According to the electron microscope studies of Sharp, *et al.*[2b] the virus particles are essentially spherical. Assuming the hydration of the virus is 58% by volume, a value of about 5.9 can be calculated for the intrinsic viscosity of virus solutions. In the present study the lowest value of the intrinsic viscosity is 14.5 and some values are as high as 21. Such high viscosities cannot be caused by spherical particles hydrated to the extent calculated by Sharp, *et al.* The viscosity studies suggest, then, that the virus solutions contain a viscous impurity. It is believed, therefore, that the variations in the sedimentation constants of the different samples examined in the present study are attributable to the presence of different amounts of a viscous impurity in the preparations rather than to inherent differences in the nature of the virus. This conclusion is based on the observation that the reduced viscosity of the solution decreases and the sedimentation constant of the main component increases as the amount of the trailing component decreases. In addition, the same virus preparation, on further purification, decreased in viscosity and the sedimentation constant of the principal component increased.

Lauffer and Stanley[9] in studies on influenza virus obtained results similar to those described here. The impurity in the preparations of influenza virus is believed to be a normal host component.[10] Information as to the nature of the impurity in the rabbit papilloma virus preparations is lacking at present because of the difficulty in obtaining sufficient material for study.

Despite the fact that the impurity is visible in both the ultracentrifuge and Tiselius apparatus, it is important to note that it is very inhomogeneous and that it may escape detection by these techniques if present in very small amounts. In that event viscosity measurements would be very useful in indicating the presence of the impurity. Neurath, *et al.*,[2a] obtained about 8.4 for the intrinsic viscosity of one of their preparations of virus indicating that that preparation contained less impurity than the preparations examined in the present study. However, the range of sedimentation constants reported by these workers is about the same as that observed in this study. Thus, it appears that most of the preparations of rabbit papilloma virus studied thus far contained virus particles of essentially uniform physical properties and variable amounts of an impurity rather than virus particles which varied in their physical properties from preparation to preparation.

(9) M. A. Lauffer and W. M. Stanley, *J. Exptl. Med.*, **80**, 521 (1944).

(10) C. A. Knight, *ibid.*, **80**, 83 (1944).

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# NOTES

## Salts of Substituted Piperidines and Pyrrolidines[1]

BY CARL T. BAHNER, MARVEL FIELDEN, LYDIA MOORE RIVES AND MADGE DEEL PICKENS

Since certain quaternary salts of pyridine and substituted pyridines have been found to damage sarcoma cells *in vivo*[2] it is of interest to determine whether the corresponding hydrogenated tertiary amine hydrohalide salts or the quaternary salts derived from N-alkylated piperidine produce similar effects. The study has been extended to include a few derivatives of pyrrolidine because of its close similarity to piperidine. Turner[3] and Lutz[4] and their associates, among others, have prepared several N-substituted piperidines, but little attention has been given to the quaternary salts.

The tertiary amine hydrohalide salts were prepared in some cases by reaction of equimolecular mixtures of the secondary amine and organic halide and in other cases by treatment of previously prepared tertiary amine with the proper acid. The quaternary salts were prepared in some cases by reaction of N-ethylpiperidine with the higher molecular weight organic halide and in other cases by treatment of a large tertiary amine with methyl or ethyl iodide.

(1) This investigation was supported in part by a research grant from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

(2) Shear, *et al.*, in "Approaches to Cancer Chemotherapy," American Association for the Advancement of Science, F. R. Moulton, Editor, Washington, D. C., 1947, p. 236 ff.; *cf.* J. L. Hartwell and S. R. L. Kornberg, THIS JOURNAL, **68**, 1131 (1946).

(3) B. R. Carpenter and E. E. Turner, *J. Chem. Soc.*, 869 (1934); R. V. Henley and E. E. Turner, *ibid.*, 1182 (1931).

(4) Robert E. Lutz, *et al.*, *J. Org. Chem.*, **12**, 617 (1947).

### Experimental

The methods of preparation are illustrated by the following examples. The melting points and analytical data on the products are listed in Table I.

**1-(2-Phenylethyl)-piperidine Hydriodide.**—A mixture of 11.6 g. of 2-phenylethyl iodide and 4.5 g. of piperidine evolved heat and set to a paste within one hour. Recrystallization from ethanol yielded 4.2 g. (26%) of white crystalline product.

**1-Ethyl-1-(2-phenylethyl)-piperidinium Iodide.**—A mixture of 2.5 g. of 1-(2-phenylethyl)-piperidine, prepared from the hydriodide by treatment with ammonium hydroxide and distillation of the oil at 145–150° at 10 mm., and 2.5 g. of ethyl iodide warmed slightly to initiate reaction, then allowed to stand 12 hours, yielded 2.5 g. (55%) of recrystallized white salt. Much lower yields were obtained when the reaction was attempted in a sealed tube at 100°.

Attempts to prepare 1,1-bis-(2-phenylethyl)-piperidinium iodide by heating of phenylethyl iodide with 1-(2-phenylethyl)-piperidine at 100° resulted in the formation of 1-(2-phenylethyl)-piperidine hydriodide instead of the expected product. Perhaps the quaternary salt was formed and broke down quickly by elimination of phenylethylene.

**1-Ethyl-1-(*p*-chlorophenacyl)-piperidinium Bromide.**—A solution of 4.6 g. of *p*-chlorophenacyl bromide and 2.6 g. of 1-ethylpiperidine remained clear after standing 3 weeks at room temperature, but addition of ethyl ether threw out

TABLE I

PIPERIDINE AND PYRROLIDINE DERIVATIVES

| Product from | Empirical formula | M.p., °C.[a] | Analyses, % Calcd. | Found[b] |
|---|---|---|---|---|
| Piperidine and: | | | | |
| Glycerol-$\alpha,\gamma$-dibromohydrin[c] | $C_{13}H_{28}Br_2N_2O$ | 273–274 | 41.17 | 41.18 |
| Phenacyl bromide | $C_{13}H_{18}BrNO$ | 230–231 | 28.12 | 28.00 |
| *p*-Phenylphenacyl bromide[d] | $C_{19}H_{22}BrNO$ | 244–246 | 22.18 | 21.96 |
| $\beta$-Phenylethyl iodide | $C_{13}H_{20}IN$ | 197–198 | 40.01 | 39.95 |
| N-Ethylpiperidine and: | | | | |
| Phenacyl bromide[e] | $C_{15}H_{22}BrNO$ | 191–193 | 25.59 | 25.55 |
| *p*-Fluorophenacyl bromide[f] | $C_{15}H_{21}BrFNO$ | 183 | 24.14 | 24.06 |
| *p*-Chlorophenacyl bromide | $C_{15}H_{21}BrClNO$ | 190 | 23.08 | 22.88 |
| *p*-Bromophenacyl bromide | $C_{15}H_{21}Br_2NO$ | 211 | 20.43 | 20.61 |
| *p*-Iodophenacyl bromide | $C_{15}H_{21}BrINO$ | 232–233 | 18.28 | 18.31 |
| *p*-Methoxyphenacyl bromide | $C_{16}H_{24}BrNO_2$ | 166–168 | 23.36 | 23.20 |
| 2-($\alpha$-Bromoaceto)-thiophene[g] | $C_{13}H_{20}BrNSO$ | 210–211 | 25.11 | 24.94 |
| N-Phenylethylpiperidine and: | | | | |
| Methyl iodide | $C_{14}H_{22}IN$ | 180–181 | 38.32 | 38.81 |
| Ethyl iodide | $C_{15}H_{24}IN$ | 149–151 | 36.76 | 36.53 |
| 1-(2-Phenyl-2-hydroxyethyl)-piperidine and: | | | | |
| Methyl iodide | $C_{14}H_{22}INO$ | 138–139 | 36.55 | 36.39 |
| Phenacyl bromide | $C_{20}H_{26}BrNO_2$ | 230 | 19.77 | 19.61 |
| Pyrrolidine and: | | | | |
| Phenylethyl bromide[h] | $C_{12}H_{18}BrN$ | 161 | 31.24 | 31.02 |
| Phenylethylene oxide | $C_{12}H_{17}NO$ | 58.5–59.5 | | |
| 1-(2-Phenyl-2-hydroxyethyl)-pyrrolidine and: | | | | |
| Methyl iodide | $C_{13}H_{20}INO$ | 130.5–131.0 | 38.09 | 37.84 |

[a] The salts melted with decomposition. [b] Average of two Volhard analyses for ionic halogen. [c] Prepared by Mr. Lilburn L. Norton. [d] *Cf.* B. R. Carpenter and E. T. Turner, *J. Chem. Soc.*, 869 (1934). [e] Prepared by Miss Emma Kite and Miss Frances Pierce. [f] Prepared by Mr. Harold Lyons. [g] Prepared by Mr. Clifford Myers. [h] Prepared by Miss Emma Kite and Mr. George Biggerstaff. [i] Calcd.: N, 7.33; found by Kjeldahl analysis, N, 7.18.

white crystals which weighed 4.0 g. (58%) after repeated recrystallization by dissolving in ethanol and adding ether.

**1-(2-Phenyl-2-hydroxyethyl)-pyrrolidine.**—A mixture of 24 g. of phenylethylene oxide and 21.3 g. of pyrrolidine refluxed 5 hours and distilled at 107–122° at 0.8–1.5 mm., yielded 24.1 g. (63%) of white crystals, m.p. 58.5–59.5°, after recrystallization from isohexane. A sample was submitted to the Malaria Testing Laboratories of the National Institutes of Health which reported the following results: MED ($Q$ <0.1, MTD ($Q$ =) 2.

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## An Observation on a Partial Resolution of Racemic Compounds[1]

BY MARVIN D. ARMSTRONG

Several texts contain excellent summaries of the methods which have been used for the resolution of racemic compounds. The most convenient chemical method in general use at present for the resolution of racemic acids or bases involves their combination with an optically active base or acid to form diastereoisomeric salts.[2] In the case of an acid, *dl*A, appropriate choice of an optically active base, *l*B results in the formation of salts *d*A·*l*B and *l*A·*l*B which may be separated by fractional crystallization from suitable solvents. The differences in the solubility of the salts makes possible the resolution and one or both of the crystalline salts may be obtained in a pure form.

The experiment reported here may be regarded as a variation of this procedure. One-half the theoretical amount of base, *l*B, is added to a solution of *dl*A under conditions where the salts are very soluble and A crystallizes as the solution is allowed to cool. If the salts are completely ionized, the solution should contain equal amounts of $d\text{A}^-$ and $l\text{A}^-$, hence equal amounts of *d*A and *l*A, along with $l\text{B}^+$, and no enrichment of either form of A should occur in the A which crystallizes. Actually, in the case reported, where A is S-carboxymethyl-DL-homocysteine and B is brucine, a considerable enrichment of the D form of the amino acid occurred in the carboxymethylhomocysteine that crystallized. A similar experiment involving DL-phenylalanine and *d*-camphorsulfonic acid (Reychler acid) resulted in a small but definite enrichment of the L-form in the phenylalanine that crystallized.

(1) This research was supported by a grant from the U. S. Public Health Service.

(2) Gilman, "Organic Chemistry," Vol. I, second ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 254–264.