated to 50–60°C. After 10 min the solution becomes completely clear. This is washed several times with ether and evaporated on a boiling water bath to the consistency of a thick syrup which, on energetic mixing, is converted to a moist hygroscopic powder. This is dried in a desiccator over phosphorus pentoxide. The yield is 92%.

To prepare XVIII and XXI the same method is used, but the products are dried in a desiccator with calcium chloride at atmospheric pressure since these compounds are monohydrates and deliquesce on complete loss of water.

Triethylundecylammonium Bromide

Melting point 211–212°C (from alcohol). Found, %: C 60.61; H 11.29; N 4.17. $C_{17}H_{35}BrN$. Calculated, %: C 60.89; H 11.34; N 4.16.

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*In the case of the absence of the ready-made salt required for homogenization of the reaction mixture, the reaction proceeds somewhat more slowly but accelerates as the quaternary ammonium salt is formed, since this salt solubilizes the amines and benzyl chloride [5].