mined, and for the sake of identification, a mixed melting-point determination with the respective known ephedrine halides was made.

The compound formed by the reaction of ephedrine base with *o*-chlorobenzaldehyde crystallized in colorless prisms melting at 123° C. (corrected) and had a specific rotation of $[\alpha]^{27}_{D} = -74.5°$ in alcohol. The substance was insoluble in water and soluble in all common organic solvents, such as ether, acetone, chloroform, ethyl acetate, benzene and alcohol. The reaction took place with great facility, 15 minutes being sufficient for its completion. That it is an addition product of ephedrine and *o*-chlorobenzaldehyde, having the empirical formula $C_{17}H_{18}ONCl$, with the loss of one molecule of water, was proved by combustion analyses as follows:

For $C_{17}H_{18}ONCl$:
Calculated $C = 70.93$; $H = 6.31$; $N = 4.87$; $Cl = 12.33$.
Found $C = 70.94$; $H = 6.25$; $N = 4.71$; $Cl = 12.12$.
$C = 70.92$; $H = 6.23$; $N = 4.69$; $Cl = 11.88$.

In consideration of the results, it becomes apparent that ephedrine readily extracts the halogens from the alkyl, allyl and substituted alkyl halides to form the corresponding halogen salt. To the last class belong the halohydrins, benzyl chloride, benzotrichloride, chloral, bromal and avertin. It fails to react with less reactive substances such as *tert*-butyl chloride. It also fails to react with the halogen atom attached to the benzene ring, although it easily attacks the same when located on the side chain of aromatic compounds. The addition compound with *o*-chlorobenzaldehyde follows a different pattern of reaction since the position of the chlorine atom is obviously not altered.

The exact mechanism of the reaction between ephedrine base and halogenated organic compounds is not yet known, although suggestive explanations may be found in the works of organic chemistry. According to Whitmore (3), (4), amines can react with allyl and alkyl halides to remove halogen acid—this property of amines being due to their basic nature. Similarly, halohydrins (5) hydrolyze rapidly in the presence of weak bases. Since our tests were not made under strictly anhydrous conditions, there was the possibility that the moisture present in the reagents and the atmosphere may have been sufficient for hydrolysis. The insolubility of the ephedrine salts in the reagents used perhaps also favors the displacement of the equilibrium toward their stability after they are formed. Further investigations will be necessary in order to determine the true mechanism of this reaction.

CONCLUSION

1. Of thirty-one halogenated organic compounds studied, anhydrous ephedrine base reacts with alkyl, allyl and substituted alkyl halides to form the corresponding ephedrine halide salt.
2. Carbon tetrachloride, chloral and avertin (tribromoethanol) are therefore incompatible with ephedrine base in prescription compounding.
3. Anhydrous ephedrine base does not react with the halogen atom that is attached to the benzene ring.
4. Anhydrous ephedrine base combines with *o*-chlorobenzaldehyde to form an addition product, $C_{17}H_{18}ONCl$, by the elimination of one molecule of water.

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The Preparation of Alkaline Bismuth Saccharates*

By G. O. Doak, Ph.D.

Bismuth in the form of the hydroxide or a soluble salt will dissolve in alkaline solutions of polyhydroxy acids or other polyhydroxy compounds to form solutions which vary in stability with the nature of the hydroxy compound used. In many cases the resulting bismuth complex can be precipitated from solution by the addition of alcohol. The literature contains innumerable examples of this reaction and a number of different structures have been advanced for the resulting bismuth complexes. Warren (1) has discussed the extreme variation in the different bismuth tartrates appearing on the market. Corfield and Adams (2) state that the composition of the bismuth tartrates varies with the method used for preparation. Other authors have recorded similar results with other polyhydroxy acids. Rosenheim (3) has studied these compounds and has assigned structures in

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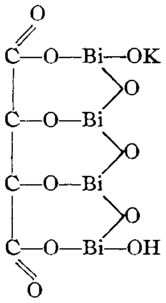
which the bismuth is linked to at least two oxygen groups of the polyhydroxy acid. Browning (4) and Maschmann (5) have assigned similar structures to the alkali bismuthyl tartrates and other alkali bismuthyl salts. Hepner and Likiernik (6) have explained these compounds by means of Werner's theory. Very little work however has been done on the experimental proof of the structure of these compounds and it may be said that as yet there is some doubt that all the bismuth complexes of polyhydroxy compounds represent true chemical compounds.

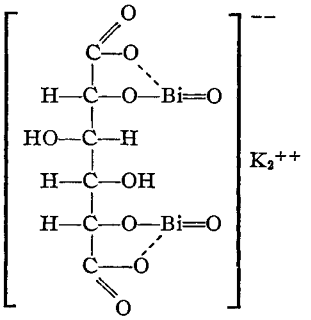
An essential feature in the preparation of these bismuth complexes is that there be two hydroxyl groups in adjacent positions to each other. Thus we have found that alkaline solutions of such glycols as ethylene glycol and 1,2-propylene glycol will dissolve large quantities of bismuth hydroxide, while 1,3-trimethylene glycol and diethylene glycol, in which the hydroxyl groups are not on adjacent carbon atoms will not dissolve bismuth hydroxide. This would support Rosenheim's structure whereby the bismuth is joined to at least two oxygen atoms on adjacent carbon atoms. The function of the polyhydroxy compounds may possibly be similar to the complexes of boric acid and polyhydroxy compounds in which two hydroxyl groups must be on adjacent carbon atoms for complex formation (10), (11). That the carboxyl group also enters into the binding of the bismuth is apparent from several facts. Alkaline bismuth complexes of glycols cannot be isolated as solid compounds. On the addition of alcohol to the solutions, the bismuth is precipitated as bismuth hydroxide leaving the glycol behind. This does not occur with the alkaline bismuth complexes of the hydroxy acids. They may be precipitated with alcohol, and redissolved in water and there is no change in their composition.

Rosenheim (3) and Browning (4) report the preparation of soluble alkaline derivatives of glycolic and malic acids. In repeating the work of these authors we have found that bismuth hydroxide will not dissolve in alkaline solutions of glycollic or malic acid, but if a soluble bismuth salt such as bismuth nitrate in acetic acid solution is warmed with an acetic acid solution of glycolic acid, a bismuthyl glycolic acid is precipitated which dissolves readily in alkali. It has been found impossible, however, to prepare bismuthyl oxalates, so that at least one hydroxyl group and one carboxyl group must be present to form a bismuthyl complex. However, there are compounds in which more than one bismuth is bound by two hydroxyl groups. Thus Rosenheim has prepared potassium tri-bismuthyl tartrate, to which the formula $K[(BiO)_3C_4H_2O_6].4H_2O$ has been assigned. Kober (7) has prepared a tetra-bismuth tartrate to which he assigned the formula



Such a formula appears to be unlikely since one bismuth would be functioning as both an acid and base at the same time. Lauter and Braun (8) have prepared both di- and tri-bismuthyl gluconates but failed to obtain a tetra-bismuthyl gluconate.

Rosenheim (3) also succeeded in preparing in crystalline form mono-potassium di-bismuthyl saccharate with the formula $K[Bi_2(C_6H_{19}O_{16})]$ while Browning (4) prepared a di-bismuthyl saccharic acid and its sodium salt. We have prepared a di-potassium di-bismuthyl saccharate and a di-potassium tri-bismuthyl saccharate. Careful acidification of the di-bismuthyl compound gave di-bismuthyl saccharic acid which was apparently identical with Browning's compound. We could not prepare stable di-sodium or di-ammonium salts of this acid as they tended to hydrolyze in water. Further we could not prepare a potassium bismuthyl saccharate with more than 3 atoms of bismuth per mole of saccharic acid, corresponding to Kober's potassium or sodium tetra-bismuthyl tartrate. While the structure of the bismuth complexes with polyhydroxy compounds is still an unsettled question, in view of the results reported in this paper, the formulas suggested by Rosenheim (3) seem to best satisfy the properties of the alkaline bismuth saccharates and the following formula is tentatively suggested for di-potassium di-bismuthyl saccharate:



Such a formula then explains why the polyhydroxy alcohols dissolve bismuth hydroxide but the presence of a carboxyl group is necessary for their isolation in the solid state. It also explains our failure to obtain a potassium bismuthyl saccharate containing more than three moles of bismuth per mole of saccharic acid; the failure of polyhydroxy alcohols without hydroxyl groups on adjacent carbons atoms to dissolve bismuth hydroxide; and the instability of the di-potassium tri-bismuthyl saccharate, since in this compound the third bismuth atom must be linked with the two center hydroxyl groups and the carboxyl groups contribute little or nothing to the stability of this linkage. Both the potassium di- and tri-bismuthyl saccharates are white solids, soluble in water, insoluble in organic solvents. Attempts to recrystallize them from water or water-alcohol mixtures were unsuccessful. They were purified by reprecipitating several times with alcohol from aqueous solution. On redissolving the di-bismuthyl saccharic acid in potassium hydroxide and precipitating with alcohol there was no appreciable change in bismuth content from the original potassium di-bismuthyl saccharate, so it would seem probable that the compound was of uniform composition. In solution the potassium di-bismuthyl saccharate appears to be less affected by light than the corresponding tartrate and gluconate. On exposing ampuls of solutions of these compounds to light metallic bismuth is precipitated; most rapidly by the tartrate, slowly by the gluconate and hardly at all by the saccharate. Potassium di-bismuthyl saccharate forms a solution which appears to be stable indefinitely and consequently it is of interest as a drug for the treatment of those diseases for which bismuth is used. Von Oettingen, Sollmann and Schweid (9) have shown that sodium bismuthyl tartrate precipitates rapidly with cattle serum, while sodium bismuthyl citrate precipitates much more slowly under the same conditions. These authors suggest that the immediate toxic effect of these compounds on injection is due to this precipitation. In repeating these experiments with both horse and human serum we have found an immediate precipitate with sodium bismuthyl tartrate, which became progressively heavier on standing, a faint cloudiness after several hours with potassium bismuthyl gluconate and no precipitation or cloudiness even after three days with potassium bismuthyl saccharate.

EXPERIMENTAL

Di-Potassium Di-Bismuthyl Saccharate.—Seventeen cubic centimeters of a 60% solution of saccharic acid (or 12.4 Gm. of pure potassium acid saccharate) ($^1/_{20}$ mole) were dissolved in 250 cc. water and just neutralized with KOH, and 10 cc. of 25% KOH added in addition. Bismuth hydroxide, freshly precipitated from 48.5 Gm. ($^1/_{10}$ mole) of bismuth nitrate and suspended in 500 cc. of water were added slowly over several hours to the potassium saccharate solution. The reaction was stirred vigorously during the addition. When all the bismuth hydroxide had dissolved, the solution was filtered and the bismuth complex precipitated with 95% alcohol. This was redissolved and reprecipitated three times, washed with alcohol and then with ether and dried *in vacuo* at 100°. The yield was 35 Gm.

Calculated for $C_6H_6H_{10}Bi_2K_2.H_2O$: Bi = 55.58; K = 10.40; C = 9.58; H = 1.07.
Found: Bi = 56.75%; K = 8.58%; C = 9.76%; H = 1.65%.

Di-Bismuthyl Saccharic Acid.—Ten grams of potassium di-bismuthyl saccharate dissolved in water were precipitated by the cautious addition of 10% hydrochloric acid. The precipitate was washed free from chlorides, then washed with alcohol and ether and finally dried *in vacuo.*

Calculated for $C_6H_8O_{10}Bi_2$: Bi = 63.53%.
Found: Bi = 63.50%.

Sodium Di-Bismuthyl Saccharic Acid.—An attempt to prepare sodium di-bismuthyl saccharate by the same procedure used for the preparation of potassium di-bismuthyl saccharate yielded a white solid which after precipitation with alcohol was no longer soluble in water. The sodium salt, however, was made directly from di-bismuthyl saccharic acid. Ten grams of the acid as prepared above were suspended in water and 10% sodium hydroxide added until the acid just dissolved. This was then precipitated with alcohol three times as in the preparation of the potassium compound, washed with alcohol and ether and dried *in vacuo.* Analyses indicated however that the product was the acid salt.

Calculated for $C_6H_7O_{10}Bi_2Na.H_2O$: Bi = 59.89; Na = 3.29.
Found: Bi = 61.48; Na = 3.60.

Sodium Potassium Di-Bismuthyl Saccharate.—Twelve and four-tenths grams ($^1/_{20}$ mole) of potassium acid saccharate were just neutralized with sodium hydroxide and then 25 cc. excess of 25% sodium hydroxide added. To this was added freshly precipitated bismuth hydroxide from 48.5 Gm. ($^1/_{10}$ mole) of bismuth nitrate and the product precipitated with alcohol and purified in the same manner as the di-potassium compound. The resulting white compound was dried *in vacuo.*

Calculated for $C_6H_7O_{10}Bi_2NaK.H_2O$: Bi = 56.80; Na = 3.12.
Found: Bi = 59.14; Na = 3.32.

Di-Potassium Tri-Bismuthyl Saccharate.—Seventeen cubic centimeters of a 60% solution of saccharic acid ($^1/_{20}$ mole) were just neutralized with potassium hydroxide and 50 cc. of 25% solution added in excess. To this was added freshly precipitated bismuth hydroxide from 72.7 Gm. ($^3/_{20}$ mole) of bismuth nitrate in 200 cc. of water. The mixture was shaken for 48 hours as described by Kober (7), filtered and the bismuth complex precipitated with alcohol and purified in the same manner as the previous compounds. The resulting white compound appeared to be less stable than the di-bismuthyl compounds and turned brown when warmed *in vacuo.* It was dried at room temperature over calcium chloride.

Calculated for $C_6H_5O_{11}Bi_3K_2.2H_2O$: Bi = 63.06; K = 7.86.
Found: Bi = 63.13; K = 7.05.

An attempt was also made to prepare a compound containing 4 atoms of bismuth per mole of saccharic acid using the same procedure as in the preparation of the tri-bismuthyl saccharate but with a large excess of bismuth hydroxide. The resulting compound contained only 63% bismuth. It is apparently impossible to prepare potassium bismuthyl saccharates with more than 3 atoms of bismuth per mole of saccharic acid.

SUMMARY

1. Methods are described for preparing di-potassium di-bismuthyl saccharate, di-bismuthyl saccharic acid, mono-sodium di-bismuthyl saccharate, sodium potassium di-bismuthyl saccharate and di-potassium tri-bismuthyl saccharate.
2. Potassium bismuthyl saccharate has been shown to be a more stable complex than the corresponding tartrate and gluconate.

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Studies on Cantharides

II. The Assay of Cantharides*

By Benjamin P. Hecht and Lloyd M. Parks†

INTRODUCTION

It is generally acknowledged that the present pharmacopœial process for the assay

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