obtained are both optically active. The example of des-N base being optically active in spite of the absence of asymmetric carbon atom, is rare among the biscoclaurine type bases, and is the second one following that of insularine. It has been surmised that this might be due to the molecular asymmetry, as in the case of insularine.

(Received September 18, 1953)

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90. Takeo Ueda, Kiyoshi Takahashi, Shigeshi Toyoshima, and Masasuke Ose: Researches on Chemotherapeutic Drugs against Viruses. XIV.[1] Syntheses of several Quinolinium and Pyridinium Anionides.

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Antiviral chemotherapeutic drugs have hitherto been studied in our Institute and it has been made clear from the results obtained that the drugs possessing activities against neurotropic viruses were not effective against the influenza viruses. Accordingly alternate studies on chemotherapeutic drugs against the influenza viruses have been conducted.

As reported at the previous Annual Meeting of the Pharmaceutical Society[2], it has been suggested from investigations on Hirst's phenomenon that some compounds of carbamic esters, capable of prohibiting cholinesterase, should exert remarkable activities on the influenza virus. Prompted by this interesting prediction, several quinolinium and pyridinium salts were synthesized in order to examine their effects against the virus.

This paper describes the syntheses of several compounds of the carbamyloxy-quinolinium and -pyridinium series, and their antiviral properties will be reported in the following paper.

Some compounds of the carbamyloxypyridinium series were already reported by Wuest[3] while compounds of the carbamyloxyquinolinium series are not known yet.

Carbamyloxypyridinium halides are usually prepared by combining carbamic esters of pyridine with alkyl or aralkyl halides, and carbamic esters of pyridine, by condensing hydroxyl derivatives of pyridine with carbamination agents such as dimethylcarbamyl chloride and phenyl isocyanate.

According to these methods, carbamic esters of quinoline were synthesized by condensing hydroxyquinoline with carbamination agents, and carbamyloxyquinolinium salts, by combining the carbamic esters with alkyl and aralkyl halides. The methods of the syntheses of these compounds were somewhat improved in detail.

Dimethylcarbamic ester of quinoline and pyridine were prepared by refluxing the equimolar mixtures of hydroxyl derivatives of these bases and dimethylcarbamyl chloride in dehydrated pyridine for four to five hours. In contrast to employing dehydrochlorination agents such as triethylamine in benzene[4] medium, this method of using pyridine was found to be successfull in all cases, which was employed throughout these studies.

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[1] Part XIII: This Bulletin, 1, 278(1953).

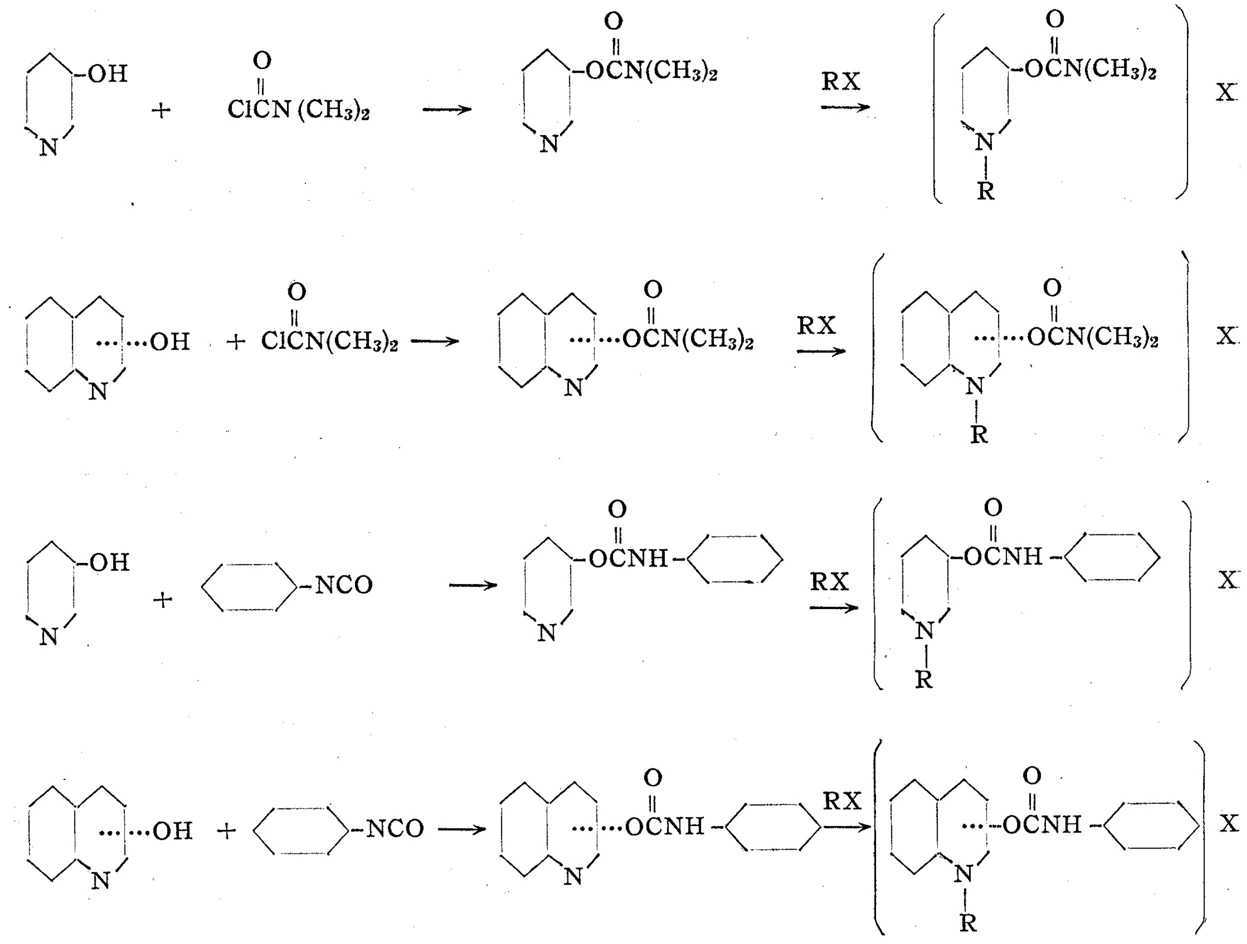
[2] T. Ueda, S. Toyoshima, M. Taniguchi, K. Takahashi: Papers read before the Annual Meetings of the Pharmaceutical Society of Japan (1951, 1952).

[3] H. M. Wuest: C. A., 44, 3037(1950).

[4] K. Nádor: C. A., 46, 7547(1952).

Phenylcarbamic esters of quinoline and pyridine were prepared by condensing hydroxyl derivatives of these bases with phenyl isocyanate. The carbamic esters thus obtained were converted into the quaternary ammonium salts by combining the former with alkyl or aralkyl halide in the usual manner.

The whole process of the reaction is illustrated as follows:



where R=alkyl or aralkyl and X=Cl or Br.

The quaternary ammonium salts prepared above are summarized in Table I.

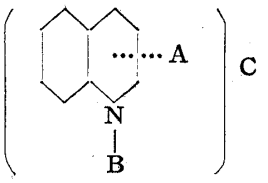
Experimental

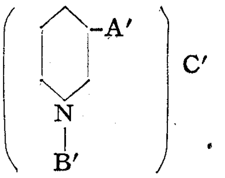
3-Dimethylcarbamyloxyquinoline (I)—A mixture of 4.4 g. of 3-hydroxyquinoline and 4.4 g. of dimethylaminocarbonyl chloride in 30 cc. of dehydrated pyridine was gently boiled for 4~5 hours. Ten cc. of water was added to the reaction mixture and the solvent was removed by distillation *in vacuo*. Two g. of sodium hydroxide and 20 cc. of water were added to the residue followed by exclusion of solvent *in vacuo* on a water bath for complete elimination of pyridine. The residue was made strongly alkaline by adding aqueous caustic soda solution, extracted three times with 100 cc. of ether, and the ether solution was dried over potassium carbonate. After eliminating ether, the residue was distilled under a diminished pressure, b.p$_4$ 172~174°. The distillate soon solidified to white crystals melting at 66~68°. Yield, 5.7 g. This substance was very slightly soluble in water and was not colored by ferric chloride.

8-Dimethylcarbamyloxyquinoline (II)—Five g. of 8-hydroxyquinoline was condensed with 5 g. of dimethylaminocarbonyl chloride by the same procedures as described for (I), and was purified by vacuum distillation, b.p$_{3\sim4}$ 168~175°. The distillate soon solidified to white thick plates melting at 79~80°: Yield, 6.3 g. This substance was very slightly soluble in water and colored faintly by ferric chloride.

2-Methyl-4-dimethycarbamyloxyquinoline (III)—Five g. of 2-methyl-4-hydroxyquinoline was

TABLE I





No.	A	B	C	Mol. formula	Appearance	m.p. °C	N % Calcd.	N % Found
Q-1	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2\text{(8)}$	$-\text{CH}_2\text{-C}_6\text{H}_5$	Br	$C_{19}H_{17}O_2N_2Br$	Yellowish white	67~69	7.24	7.08
Q-2	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2\text{(8)}$	$-\text{CH}_2\text{CH}_2\text{NH}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-C}_6\text{H}_5$	Br	$C_{21}H_{22}O_3N_3Br$	Yellowish white	65~67	9.46	9.42
Q-3	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NH-C}_6\text{H}_5\text{(8)}$	$-\text{CH}_2\text{-C}_6\text{H}_5$	Br	$C_{23}H_{19}O_2N_2Br$	Yellow fine needles	159	6.45	6.29
Q-4	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NH-C}_6\text{H}_5\text{(8)}$	$-\text{CH}_2\text{-CH}_2\text{-NH}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-C}_6\text{H}_5$	Br	$C_{25}H_{22}O_3N_3Br$	White	133~135	8.54	8.31
Q-5	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2\text{(3)}$	$-\text{CH}_2\text{-C}_6\text{H}_5$	Br	$C_{19}H_{17}O_2N_2Br$	White needles	221~222	7.24	7.15
Q-6	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2\text{(3)}$	$-\text{CH}_2\text{CH}_2\text{NH}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-C}_6\text{H}_5$	Br	$C_{21}H_{22}O_3N_3Br$	Yellowish white	85~87	9.46	9.41
Q-7	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2\text{(4)}$	$-\text{CH}_2\text{CH}_2\text{NH}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-C}_6\text{H}_5$ $(-\text{CH}_3\text{(2)})$	Br	$C_{22}H_{24}O_3N_3Br$	White needles	236~238	9.17	8.98
Q-8	-H	$-\text{CH}_2\text{-C}_6\text{H}_5$	Br	$C_{16}H_{14}NBr$	White needles	145~146	4.67	4.70

No.	A′	B′	C′	Mol. formula	Appearence	m.p. °C	N% Calcd.	N% Found
P-1	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2$	$-\text{CH}_2\text{-C}_6\text{H}_5$	Br	$C_{15}H_{17}O_2N_2Br$	White	115~116	8.31	8.22
P-2	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2$	$-\text{CH}_2\text{-CH}_2\text{-NH}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-C}_6\text{H}_5$	Br	$C_{17}H_{20}O_3N_3Br$	White	107~109	10.66	10.54
P-3	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2$	$-\text{CH}_2\text{-O-C}_{12}\text{H}_{25}$	Cl	$C_{21}H_{37}O_3N_2Cl$	White	*—	—	—
P-4	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2$	$-\text{C}_{12}\text{H}_{25}$	Br	$C_{20}H_{35}O_2N_2Br$	White	84~86	6.25	6.17
P-5	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{N(CH}_3\text{)}_2$	$-\text{C}_{18}\text{H}_{37}$	Br	$C_{26}H_{47}O_2N_2Br$	White	91~94	5.61	5.49
P-6	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NH-C}_6\text{H}_5$	$-\text{CH}_2\text{C}_6\text{H}_5$	Br	$C_{19}H_{17}O_2N_2Br$	White	60~62	7.28	7.30
P-7	$-\text{O}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NH-C}_6\text{H}_5$	$-\text{CH}_2\text{-CH}_2\text{-NH}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-C}_6\text{H}_5$	Br	$C_{21}H_{20}O_3N_3Br$	White	94~96	9.50	9.42

* Substances obtained as a semi-solide.

condensed with 3.6 g. of dimethylaminocarbonyl chloride by the same procedures as described above and was purified by vacuum distillation, b.p$_2$ 130~133°. Yield, 4.5 g. This substance was a faintly colored, viscous oil, miscible with alcohol and benzene.

8-Phenylcarbamyloxyquinoline (**IV**)—A mixture of 3 g. of 8-hydroxyquinoline and 2.5 g. of phenyl isocyanate was boiled on a sand bath for several minutes. After cooling, the reaction mixture was washed at first with benzene to remove unchanged phenyl isocyanate, treated with 10% hydrochloric acid to remove the starting substance, and then recrystallized several times from absolute alcohol to colorless needles melting at 162~163°.

3-Dimethylcarbamyloxypyridine (V)—Four and a half g. of 3-hydroxypyridine was condensed with 5 g. of dimethylaminocarbonyl chloride by the same procedures as for (IV) and was purified by vacuum distillation, b.p$_3$ 112~114°. Yield, 4.8 g. This substance was a colorless, viscous oil and was not colored by ferric chloride.

3-Phenylcarbamyloxypyridine (VI)—Two g. of 3-hydroxypyridine was condensed with 2.5 g. of phenyl isocyanate by the same procedures as for (IV). Yield, 1.4 g. This substance formed needles, mp 43~45°.

On preparing cationic agents from the derivatives of quinoline and pyridine obtained above, a mixture of alkyl or aralkyl halide and the equivalent of each compound, (I) to (VI), in absolute alcohol or in dehydrated benzene was warmed on a water bath for a few hours. The solvent was removed by distillation *in vacuo* and the residue was purified by recrystallization several times from absolute alcohol, or by reprecipitation with petroleum ether from the solution of it in absolute alcohol or ethyl acetate. The properties of these compounds are shown in Table I.

1-Benzyl-8-(dimethylcarbamyloxy)-quinolinium Bromide(Q-1)—Prepared from compound (II) and benzyl bromide.

1-Benzoylaminoethyl-8-(dimethylcarbamyloxy)-quinolinium Bromide(Q-2)—Prepared from compound (II) and 2-bromoethylbenzamide.

1-Benzyl-8-(phenylcarbamyloxy)-quinolinium Bromide(Q-3)—Prepared from compound (IV) and benzyl bromide.

1-Benzoylaminoethyl-8-(phenylcarbamyloxy)-quinolinium Bromide(Q-4)—Prepared from compound (IV) and 2-bromoethylbenzamide.

1-Benzyl-3-(dimethylcarbamyloxy)-quinolinium Bromide(Q-5)— Prepared from compound (I) and benzyl bromide.

1-Benzoylaminoethyl-3-(dimethylcarbamyloxy)-quinolinium Bromide(Q-6)—Prepared from compound (I) and 2-bromoethylbenzamide.

1-Benzoylaminoethyl-2-methyl-4-(dimethylcarbamyloxy)-quinolinium Bromide (Q-7)—Prepared from compound (III) and 2-bromoethylbenzamide.

1-Benzylquinolinium Bromide(Q-8)—Prepared from quinoline and benzyl bromide.

1-Benzyl-3-(dimethylcarbamyloxy)-pyridinium Bromide(P-1)—Prepared from compound (V) and benzyl bromide.

1-Benzoylaminoethyl-3-(dimethylcarbamyloxy)-pyridinium Bromide(P-2)—Prepared from compound (V) and 2-bromoethylbenzamide.

1-Dodecyloxymethyl-3-(dimethylcarbamyloxy)-pyridinium Chloride (P-3)—Prepared from compound (V) and dodecyloxymethyl bromide.

1-Dodecyl-3-(dimethylcarbamyloxy)-pyridinium Bromide (P-4)—Prepared from compound (V) and dodecyl bromide.

1-Octadecyl-3-(dimethylcarbamyloxy)-pyridinium Bromide (P-5)—Prepared from compound (V) and octadecyl bromide.

1-Benzyl-3-(phenylcarbamyloxy)-pyridinium Bromide (P-6)—Prepared from compound (VI) and benzyl bromide.

1-Benzoylaminoethyl-3-(phenylcarbamyloxy)-pyridinium Bromide (P-7)—Prepared from compound (VI) and 2-bromoethylbenzamide.

Summary

Several quinolinium and pyridinium salts were synthesized in order to examine their effects against the influenza viruses.

The carbamyloxypyridinium halides were prepared by combining carbamic esters of pyridine with alkyl or aralkyl halides, and carbamic esters of pyridine, by condensing hydroxyl derivatives of pyridine with carbamination agents such as dimethylcarbamyl chloride and phenyl isocyanate.

The carbamyloxyquinolinium series were [synthesized by the same procedures described above.

(Received September 24, 1953)