ing during photographing and to prevent reflections from the surface of the bone, it is suspended (with spring clothes pin) in a battery jar of water. Scotch tape attached to the outside of the battery jar facilitates in the placing of the tibia in proper alignment with the camera. While the tibia is being photographed it is illuminated by a Photoflood Bulb No. 1 in an ordinary reading lamp equipped with a metal cone for converging the light directly upon the tibia. The "exposure time" for making the photographs is materially shortened when a low power magnifying lense is installed in the opening of the metal cone. However such a magnifying lense is not a necessary part of the photographic equipment.

Trials with various types of backgrounds have proved that the most satisfactory results are obtained, when the background is ground glass thoroughly illuminated with a 60-watt Mazda lamp. The distance from the end of lense combination to face of battery jar is $3^3/_4$ inches, from photoflood bulb to specimen is 8 inches, from background to specimen 12 inches and the distance from the ground glass background to the lamp illuminating it will be varied according to conditions, principal of which is the degree of illumination of the room in which the photographs are made.

For rapid quantity production the camera is not focused for each exposure but is adjusted so that it will turn from side to side. It is focused for the first tibia on the center of the plate, the cardboard duplicator is then inserted in back of camera. The camera may then be turned from side to side and the image of the bone will be in the correct location for photographing on one half of the $3^1/_4$ x $4^1/_4$-inch plate. After an exposure is made on one half of the plate the duplicator is slid over and the camera is turned so that image is on the other half of plate where a second exposure is made. The Wratten and Wainwright regular Panchromatic plates seem to be preferable and for best results the plate is over exposed and under developed. By slightly over exposing the plate greater detail is obtained in the shadows and dark portions of the tibiæ. Then by under developing slightly, extreme contrast in the high lights can be avoided. For a well-stained specimen the average exposure is 25 seconds with lense stop at F32 and the negative is developed for about $1^1/_2$ minutes. The prints of the tibia are made on glossy contact single weight paper but this is optional with the photographer.

When the photographs of the tibiæ have been completed they are mounted in a permanent record book (Fig. 5). The record book illustrated is specially prepared in this laboratory by assembling alternately sheets of plain Bond paper and printed forms for recording vitamin D assay results and having them permanently bound. From a legal aspect this type of record book has very decided advantages over a loose-leaf type of record book since there can be no possibility of the data having been changed at any time subsequent to the initial recording of it.

The vitamin D assay results which appear on the right of the record book comprise data concerning the identification of the sample, the dilution at which it was fed, data for each experimental animal relative to its identification number, sex, its initial, final and increase in weight, relative to the amount of the sample consumed daily, the dates for the beginning and ending of the assay period, the amount of ration consumed, the extent of the healing of the tibiæ and remarks.

The photographs of the tibiæ are mounted on the left-hand page of the record book facing the vitamin chart and definite attention must be given to the type of adhesive used for mounting the photographs. Formerly a rubber cement type of adhesive was used in this laboratory because of its excellent adhesive qualities. Unfortunately with the passage of time the photographs became badly discolored due, presumably, to interaction between the "rubber cement" and materials used in preparing the photographs. At present "Foto-Flat" appears to be the best type of adhesive for permanently mounting photographs of tibiæ.

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Salts of Alkaloids with Bromocomplexes of Some Heavy Metals*

By E. P. White

INTRODUCTION

It has been found by Meurice (1) that dilute brucine sulfate solution and potassium bromide with a trace of cadmium salt produce separation of a white double bromide, while copper, aluminum, iron, chromium and chloride give no precipitate. Preliminary experiments suggested that a detailed investigation of the precipitates formed under these conditions would be of theoretical interest, and might lead to microanalytical reactions of value. To our knowledge salts of this series have not been analyzed formerly nor their properties described. After this

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work had been completed Whitmore and Wood (2) described the use of some bromosalts of this type for the detection of alkaloids. Elsewhere White (3) describes the microanalytical applications of bromosalts, the chemistry of which is described here.

There is considerable analytical literature on the use of iodides of mercury, cadmium, bismuth, antimony, zinc and other metals for the detection and determination of basic nitrogen compounds, especially alkaloids. Such precipitates tend to be amorphous, insoluble in water and of formulas types $HHgI_3$ xB, H_2BiI_4 xB, H_2BiI_4 xB, where x is 1, 1.5 or 2 though complex ratios are common. Francois and Blanc (4) give for mercury the general formulas $(HgI_2)m(BHI)n$ and for bismuth $(BiI_3)m(BHI)n$.

The property of forming sparingly soluble complexes of the type $HgBCl_2$ is one of most nitrogen compounds, primary, secondary or tertiary, strongly or weakly basic. Sparingly soluble chlorosalts are restricted almost entirely to the types $HHgCl_3$ xB, $HAuCl_4$ xB and H_2PtCl_6 xB, where B contains a fairly complex nitrogen system. Numerous chlorosalts of other metals with amines and alkaloids are either soluble or largely dissociated by water. Examples are the type H_2CuCl_4 2B described by Amiel (5), similar ones of certain cinchona alkaloids sparingly soluble in hydrochloric acid, described by Cohen (6) and soluble salts of tin and zinc described by Slagle (7) and Base (8).

Certain mercuric bromide complexes and mercury, gold and platinum bromosalts of the same general properties as the chloro-analogs have been recorded and a few used in analysis. Corresponding bromosalts are often recorded by the authors quoted above, and are of the same general formula and properties. During the course of this work certain of the mercuric bromide complexes have been obtained insoluble in excess bromide. The ethylenediamine complex $HgEnBr_2$ is precipitated only in the presence of excess bromide, but most of this type such as the pyridine complex $HgPyBr_2$ are dissolved by bromide ions. Most alkaloids in neutral or acid solution form sparingly soluble bromosalts of the type $HHgBr_3$ xB with mercuric bromide without the addition of potassium bromide. Examples are those of brucine m. p. 211° and sparteine m. p. 184° where x is 1. In the presence of excess bromide the only salt analyzed of the type $HMBr_3$ B was that of lead and tropacocaine. A H_2PgBr_4 formula would require two alkaloid ions, an arrangement which is apparently impossible.

BROMOSALTS—THEIR PROPERTIES AND FORMATION BY METALS AND ALKALOIDS

Mercuric complexes and bromosalts of the type formed by mercuric bromide in acid solution are to be distinguished clearly from that type of bromosalt described here, precipitated only when excess bromide is present, sparingly soluble in bromide, and formed only by some half-dozen heavy metals and by alkaloids containing certain types of tertiary nitrogen.

Bromosalts of our type H_2MBr_4 xB or H_2MBr_5 xB (for a tervalent metal) have been obtained sparingly soluble (that is, with metal and alkaloid solutions less concentrated than 1 in 10) only with ions of Cd, Hg, Bi, Sb, Sn, Pb, Au and Pt, though the formation of soluble salts by other common metals is not excluded. Bromosalts of silver cannot be obtained, as silver bromide is insoluble in potassium bromide. Salts of least solubility are formed by those metals lowest in the periodic table, and the crystalline form shows the expected similarity of cadmium to mercury and bismuth to antimony. Lead forms insoluble bromosalts with a small number of alkaloids while tin gives them only with those giving the least soluble salts, brucine and cocaine.

The low range and the sluggishness of the melting points, the slight decomposition occurring then, and the similarity of the values to those of the alkaloid hydrobromides suggests linkages composed of electrovalent and covalent forces. The bromocadmium salts are soluble in water up to a few per cent, those of mercury and lead less so and those of antimony and bismuth strongly hydrolyzed. Alcohol and covalent solvents are without appreciable action. In aqueous solution the reactions of metal, alkaloid and bromide ion are given, and simple precipitation methods will remove these ions completely. In solution the class of compounds is represented

adequately by the formula B_xMBr_4 where there is an alkaloid ion B and a bromometallic ion largely dissociated. Addition of bromide ion causes complete reprecipitation from solution, cadmium is less effective and alkaloid still less. p_H determinations in solution yielded values to be expected from a slight dissociation of the alkaloid ion, and would not account for a free hydrogen ion per molecule. X-ray analysis appears to be the only means of obtaining definite evidence of the solid state.

To follow in detail the correlation between sparingly soluble bromosalt formation and the nature of the nitrogen in the base, it will be necessary to make a list of structures of alkaloids mentioned, found conveniently in an alkaloid treatise (9). From the following study it will be apparent that the presence of at least one atom of tertiary nitrogen of a special nature is required for the formation of the sparingly soluble bromosalts, that in any reactive series the effect of substituents apparently remote from the reactive nitrogen may accentuate or hinder the ability to form the salts, that steric effects may be pronounced, that in alkaloids containing more than one nitrogen system, the effect of the two systems on one another is relatively negligible (that is the total effect can be predicted roughly from the known ability of each system to form these salts). It must be realized that unreactive nitrogen systems may contribute to the formation of salts by assuming an ion of hydrogen, provided one reactive system is present in the molecule.

Of the alkaloids investigated the following failed to give any sparingly soluble bromosalts: adrenaline, arecoline, caffeine, colchicine, coniine, cytisine, ephedrine, eserine, homatropine, hyoscine, hyoscyamine, *d*-lupanine, nicotine, taxine and theobromine. Primary and secondary amines, including the alkaloids adrenaline and ephedrine (—NH—CH_3), colchicine (—NH—CO—CH_3) and cytisine (—NH—) are unreactive. So are purines shown by caffeine and theobromine, and the ring systems of pyridine, quinoline, iso-quinoline and piperidine as shown by the bases themselves. Combined in nicotine the pyridine system is unreactive; in piperine the —CO on the piperidine nitrogen makes the substance an acid and unreactive. Papaverine, a highly substituted piperidine does yield some precipitate under these conditions, not of the bromosalt type but similar to that given by pyridine with almost any metal ion under the same conditions.

The N-methyl pyrollidine nucleus of nicotine, and as two nuclei joined in eserine (physostigmine) is unreactive; so is the N-methyl tetrahydropyridine of arecoline, though these nuclei are capable of reacting and show considerable differences in reactivity according to the effects of substituent groups. In narcotine where this nucleus is joined to another carbon ring amorphous salts are given with five metals, while narceine whose formula is normally given with the N—Me in an open chain (potentially a ring) gives salts of medium solubility with mercury, cadmium and bismuth. From this it would appear that narceine has a tautomeric ring form known to occur with other alkaloids of this series, though the precise nature of the rearrangement is not obvious. Cotarnine, which is known to have a tautomerism between the open-chain and ring form containing one double bond in the nitrogen ring, and in its salts a ring form containing two double bonds (dihydropyridine), yields three sparingly soluble crystalline salts and two less soluble amorphous ones. In this respect it is almost identical with hydrastinine which gives a similar tautomerism leading to an identity of ring systems.

The morphine series on the formula of Gulland and Robinson contains a N-methyl piperidine ring attached to a phenanthrene nucleus. Morphine itself gives an indefinite precipitate only with mercury in concentrated solution. Dionine with EtO— in place of the alcoholic HO— gives amorphous salts of considerable solubility with mercury, cadmium and bismuth, while the corresponding MeO— derivative, codeine, gives crystalline salts with mercury and cadmium only, to a considerable dilution. Thus a modification of the HO— remote from the nitrogen can exert a strong electronic effect that is transmitted through the ring systems, and alters the reactivity of the distant reac-

tive nitrogen. Apomorphine in which the points of attachment of the N-methyl piperidine are different from the morphine series again shows varied properties, giving salts only with mercury and antimony in concentrated solution.

In the quinine series the quinuclidine nucleus is the reactive one, the isoquinoline being in itself unreactive, yet capable of accepting a hydrogen in the formation of salts. The alkaloids quinine and cinchonine, quinidine and cinchonidine are characterized by forming no lead salts, ones with mercury and cadmium sometimes crystalline, and amorphous ones with bismuth and antimony, never of any great insolubility. With quinidine and cinchonidine, stereo-isomers of quinine and cinchonine, respectively, the salts are more soluble and solutions of alkaloid more concentrated than 1 in 100 are required to give them. This constitutes a steric effect.

In the tropine series there is a considerable variation in reaction with the effect of substituents, and a marked selectivity for lead. Tropine itself gives a bromosalt with lead only down to about 1 in 600. Tropacocaine, 3-benzoyl-pseudo-tropine, is extremely reactive giving crystalline salts of low solubility with mercury, cadmium, antimony and lead, and an amorphous one with bismuth. Similar great reactivity is shown by cocaine, the 2-methyl carboxylic ester of 3-benzoyl tropine; the selectivity for lead is shown by the formation of a crystalline salt down to 1 in 25,000 of lead, amorphous ones with the other metals, and even crystals with tin in very concentrated solution. However the atropine alkaloids, with the benzoyl substituted are feebly reactive. Atropine, the *dl*-3-tropic ester of tropine, that is, with the benzoyl replaced by —O—CO—CH(OH)—Ph reacts with lead only in very concentrated solution. Hyoscyamine, the *l*-isomer gives no salts, nor does homatropine with the group —O—CO—CH(OH)Ph or hyoscine (scopolamine) a *dl*-tropic ester with two end —CH_2— groups modified by the introduction of an oxygen ring.

In the lupin series with the nitrogen at the junction of two six-membered rings having one common —CH—, the lupinane nucleus, *l*-sparteine with the basic nucleus doubled shows some reactivity by the formation of crystalline salts with mercury and cadmium, while the *dl*-form gives more soluble salts. Its keto derivative *d*-lupanine, with one group as —CO—N is unreactive showing that the effect of the —CO— on the one N has been relayed to the other nitrogen and has made it unreactive. Cytisine, with a —CO— on one N and the other as —NH— is unreactive as expected.

Strychnine and brucine with one nitrogen at the junction of two complex ring systems, and the other bearing a —CO— at a similar junction, form very insoluble salts. Strychnine salts could not be investigated owing to interference from the sparingly soluble hydrobromide, but definite evidence of their formation was obtained. With brucine, dimethoxy styrchnine, salts could be obtained pure, were crystalline and of low solubility for mercury and cadmium, were extremely insoluble (of the order 1 in 10–30,000) for bismuth and antimony and with lead a more soluble amorphous one formed.

Certain alkaloids of indefinite structure have been investigated. From the work on the comparatively small number of alkaloids it is evident that the property of forming these sparingly soluble salts is one which will give some evidence as to the nitrogen type in a base of unknown constitution. Yohimbine gives amorphous salts with the metals except lead and tin in concentrated solution; on its provisional formula it contains a nitrogen ring system basically similar to that of lupanine, and another nitrogen as —NH— in a saturated indole ring. Aconitine known to have its single nitrogen as a N—Me gives a salt formation with mercury and cadmium only, suggesting one of the simpler types of reactive ring systems. Veratrine (cevadine) of unknown structure yields crystals with lead and more soluble amorphous salts with the remaining metals showing the nitrogen to be in a reactive system. Taxine, on the available evidence, has its single nitrogen as a tertiary amine form attached to a cyclopentenophenanthrene nucleus, and the failure of this alkaloid to give any precipitate under our conditions is in agreement with these findings.

EXPERIMENTAL

Dilute acid solutions of the nitrogen bases were mixed with an excess of potassium bromide and a dilute solution of the metallic ion in water or dilute acid added. Previous microchemical tests in which exact drop-ratios were used had indicated any special precautions to be taken to prevent interference from alkaloid hydrobromide formation (3). Extremely careful washing is required to remove traces of bromide ion that are held in the salts with some tenacity. Drying was done at 50°. In most cases small deviations of the analytical results from exact formulas are noted, but these are not sufficient to cause any doubt as to the formula. The values given are typical, and in nearly all cases have been confirmed by analysis of separate preparations, analytical results being in good agreement. Bromide has been determined by precipitation of silver bromide from aqueous solution with the addition of nitric acid. In recording results the formula is written in the particular manner for the sake of clarity, though the hydrogen is actually attached to the alkaloid, the first figure is the theoretical percentage and the second an experimental one. Melting points are average ones determined by the normal method.

In *cadmium salts* the Cd was determined by ignition with sulfuric acid and weighed as sulfate.

Brucine: H_2CdBr_4 $2C_{23}H_{26}O_4N_2$. M. p. 218°. Cd 9.2, 8.7. Br 26.5, 27.2.

Quinine: H_2CdBr_4 $C_{20}H_{24}O_2N_2$. M. p. 265°. Cd 14.8, 14.6. Br 42.0, 42.5.

Cinchonine: H_2CdBr_4 $C_{19}H_{22}ON_2$ $2H_2O$. Dehydrated 120°, m. p. (anhyd.) 256°. Cd 15.4, 14.9. Br 42.0, 42.5. H_2O (drying to constant wt. at 120°) 4.7, 4.3.

Cinchonidine: H_2CdBr_4 $C_{19}H_{22}ON_2$ $2H_2O$. Dehydrated 120°, m. p. (anhyd.) 226°. Cd 15.4, 15.2. Br 42.0, 42.5. H_2O (drying to constant wt. at 120°) 4.7, 3.7.

Sparteine: H_2CdBr_4 $C_{15}H_{26}N_2$. Cd m. p. 238°. Cd 16.8, 16.8. Br 46.5, 47.5.

Tropacocaine: H_2CdBr_4 $2C_{15}H_{19}O_2N$. M. p. 228°. Cd 12.2, 13.0. Br 34.4, 33.9.

Narcotine: H_2CdBr_4 $2C_{22}H_{23}O_7N$ $4H_2O$. Dehydrated 120°, m. p. (anhyd.) 227°. Cd 8.4, 8.5. Br 23.9, 24.3. H_2O (drying to constant wt. at 120°) 5.4, 5.3.

Hydrastinine: H_2CdBr_4 $2C_{11}H_{13}O_3N$ xH_2O. Dehydrated 120°, decomp. above Cd 13.2, 12.8. Br 37.8, 38.4.

Cotarnine: H_2CdBr_4 $2C_{12}H_{15}O_4N$. M. p. 202°. Cd 12.9, 12.3. Br 36.9, 36.0.

Veratrine: $2H_2CdBr_4$ $3C_{32}H_{49}O_9N$. Darkens 162°, m. p. 261. Cd 8.5, 8.4. Br 24.3, 24.0.

In *mercury salts* the bromide was removed by acid and hydrogen peroxide, HgS precipitated and dissolved in bromine water, and the Hg weighed as zinc mercuric thiocyanate. (B refers to the alkaloid molecule.)

Brucine: H_2HgBr_4 2B. M. p. 233°. Hg 15.3, 15.1. Br 24.1, 24.1.

Quinine: H_2HgBr_4 B. M. p. 257°. Hg 21.8, 21.0. Br 37.8, 37.7.

Cinchonine: H_2HgBr_4 B H_2O. Dehydrated 130° m. p. (anhyd.) 246°. Hg 24.1, 23.6. Br 38.6, 39.3. H_2O (drying to constant wt. at 130°) 2.2, 2.0.

Sparteine: H_2HgBr_4 B. M. p. 278°. Hg 26.7, 27.2. Br 42.5, 42.2.

In *lead salts* the lead was determined by sulfuric ignition and weighed as sulfate.

Brucine: H_2PbBr_4 2B. M. p. 230–260°. Pb 15.6, 15.8. Br 26.0, 26.7.

Tropacocaine: $HPbBr_3$ B. Darkens 265°, shrinks 290°. Pb 30.0, 29.2. Br 34.5, 35.5.

With *bismuth and antimony salts* the pronounced hydrolysis with water and alcohol makes it difficult to prepare very pure samples. Washing with hydrochloric acid led to halogen absorption, but with glacial acetic acid washing hydrolysis was slight, and analytical results sufficiently close to expected simple formulas could be obtained.

In *bismuth salts* bismuth was determined by precipitation as sulfide, solution of this in nitric acid, and finally weighed as phosphate.

Brucine: H_2BiBr_5 2B. M. p. 273°. Bi 14.9, 14.0. Br 28.5, 27.9.

Quinine: H_2BiBr_5 B. M. p. with gassing, 210–230°. Bi 22.4, 20.7. Br 42.7, 41.5.

Veratrine: H_2BiBr_5 2B. Bi 11.7, 11.3. Br 22.3, 23.1.

In *antimony salts* the metal was determined by precipitation as sulfide, solution of this in HCl and titration by iodate, using starch indicator.

Brucine: H_2SbBr_5. Gasses 186–197°. Sb 13.2, 13.8. Br 43.6, 41.9.

Quinine: H_2SbBr_5 B. Gasses 50–60°. Sb 14.2, 12.9. Br 47.0, 48.5.

SUMMARY

Certain types of tertiary nitrogen compounds of the complexity of alkaloids yield bromosalts with ions of bromide and certain metals, sparingly soluble in bromide solutions. These have been investigated and the formulas of selected ones obtained, and are found to be of the type $BxMBr_4$ or $BxMBr_5$ where B is an alkaloid ion. Some char-

acteristic physical properties are described. The property of forming these bromosalts is correlated with the type of nitrogen in the base; some effects of steric factors and of substituents on the reactivity of the nitrogen of the alkaloid is noted in some cases, and it is shown that some prediction of the type of nitrogen in the base is possible from a study of these reactions.

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The Decomposition of Sulfanilamide in Tablets

*By Felice A. Rotondaro**

Through the courtesy of Dr. Paul Nicholas Leech of the American Medical Association, our attention was directed to a report of untoward reactions in four patients who had received sulfanilamide tablets showing a brownish discoloration. It was stated that substitution of another brand of sulfanilamide tablets eliminated the difficulty. In view of this report and the importance of sulfanilamide in the field of chemotherapy, investigation of the extent of the decomposition of sulfanilamide on the market and the factors concerned in such decomposition was undertaken.

A preliminary examination of the questionable tablets by extraction with acetone, followed by several recrystallizations, yielded a residue which was appreciably darker in color and which had a lower melting point than the residue similarly obtained from the second brand of tablets used. However, the chemical nature of the residues was not determined and no evidence was at hand to indicate their therapeutic significance.

It was decided that a survey of a fairly representative number of sulfanilamide tablets, as well as various brands of U. S. P. quality sulfanilamide powder on the market, would give some clue to the nature and significance of the residues. Nineteen samples representing thirteen brands of tablets, and seven samples representing four brands of U. S. P. quality powder were examined.

EXPERIMENTAL

The quantitative results obtained for sulfanilamide on all samples by the U. S. P. method showed that all were well within the limits of good manufacturing practice. However, this method of analysis is based on a general type reaction and is not specific for sulfanilamide. This is also true of methods based on the determination of an element such as nitrogen or sulfur. Therefore, small quantities of decomposition products or other impurities cannot be readily detected in the presence of large amounts of comparatively pure drug by the above methods.

Extraction of the tablets with anhydrous acetone followed by several recrystallizations, served to concentrate the impurity. The residue obtained from the acetone extractions and recrystallizations was shown to differ from similar residues from pure sulfanilamide and from tablets of sulfanilamide of known purity. The presence of an impurity was shown from the fact that the residue was of a dark brown color—in contrast to the pure white color of the pure drug—and that the melting point range was between 156–170° C. (Melting point of sulfanilamide = 164.5–166.5° C. U. S. P. XI.) Further, an examination of the solidified melt by polarized light showed that the crystal structure was broken up by a foreign substance; whereas, pure sulfanilamide yielded a beautiful continuous fan-like crystal branching from the point of crystallization.

From the fact that some crystals of pure sulfanilamide developed a brown color when exposed to rather bright daylight, it was inferred that the brown color of the tablets in question was due to some photochemical decomposition product of sulfanilamide.

A number of other brands of sulfanilamide tablets, about which no complaint was reported following their use, yielded acetone residues essentially similar to those obtained from the tablets reported to have caused untoward effects. This suggested that some substance commonly used by a number of manufacturers was the interfering agent in the determination of the melting point and optical characteristics of the acetone residues. It thus became apparent that

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