5-methoxybenzoxazolone was added. The solvent was removed under reduced pressure and the dry solid residue was treated with 25 cc. of acetic anhydride. The mixture was swirled thoroughly and allowed to stand for ten minutes, after which it was poured into water. The product was filtered to give 11.8 g. (95%); m. p. 100–103°.

Pharmacologic Evaluation

The compounds were tested for analgesic activity in dogs by a modification of the method of Andrews and Workman.[19] These determinations were carried out by Dr. R. K. Richards and Mr. K. E. Kueter of our laboratories to whom we express our thanks. Doses of 100–200 mg./kg. were used, at which level toxic symptoms rarely appeared. Several of the derivatives raised the pain threshold 10–20%; a few 20–30%. The best compounds, therefore, have an activity comparable to that of aspirin, which gives a 15–20% increase in 100 mg./kg. doses. They are much weaker analgesics than Demerol, which is capable of raising the pain threshold 30–40% in 15 mg./kg. quantities. Pharmacologic data for all of the benzoxazolones tested are included in the table.

Summary

1. The synthesis of approximately forty N-alkyl, N-acyl, and N-dialkylaminoalkyl derivatives of benzoxazolone and nuclear substituted benzoxazolones is described.

2. About two-thirds of the derivatives induced mild analgesia in dogs.

RECEIVED AUGUST 7, 1948

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[19] Andrews and Workman, *J. Pharmacol.*, **73**, 99 (1941).

[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY, SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Streptomycin. XII. Streptamine Isomers from *meso*-Inositol

BY A. E. O. MENZEL,[1] M. MOORE AND O. WINTERSTEINER

In 1915 Griffin and Nelson,[2] in a study of the action of acetyl bromide on *meso*-inositol, obtained besides other products two isomeric dibromotetraacetoxycyclohexanes, melting at 225 and 130°, respectively, which Müller[3] had previously prepared from *meso*-inositol in a slightly different manner. In the absence of information on the position of the bromine atoms the higher-melting isomer was arbitrarily termed α-, and the lower melting isomer, β-. Soon after the structure of streptamine had been established,[4,5] we began an investigation of the aminolysis of these compounds and of the corresponding dibromotetrols (of which only the β-isomer had been previously described[2]), in the hope to arrive, if not at streptamine itself, at some isomers of it. While Griffin and Nelson were unable to effect amination of the β-dibromotetraacetoxycyclohexane by treatment with liquid ammonia at room temperature, we found that both the α- and the β-dibromotetrol reacted with aqueous ammonia at 100° with the formation of diamines. The crude products were isolated as picrates, which in both cases could be separated into a methanol-soluble fraction (I) and a much smaller methanol-insoluble fraction (II). The four picrate fractions were purified by recrystallization and converted to dihydrochlorides. The two pairs of diamines thus obtained are designated here for convenient reference as α- and β-diamines I, and α- and β-diamines II, the Greek letters signifying derivation from the corresponding dibromotetrol isomers, and the Roman numerals derivation from the methanol-soluble and methanol-insoluble picrate fraction, respectively. They were converted into suitable acyl derivatives for comparison with each other and with streptamine.

As could be anticipated from the properties of the salts and acyl derivatives of streptamine, the crystal shape and melting point data were of limited value as criteria for establishing identity or non-identity because the new compounds were generally microcrystalline and melted or decomposed over a considerable range. This was for instance the case with the dipicrates, sulfates, N,N′-diacetates and hexaacetates of α-diamine I and β-diamine I, respectively. Notwithstanding these limitations the picrates, sulfates and hexaacetates showed such close correspondence of their properties that identity of the parent diamines was at first suspected. Subsequently, however, certain differences in melting point behavior were observed with the N,N′-diacetates and the hexabenzoates. Particularly with the latter pair these discrepancies could not be dismissed as being due to accidental causes, because both compounds, in contradistinction to the acetyl derivatives, exhibited fairly well-defined melting points. Thus, while the β-hexabenzoate melted at 262–263°, it was not possible to raise the melting point of the α-hexabenzoate beyond 252–255°, and a small but distinct depression (251–253°) was observed in mixture. Furthermore, the X-ray diffraction patterns[6] of the two compounds were quite dissimilar, but the significance of this finding is not quite clear in view of the fact that the pattern given by the α-hexabenzoate raised some doubt as to its completely crystalline character (*cf.* Experimental). Nevertheless, we believe that the weight of the evidence is against identity, and that α-di-

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[1] Present address: Roosevelt Hospital, W. 59th St., New York 19, N. Y.

[2] E. G. Griffin and J. M. Nelson, THIS JOURNAL, **37**, 1552 (1915).

[3] H. Müller, *J. Chem. Soc.*, **91**, 1788 (1907).

[4] R. L. Peck, C. E. Hoffhine, Jr., E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 776 (1946).

[5] H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, P. S. Skell and W. A. Strong, *Science*, **103**, 540 (1946).

[6] We are greatly indebted to Prof. G. L. Clark, of the Department of Chemistry, University of Illinois, for these measurements.

amine I and β-diamine I should be considered as separate entities. It was not vital for the purpose of this investigation to establish this point more conclusively.

There can be little doubt that neither of the isomers is identical with streptamine, since the N,N′-diacetates, hexaacetates and hexabenzoate of the latter all exhibit much higher melting points than the corresponding derivatives of the two diamines.

The dihydrochlorides of both isomers consumed, as expected, 6 moles of periodic acid while the N,N′-diacetates consumed 2 moles. This parallels the results obtained with streptamine and its N,N′-diacyl derivatives.[4,5] The amino groups in either diamine could therefore be in 1,3- or 1,4-position to each other.

The dihydrochlorides of α-diamine II and β-diamine II could be secured in small amounts only, since the yields of the purified methanol-insoluble picrates were poor and in some runs insignificant. Of acyl derivatives only the N,N′-diacetates were prepared. Both products melted sharply at 268–269° after slight sintering at 265°, and did not depress each other's melting point, whereas admixture of streptamine N,N′-diacetate gave a marked depression. It is therefore highly probable that these two diamines are identical. Identity with either of the diamines I is excluded not only by the different melting point properties of the dihydrochlorides and N,N′-diacetates of the latter, but also by the results obtained by the periodic acid method. The dihydrochlorides of the "α-" as well as of the "β-" diamine II consumed the expected 6 moles, but the N,N′-diacetates consumed 3 moles, indicating that the amino groups occupy vicinal positions. The fact that the isomeric α- and β-dibromotetrols give rise to the same diamine must be ascribed to the formation, in the initial phase of the amination reaction, of a common intermediate, *i. e.*, an epoxide.

The investigation had to be discontinued at this point for extraneous reasons so that no effort could be made to obtain further information on the structure of the diamines I and of the isomeric dibromotetrols. It might be mentioned in this connection that the application of the periodate method to the bromine compounds gave a definitive result only with the β-isomer, which in slow reaction consumed 3 moles of periodic acid and hence appears to carry the bromine atoms at adjoining carbon atoms. In the case of the α-dibromotetrol the oxidative attack was evidently complicated by side reactions. Consumption came to a standstill at 4 moles whereas no more than 3 moles could be consumed if the oxidation were confined to glycol groupings.

Experimental

α- and β-Dibromotetrahydroxycyclohexane.—*meso*-Inositol was subjected to the reaction with acetyl bromide as described by Griffin and Nelson.[2] For the separation of the reaction products we followed in general their procedure of fractional crystallization, and were able to isolate most of the compounds reported by them, *e. g.*, α-dibromotetraacetoxycyclohexane, m. p. 222–223°[7]; β-dibromotetraacetoxycyclohexane, m. p. 128–129°; monobromopentaacetoxycyclohexane, m. p. 240–241°; dibromodiacetoxydihydroxycyclohexane, m. p. 220–222°; and β-dibromocyclohexanetetrol m. p. 214–216°. However, the yields of these compounds, as well as the proportion of the two dibromotetraacetoxy isomers, varied markedly from run to run. The purification of the α-isomer was greatly facilitated by chromatographing the crude product in benzene solution on aluminum oxide. For instance, the sirupy reaction product obtained from 50 g. of *meso*-inositol was taken up in hot absolute ethanol (1.4 l.). The resulting crystalline mass was filtered off from the hot solution, washed and dried (19.5 g.), then dissolved in benzene and chromatographed on a column (35 × 480 mm.) of acetic acid-washed alumina. Continued washing with benzene (2.1 l.) eluted crystalline material, which on recrystallization from ethyl acetate–ethanol (1:9) yielded slightly impure α-dibromotetraacetoxycyclohexane, m. p. 218–222° (10.9 g.). Subsequent elution with benzene-ethanol (9:1) removed from the column the chief contaminant of this fraction, monobromopentaacetylcyclohexane. The original alcoholic mother liquor on concentration yielded a second crop of crystals consisting mainly of β-dibromotetraacetoxycyclohexane (after recrystallization 10.4 g., m. p. 126–128°). A third crop of crystals obtained from this mother liquor was treated with hot chloroform. From the chloroform-insoluble fraction crude dibromodiacetoxydihydroxycyclohexane (9.2 g.) was isolated, while the chloroform-soluble fraction afforded an additional amount (1 g.) of α-dibromotetraacetoxycyclohexane m. p. 219–221°. The identity of the purified preparations was in all cases confirmed by analysis.

It was found preferable to secure **β-dibromocyclohexanetetrol** by acid hydrolysis of its tetraacetate rather than by direct isolation. A solution of the tetraacetate in about 20 parts of a 1:1 mixture consisting of ethanol and 2 *N* hydrochloric acid was boiled on the steam-bath for five hours and then concentrated to a small volume *in vacuo*. The excess hydrochloric acid was removed by twice repeating the distillation after the addition of absolute ethanol. The residue was taken up in warm ethanol, and the tetrol was precipitated by the addition of excess ether. After recrystallization from acetone it melted at 214–216° (dec.) after softening at 210°, yield, 58–65%.

Anal. Calcd. for $C_6H_{10}O_4Br_2$: C, 23.55; H, 3.29; Br, 52.2. Found: C, 23.14; H, 3.50; Br, 51.9.

The hitherto undescribed **α-dibromocyclohexanetetrol** was prepared from the tetraacetate in the same manner. The crude product was triturated with dry ether, and the insoluble part recrystallized from methanol–benzene or ethyl acetate–chloroform; prisms, m. p. 186–188°. The melting point of a mixture with the β-isomer was 175–180°. The solubility properties were similar to those of the β-isomer (readily soluble in water, moderately in methanol or ethanol, sparingly in acetone, insoluble in benzene and chloroform).

Anal. Calcd. for $C_6H_{10}O_4Br_2$: C, 23.55; H, 3.29; Br, 52.2. Found: C, 23.42; H, 3.59; Br, 51.9.

Amination of Dibromotetrols.—One gram portions of the tetrols were dissolved in concentrated aqueous ammonia (50 cc.), and the solutions heated in pressure bottles on the steam-bath for fifteen hours. (This ratio of tetrol to ammonia was retained from preliminary experiments, and could probably be decreased considerably.) After cooling the contents of several bottles were combined, and the excess ammonia was removed by repeated distillation *in vacuo* with water. The final aqueous solution was lyophilized, yielding the crude dihydrobromide as an amorphous white hygroscopic mass. Attempts to crystallize these products were unsuccessful.

It might be mentioned that other methods of amination previously explored had proved ineffective. Thus β-

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(7) All melting points were taken in the capillary and are corrected for stem exposure.

dibromotetraacetoxycyclohexane was recovered unchanged after treatment with potassium phthalimide at 165° in the bomb tube, or at 100° in the presence of xylene or amyl alcohol, nor would this compound react with sodium amide in boiling xylene. On standing for a week in alcoholic ammonia partial amination occurred, but only a small amount of picrate was obtained.

Isolation of Diamines as Picrates.—The crude dihydrobromide (525 mg., 1.54 millimole) from α-dibromocyclohexanetetrol was dissolved in water (3 cc.), and a saturated solution of picric acid in absolute ethanol (7.2 cc., about 3 millimoles) was added. Since only a small amount of precipitate appeared within an hour, the solution was concentrated at room temperature to *ca.* 6 cc. and allowed to stand in the refrigerator overnight. The resulting microcrystalline precipitate was collected by centrifuging, washed with 50% ethanol and dried (600 mg.). The product was suspended in dry methanol (3 cc.), and the mixture was centrifuged after short boiling while still warm. The insoluble part was subjected to the same treatment with 1 cc. of methanol. On addition of benzene (12 cc.) to the combined supernatants and standing clumpy aggregates separated out on the walls of the vessel (322 mg.). Recrystallization from the same solvents yielded **α-diamine I dipicrate** in form of indistinctly crystalline particles. A somewhat better-looking preparation (microscopic rods) could be obtained from warm *t*-amyl alcohol containing a small amount of water and chilling; m. p. 235–236° (dec.) after sintering and darkening from about 210° on (block preheated to 180°). With some preparations a somewhat higher decomposition point (240–242°) was observed. The picrate is fairly readily soluble in water (difference from diamine II dipicrate) and methanol, and sparingly soluble in ethanol and dioxane.

Anal. Calcd. for $C_{18}H_{20}O_{18}N_8$: C, 33.97; H, 3.17; N, 17.6. Found: C, 33.93; H, 3.64; N, 17.0.

A **picrolonate**, which is probably that of α-diamine I, was prepared from the same dihydrobromide; hair-like needles from methanol–water, m. p. 265° after sintering and darkening from 235° on.

Anal. Calcd. for $C_{26}H_{30}O_{14}N_{10}\cdot H_2O$: C, 43.10; H, 4.45; N, 19.3. Found: C, 43.36; H, 4.51: N, 20.0.

The methanol-insoluble fraction (31 mg.) of the mixed picrate was recrystallized twice from hot water. **Diamine II dipicrate** was obtained as small prisms melting gradually with decomposition at 260–290° after darkening at about 235°.

Anal. Calcd. for $C_{18}H_{20}O_{18}N_8$: C, 33.97; H, 3.17; N, 17.6. Found: C, 34.03; H, 3.55; N, 17.4.

Essentially the same procedure was used with the dihydrobromide prepared from β-dibromocyclohexanetetrol. For example, to a solution of the dihydrobromide (4.75 g.) in water (40 cc.) picric acid (6.65 g.) in ethanol (75 cc.) was added. After concentration to about 50 cc. the solution was chilled; and the precipitate (7.2 g., m. p. 155–220°) collected after one hour. For removal of the picric acid present the product was extracted with cold benzene, and the residue leached with methanol (150 cc.). After filtering off of the insoluble portion and concentration of the filtrate to 50 cc. benzene (250 cc.) was added. The solution on standing at 4° deposited 1.9 g. of **β-diamine I dipicrate** in form of indistinctly crystalline aggregates. The recrystallized product was indistinguishable in appearance and melting point from α-diamine I dipicrate (m. p. 240–242° (dec.) after darkening and sintering beginning at 207°). There was no depression of the melting point in mixture.

Anal. Calcd. for $C_{18}H_{20}O_{18}N_8$: C, 33.97; H, 3.17; N, 17.6. Found: C, 33.71; H, 3.35; N, 17.8.

The methanol-insoluble fraction (187 mg.) was recrystallized twice from water, yielding 107 mg. of diamine II dipicrate. The product showed the same melting point behavior as the diamine II dipicrate prepared from the α-tetrol.

Anal. Calcd. for $C_{18}H_{20}O_{18}N_8$: C, 33.97; H, 3.17; N, 17.6. Found: C, 34.27; H, 3.66; N, 17.8.

Salts and Acyl Derivatives of α-Diamine I.—α-Diamine I dipicrate (1.62 g.) was decomposed in the usual way with dilute hydrochloric acid and toluene–benzene. The lyophilized material from the aqueous phase (628 mg.) was dissolved in dry methanol and precipitated with ether. The dihydrochloride was obtained as an amorphous, hygroscopic, white product which started sintering at 90° but showed no definite melting point up to 180°. The analytical sample was dried at 78° *in vacuo.*

Anal. Calcd. for $C_6H_{14}O_4N_2\cdot 2HCl$: Cl, 28.2. Found: Cl, 28.2.

The **sulfate** was prepared from the dihydrochloride by double decomposition with one molar equivalent of silver sulfate. It was purified by dissolving it in a small volume of warm water and adding excess methanol; microscopic prisms, which darken from 260° on, and undergo pronounced decomposition from 285° to 340° without melting completely. The salt differs from streptamine sulfate by its crystal shape and its much higher solubility in water.

Anal. Calcd. for $C_6H_{14}O_4N_2\cdot H_2SO_4$: N, 10.14; S, 11.6. Found: N, 10.14; S, 11.2.

For the preparation of the **N,N′-diacetate** a mixture of the dihydrochloride (100 mg.), silver acetate (133 mg.), acetic anhydride (1.2 cc.) and dry methanol (0.9 cc.) was shaken for 2.5 hours, allowed to stand overnight and then heated on the steam-bath for five minutes. The silver chloride was filtered off from the warm solution and washed with hot water (10 cc.). A few drops of 1 *N* HCl were added to the filtrate for the removal of dissolved silver and the filtered solution was concentrated *in vacuo* to a small volume. On addition of ethanol (2 cc.) and standing in the refrigerator a precipitate formed, which was recrystallized twice by dissolving it in the minimal volume of hot methanol and adding excess ethanol. The purified product (69 mg.) consisted of small rods melting without decomposition at 210–212°. The analytical sample was dried at 155° *in vacuo* and then melted at 213–215°.

Anal. Calcd. for $C_{10}H_{18}O_6N_2$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.75; H, 7.12; N, 10.42.

The **hexaacetate** was prepared by boiling a mixture of the sulfate (26 mg.), anhydrous sodium acetate (22 mg.), and acetic anhydride (2 cc.) under reflux for one hour. The acetic anhydride was removed by vacuum distillation and the residue was extracted several times with chloroform. The product obtained by evaporating the filtered chloroform extract (40 mg.) was sublimed at 140–150° (0.07 mm.). The sublimate consisted of microscopic rods (23 mg.) melting to a viscous droplet at 142–146° with meniscus formation at 177°. The analysis of this and another preparation was not quite satisfactory.

Anal. Calcd. for $C_{18}H_{26}O_{10}N_2$: C, 50.23; H, 6.09; $COCH_3$, 60.0. Found: C, 49.31; H, 5.88; $COCH_3$, 56.5.

For the preparation of the **hexabenzoate** a mixture of the dihydrochloride (199 mg.), pyridine (2.5 cc.) and benzoyl chloride (1 cc.) was heated just to boiling. After cooling the mixture was poured into ice water, acidified with hydrochloric acid, and extracted with chloroform. The extract was washed with bicarbonate solution and water, dried and evaporated. The residue was triturated with warm ether, and the insoluble portion (472 mg.) recrystallized twice from chloroform–ether. Small rods (408 mg.), melting without decomposition at 252–255°. On drying for the analysis at 155° *in vacuo* the melting point remained unchanged.

Anal. Calcd. for $C_{48}H_{38}O_{10}N_2$: C, 71.81; H, 4.77. Found: C, 71.86; H, 4.85.

Salts and Acyl Derivatives of β-Diamine I.—In general the same procedures were used as in the case of α-diamine I.

The **dihydrochloride** was obtained from the dipicrate in 72% yield, amorphous, gradually decomposed with effervescence after sintering at about 95°. The material was dried for analysis at 78° *in vacuo.*

Anal. Calcd. for $C_6H_{14}O_4N_2\cdot 2HCl$: C, 28.70; H, 6.42. Found: C, 28.63; H, 6.51.

Sulfate: microscopic prisms, darken above 280°, no m. p. up to 340°.

Anal. Calcd. for $C_6H_{14}O_4N_2 \cdot H_2SO_4$: C, 26.12; H, 5.84; N, 10.14. Found: C, 25.80; H, 6.10; N, 9.84.

The **N,N'-diacetate** was prepared from the dihydrochloride (101 mg.) with acetic anhydride (0.12 cc.) and methanol (0.9 cc.) as described for the α-diamine. The crude product was thrice recrystallized from methanol-ethanol, yielding small prisms (42 mg.) which started sintering at 194° and then gradually decomposed over the range 208–245°. This behavior is in marked contrast to that of the α-diamine I N,N'-diacetate (see above). A mixture of the two compounds melted over the same range as the α-isomer. The analytical sample was dried at 150° *in vacuo*.

Anal. Calcd. for $C_{10}H_{18}O_6N_2$: C, 45.79; H, 6.92; N, 10.68. Found: C, 46.14; H, 6.99; N, 10.57.

The **hexaacetate** was prepared from the dihydrochloride (213 mg.) with sodium acetate (145 mg.) and acetic anhydride (14 cc.) as described for the α-isomer. Like the latter, it could be sublimed in a high vacuum, but the bulk of the material was in this case purified by precipitation from chloroform or dioxane with dry ether. The final product was not distinctly crystalline. The melting point properties were similar to those of the α-isomer (liquefication at 145–149°, meniscus at 170°). A mixture of the isomers showed the same behavior. The compound was dried for analysis at 110° (2 mm.).

Anal. Calcd. for $C_{18}H_{26}O_{10}N_2$: C, 50.23; H, 6.09; N, 6.51; 6 $COCH_3$, 60.0. Found: C, 49.83; H, 6.17; N, 6.26; $COCH_3$, 58.6.

The **hexabenzoate** was prepared from 206 mg. of the dihydrochloride and worked up as described for the α-isomer. The residue from the chloroform extract was for the most part soluble in ether (difference from α-isomer). Accordingly the ether-soluble part was recrystallized from chloroform–hexane, and then twice from benzene–hexane, from which it separated in well-defined, short needles, melting without decomposition at 262–263° (block preheated to 230°). The melting point of mixtures with the α-isomer (m. p. 252–255°) was found to be 251–253° in repeated determinations. Admixture of a small amount of streptamine hexabenzoate (m. p. 314–316°) to the β-hexabenzoate depressed the melting point of the latter to 258–260°. The analytical sample was dried at 110° (2 mm.).

Anal. Calcd. for $C_{48}H_{38}O_{10}N_2$: C, 71.80; H, 4.77; N, 3.49. Found: C, 71.88; H, 5.04; N, 3.47.

The X-ray diffraction diagram[6] showed the following characteristics (letters in brackets denote intensities, *i. e.*, very strong, strong, medium, faint, very faint): 12.00 (v. s.), 10.10 (m.), 8.70 (f.), 7.45 (v. f.), 6.18 (f.), 5.65 (f.), 5.12 (v. f.), 4.85 (s.), 4.62 (s.), 4.33 (s.), 3.93 (m.), 3.54 (f.), 3.41 (f.), 3.24 (f.), 3.08 (f.), 2.73 (f.), 2.38 (v. v. f.), 2.17 (v. v. f.), 2.05 (v. v. f.), 2.02 (v. v. f.), 1.95 (v. v. f.), 12.70 (s.). On the pattern of the α-diamine I hexabenzoate Dr. G. L. Clark comments as follows: "The pattern is distinguished by only one sharp crystalline interference which corresponds with the innermost, most intense diffraction line of the preceding sample. In addition, there is a broad outer halo which appears to result from the overlapping of several of the ill-defined lines which appear completely resolved for the β-hexabenzoate. This means, therefore, that this second sample is very imperfectly crystalline and that the molecules in the solid have only one direction in which there is anything like a regular arrangement, this corresponding to the longest interplanar spacing. This very diffuse pattern would not eliminate the possibility of an admixture of more than one compound, and it cannot be interpreted as conclusive evidence either that the compound is the same or different from the well-crystallized β-hexabenzoate even granted that there is an approximate (12.0 and 12.7 å.) correspondence in this longest interplanar spacing. This at least is evidence that one of the molecular dimensions must be common to the two materials."

Diamine II.—Diamine II dipicrate (83 mg.) prepared from the β-dibromotetrol was dissolved in hot water (10 cc.). After the addition of 2 *N* hydrochloric acid (0.75 cc.) the solution was extracted with toluene and then with benzene. The residue of the lyophilized phase (165 mg.) was purified by dissolving it in warm methanol and concentrating to a small volume. Repetition of the procedure yielded the **dihydrochloride** (22 mg.) as a well-particulated, possibly microcrystalline precipitate which in the capillary started darkening at about 220° but did not liquefy up to 300°. The analytical sample was dried at 110° (2 mm.).

Anal. Calcd. for $C_6H_{14}O_4N_2 \cdot 2HCl$: C, 28.70; H, 6.42. Found: C, 28.84; H, 6.65.

A sample prepared *via* the dipicrate from the α-dibromotetrol behaved similarly.

For the preparation of the **N,N-diacetate** the "α"-dihydrochloride (64 mg.) was acetylated with methanol (2.9 cc.), silver acetate (85 mg.) and acetic anhydride (0.18 cc.). After refluxing for five minutes the mixture was worked up as described for the α-diamine I N,N'-diacetate, except that excess ether was added to the aqueous-ethanolic solution of the crude product to complete the precipitation (63 mg.). Recrystallized twice from methanol-ethanol the diacetate formed long needles melting at 268–269° after some sintering at 265°. The preparation derived from the β-dibromotetrol behaved identically, as did the mixture of the two samples. The desiccator-dry specimens contained one mole of water, which was removed by drying at 150° *in vacuo*.

Anal. Calcd. for $C_{10}H_{18}O_6N_2$: C, 45.79; H, 6.92; N, 10.68. Found: (a) from α-tetrol: C, 45.61; H, 6.97; N, 10.80; (b) from β-tetrol: C, 45.60; H, 6.91.

Streptamine N,N'-diacetate was prepared as in the above instances by selective N-acetylation instead of by alkaline hydrolysis of the hexaacetate.[4] Its melting point (282–283°) was depressed to 242–262° by admixture of diamine II N,N'-diacetate.

Periodate Titration.—Accurately weighed 4–8 mg. samples of the compounds were dissolved in 10 cc. of potassium periodate solution containing 0.0128 atom of available oxygen per cc. One-cc. aliquots were withdrawn at suitable intervals, and after the addition of sulfuric acid, sodium acetate and potassium iodide, titrated with 0.01 *N* thiosulfate solution. The results are expressed in moles of periodate per mole of substance, the figures in parentheses denoting the reaction time in hours.

α-Diamine I dihydrochloride: 4.21 (0.75), 5.76 (3.25), 6.05 (22).
α-Diamine I N,N'-diacetate: 0.43 (1.0), 1.32 (6), 1.97 (23), 1.95 (30).
β-Diamine I dihydrochloride: 4.39 (0.5), 6.11 (21), 6.05 (26).
β-Diamine I N,N'-diacetate: 0.09 (0.5), 1.97 (21), 1.99 (26).
"α"-Diamine II dihydrochloride: 4.82 (0.5), 6.01 (2.5), 6.09 (24).
"α"-Diamine II N,N'-diacetate: 0.64 (0.5), 1.51 (2.5), 2.93 (24), 2.96 (44).
"β"-Diamine II N,N'-diacetate: 0.36 (0.33), 3.00 (22), 2.99 (70).
α-Dibromotetrol: 1.11 (23), 1.46 (46), 2.79 (69), 3.46 (94), 3.96 (144), 4.01 (192).
β-Dibromotetrol: 1.53 (23), 2.30 (46), 2.76 (70), 2.88 (94), 3.02 (118), 3.02 (192).

The analyses were performed by Mr. J. F. Alicino and his assistants.

Summary

The two isomeric dibromotetraacetoxycyclohexanes ("α"- and "β") which Griffin and Nelson[1] had obtained by treatment of *meso*-inositol with acetyl bromide were hydrolyzed to the corresponding free tetrols. Amination of the dibromotetrols

with aqueous ammonia afforded a mixture of diaminocyclohexanetetrols which were isolated and separated as the picrates.

The main product from the α-dibromotetrol (α-diamine I) was converted into suitable acyl derivatives and compared with the main product from the β-dibromotetrol (β-diamine I) and its derivatives. Though in many respects similar, the two diamines appear to be different chemical entities. Their N,N′-diacetyl derivatives both consumed two moles of periodate indicating that the parent diamines could be either 1,3- or 1,4-diaminocyclohexanetetrols. Identity with streptamine is excluded in either case by the properties of the acyl derivatives.

In addition both dibromotetrols yielded small amounts of an identical diaminocyclohexanetetrol (diamine II). The N,N′-diacetyl derivative consumed three moles of periodate and hence must carry the acetamido groups in vicinal ring positions.

NEW BRUNSWICK, N. J. RECEIVED OCTOBER 28, 1948

[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY]

Ultrasonic Investigation of Molecular Properties of Liquids. V. Inorganic Halides[1]

BY ALFRED WEISSLER

The relation between sound velocity and molecular structure has been studied[2] in several series of organic liquids, but thus far not in inorganic liquids. A group of compounds which seemed especially suitable for this purpose consists of the Group IV tetrahalides. Their molecules may be considered as approximately spherical, so that they are easier to treat theoretically and thus furnish an approach to a better understanding of the liquid state. Because of this, their physical and thermodynamic properties have been studied for many years by Hildebrand[3] and co-workers.

A two-fold aim motivated the present work: (a) comparison of inorganic and organic liquids with respect to sound velocity, and (b) determining further properties of the interesting tetrahalides referred to above. Several thermodynamic quantities may be calculated from the measured velocity of sound in a liquid.

In addition to CCl_4, $SiCl_4$, $TiCl_4$, $GeCl_4$ and $SnCl_4$, some of the Group V halides were included here, specifically, PCl_3, PBr_3, $POCl_3$, $AsCl_3$ and $SbCl_5$.

Experimental

The ten liquids were procured from commercial sources. Each was purified by fractional distillation (the fraction retained had a boiling-range of 0.5°) shortly before use, and protected as well as possible from deterioration due to moisture. The liquids were handled only under conditions of low atmospheric humidity.

Sound velocities at 30° were measured by means of the three-megacycle ultrasonic interferometer already described,[2] which requires only 10 ml. of sample. In order to minimize contamination of these reactive liquids, all interior surfaces were gold-plated and the usual nickel diaphragm at the floor of the cell was replaced by tantalum.

Densities, heat capacities and coefficients of thermal expansion at 30° were obtained from the "International Critical Tables" and Landolt–Börnstein tables.

Results and Discussion

The velocity of sound in each of these inorganic halides is given in Table I; the probable accuracy is ±0.1%. These values lie in the range from about 760 to 1000 meters per second, which is somewhat lower than for most other liquids, including the organic halides. Figure 1 shows that no regular change of sound velocity in the tetrachlorides occurs as the atomic number of the central atom increases. In the Group V halides also, there is no consistent trend with molecular weight.

Molar Sound Velocity.—Because it is an additive function[4,5] of the chemical bonds in the molecule, the molar sound velocity is useful in correlating molecular structure with sound velocity. It is defined, so as to be empirically almost temperature-independent, as the molar volume times the cube root of sound velocity.[6]

From the values of molar sound velocity listed in Table I, the bond increment characteristic of each bond present in these compounds was obtained by simple arithmetic. For example, the value for $SiCl_4$ was divided by 4 in order to find the Si–Cl increment, while that for PBr_3 was divided by 3 to get the P–Br increment. Table II contains the figures so derived, which again fail to vary regularly with atomic number of the central atom, in either Group IV or Group V.

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[1] The opinions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Navy service at large. Article not copyrighted.

[2] Weissler, THIS JOURNAL, **71**, 93 (1949); **71**, 419 (1949); and references contained therein.

[3] Hildebrand, *J. Chem. Phys.*, **15**, 727 (1947).

[4] Lagemann and Dunbar, *J. Phys. Chem.*, **49**, 434 (1945).

[5] See, however, Lagemann, Evans and McMillan, THIS JOURNAL, **70**, 2996 (1948), who studied a large number of organic halides and concluded that molar sound velocity is not strictly additive, but rather highly constitutive.

[6] Rao, *J. Chem. Phys.*, **9**, 688 (1941).