[COMMUNICATION FROM THE DEPARTMENT OF INDUSTRIAL AND CELLULOSE CHEMISTRY, McGILL UNIVERSITY]

STUDIES ON THE REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES. XVII. STRUCTURE OF THE ISOMERIC METHYLIDENE GLYCEROLS

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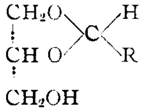
The work described in this paper is an outcome of attempts to investigate the structure and relative proportions of the isomeric cyclic acetals A and B formed when an aldehyde (RCHO) condenses with glycerol

(A)



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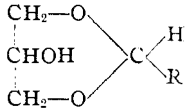
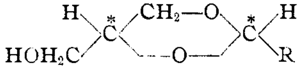


An examination of these two formulas shows that in a five-membered ring of Type I (corresponding to A), due to the presence of two asymmetric

(I)



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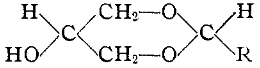

carbon atoms(*), the product should be capable of existing in two geometrically isomeric *racemic* forms, while in Type II (corresponding to B), two *geometrical* isomers are theoretically possible, optical activity being excluded due to pseudo-symmetry.

The complications thus introduced by this considerable number of possible isomeric cyclic acetals make such investigations a matter of considerable difficulty and uncertainty and most probably account for the anomalous results sometimes obtained in the process of purification[2] and the gradual change taking place on standing in the melting points of crystalline derivatives of cyclic acetals.[3]

The view that *only* the five-membered type of cyclic acetal is formed in such condensations has, unfortunately, been accepted by various investigators. Thus in the recent paper by Yoder[4] dealing with the condensation of chloral and glycerol, the assumption is made that only the five-membered acetal is formed. An investigation by the present authors of this same reaction is in progress and will presumably yield evidence of the simultaneous formation of both the five- and six-membered acetals. In the condensation

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[2] Hill, Whelen and Hibbert, THIS JOURNAL, **50**, 2237 (1928).

[3] Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 344 (1915).

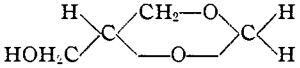
[4] Yoder, THIS JOURNAL, **45**, 475 (1923).

of chloral with glucose the number of theoretically possible isomers (structural, geometrical, optical) capable of existence, is much greater, hence the confusion arising out of the various investigations[5] dealing with this reaction.

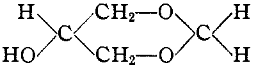
A solution not only of this but also of other problems in carbohydrate and polysaccharide chemistry, will doubtless be found in the further application of the principles enumerated in the series of investigations carried out by Hibbert and co-workers during the last eight years in this field, embracing, as they do, a recognition of the important role played by the somewhat neglected, but invaluable and indispensable "Partition Principle" of Arthur Michael[6] as well as of the deductions derivable from a consideration of the nature of the structural, geometrical and optical isomerism involved.[7]

The complications referred to above can be avoided if the study is confined to those acetals (or ketals) where such *geometrical* isomerism is impossible, as, for example, in the case of the isomeric methylidene glycerols,[8] III and IV.

(III)



(IV)



In Type III only one asymmetric carbon atom is present, so that the product should yield a single optically resolvable racemic form, while Type IV is not capable of existing in more than one, non-optically active, modification. The number of possible isomers is thus limited to one representative of each ring system, the five-membered acetal, however, being capable of active resolution.

In view of the relative stability of methylidene glycerol toward hydrolysis,[9] as compared with other acetals[10] and ketals,[11] this cyclic acetal was chosen as the simplest type conforming to the above requirements.

[5] Heffter, *Ber.*, **22**, 1050 (1889); Hanriot and Richet, *Compt. rend.*, **116**, 63 (1892); **117**, 734 (1893); **122**, 1127 (1896); *Bull. soc. chim.*, [3] **9**, 947 (1893); [3] **11**, 37, 258, 303 (1894); Hanriot, *Ann. chim. phys.*, **18**, 466 (1909); Hanriot and Kling, *Compt. rend.*, **152**, 1398, 1596 (1911); **156**, 1380 (1913); Meunier, *Ann. chim. phys.*, [6] **22**, 413 (1906); Petit and Polonowski, *Bull. soc. chim.*, [3] **11**, 125 (1894); Pictet and Reichel, *Helv. Chim. Acta*, **6**, 621 (1923).

[6] Michael, *Ber.*, **39**, 2138, 2143, 2149, 2153, 2157, 2569, 2785, 2789 (1906); **40**, 140 (1907); *J. prakt. Chem.*, **60**, 339, 341, 437 (1899).

[7] Researches dealing with many of these points are in active progress and the bearing of such in connection with the structure of cellulose, starch, etc., is to be reported on in the near future.—H. H.

[8] The name "methylidene glycerol" is employed to denote its relationship (as the lowest member) to a series of cyclic acetals, for example, ethylidene, propylidene, isopropylidene, etc., glycerols.

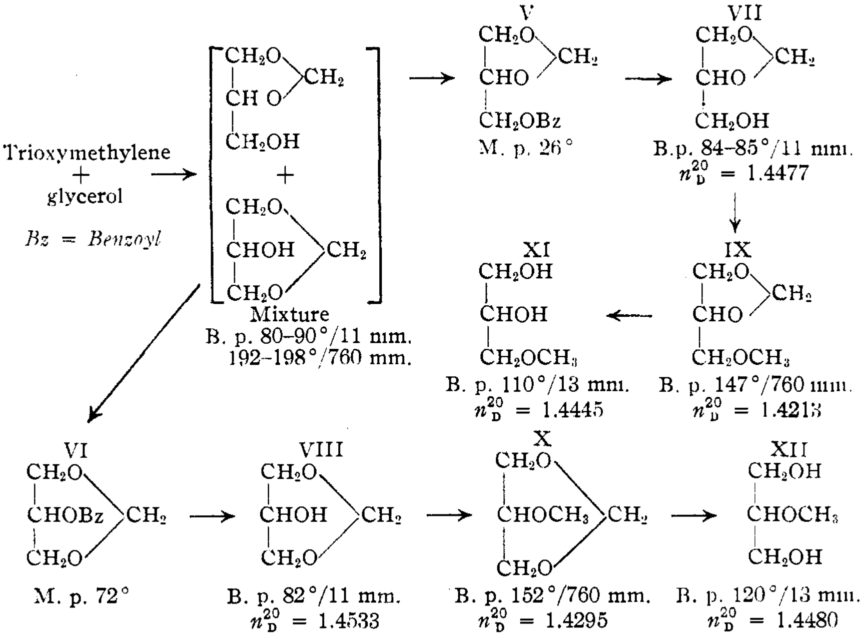
[9] Nef, *Ann.*, **335**, 215 (1904).

[10] Hibbert and Timm, This Journal, **46**, 1289 (1924).

[11] Fischer and Pfähler, *Ber.*, **53**, 1606 (1920).

Methylidene glycerol has long been known[12] and the existence of two isomeric benzoates was shown by Schulz and Tollens,[13] who, however, left open the question of their structure. Its properties were further studied by Nef,[9] and Peacock[14] obtained a partial optical resolution of his product which led him to assign to it the structure corresponding to I.

A careful study by the authors of the product formed in the reaction between formaldehyde (trioxymethylene) and glycerol has shown this to consist of the two isomeric cyclic acetals III and IV, which have been separated and identified by the method outlined in the following scheme.



This sharp separation into two isomeric series was rendered possible by the successful isolation of the two pure isomeric benzoates V and VI (as indicated in the experimental part) from which it was then possible to prepare, for the first time, the pure acetals VII and VIII and the methyl ethers IX and X.

These ethers yielded the corresponding α- and β-glycerol methyl ethers on hydrolysis, the identification of the β-derivative being definitely settled by comparison with the pure glycerol β-methyl ether recently isolated in this Laboratory.[15]

Among other attempts to obtain a separation of the isomeric acetals

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[12] Harnitzky and Menschutkin, *Ann.*, **136**, 126 (1865).

[13] Schulz and Tollens, *Ann.*, **289**, 30, 33 (1896).

[14] Peacock, *J. Chem. Soc.*, **107**, 815 (1915).

[15] Hill, Whelen and Hibbert, This Journal, **50**, 2238 (1928).

from the original reaction mixture by means of crystalline derivatives, the *p*-nitrobenzoates were prepared. These crystallize much less readily than the corresponding benzoates and were more difficult to separate. The five-membered derivative melted at 135° and its six-membered isomer at 185°.

The Interconversion of 1,2- and 1,1′-Methylidene Glycerols

The mixture of acetals obtained in the original condensation product can only be partially separated into its component isomers by fractional distillation at atmospheric pressure and it was in this connection that the observation was first made of a change in the higher boiling fraction (197–198°) on standing for several months into approximately that of the lower (192–193°). It was found later that the unseparated mixture of acetals, on treating with a few bubbles of dry hydrogen chloride gas and allowing to stand for some hours at 100°, always gave, on benzoylation, a greater yield of the benzoate of the 1,1′-acetal than the untreated mixture. On the other hand, after the pure acetals had finally been isolated, treatment of each for thirty minutes at 100° with approximately 0.01% by weight of dry hydrogen chloride showed a large percentage conversion of VII into VIII, as indicated by change in refractive index, while VIII evidenced little, if any, change into VII. In view of this transformation from a 5- to a 6-membered ring under the catalytic influence of small amounts of acid, it was necessary to show that a similar conversion does not take place during the alkaline hydrolysis of the benzoates and the methylation of resulting acetals, also carried out in *alkaline* solution. This was accomplished by first hydrolyzing separate samples of V and VI and then re-benzoylating only after the acetals had first been given an opportunity of undergoing interconversion by heating in presence of alkali. In each case the original benzoate was obtained exclusively, showing that no tendency toward such change exists under these conditions. All subsequent operations with the free acetals were therefore performed in the presence of a small piece of solid potassium carbonate to ensure alkalinity.

Due to the sensitivity toward acid media and the close similarity in chemical properties of the two liquid isomeric acetals, it is difficult to determine, other than qualitatively, the ratio of the two isomers present in the original reaction product. The evidence, however, points to a preponderance of the 5-membered ring in the ratio of approximately 3 to 2.[16]

Experimental Part

Preparation of the Mixture of Isomeric Acetals.—As a result of many preliminary experiments on the preparation of the methylidene acetals,

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[16] The problem of finding an aldehyde capable of giving crystalline isomeric cyclic acetals has been solved by the use of *p*-nitrobenzaldehyde and it has been found possible to isolate the theoretical number of isomers in the case of *p*-nitrobenzylidene glycerol derivatives. This work is to appear in the near future.

using the original method of Schulz and Tollens,[13] and also employing several of the catalysts mentioned by Adams and Adkins[17] as being advantageous in acetal formation, the best yields were eventually obtained by the following original method.

An equimolecular mixture of 75 g. of pure glycerol and 25 g. of trioxymethylene was acidified with 2 cc. of concentrated hydrochloric acid, the whole well shaken in a stoppered flask, and then kept at 100° for one and one-half hours with frequent shaking. The resultant clear solution, while still hot but without further heating, was placed under reduced pressure (12 mm.) and the vacuum maintained until no further evolution of water was observed. This removal of water with consequent displacement of the equilibrium: trioxymethylene + glycerol $\rightleftharpoons$ acetal + water, was found materially to improve the yield of acetal. The residual liquid was allowed to stand for another twelve hours at 100° and then distilled under reduced pressure in the presence of the hydrochloric acid. The first drops of acetal commenced to distil at about 90° (10 mm.) and the temperature was then gradually raised until the distillate began to appear viscous, by which time most of the acetal had distilled over. Redistillation from a boiling water-bath yielded 50 g. (63%) of the pure mixed acetals boiling between 80–90° (11 mm.) n_D^{20} = 1.4497, the latter value indicating a mixture of approximately 60% of the 1,2- and 40% of the 1,1′-methylidene glycerol.

Conversion of Mixed Acetals into Benzoates.—The mixed acetals may be benzoylated directly, but since for the purpose of this investigation as large a yield as possible of the benzoate (VI) of the 6-membered acetal was desired, advantage was taken of the action of dry hydrogen chloride in bringing about a large conversion of the 1,2- into the 1,1′-acetal. Fifty g. of the isomeric mixed acetals as obtained by direct distillation, b. p. 80–90° (11 mm.), was treated with 0.01% by weight of dry hydrogen chloride and allowed to stand for half an hour at 100°, then cooled and added to 40 g. of pure, dry pyridine. The theoretical quantity (68 g.) of benzoyl chloride was slowly run in from a dropping funnel, with constant shaking, at such a rate that the temperature of the exothermic reaction was kept below 60°. The product was allowed to stand at 20° for forty-eight hours to complete the reaction, dissolved in slightly more than the minimum quantity of ether necessary for solution, washed successively with considerable water, then with very dilute sulfuric acid and finally with dilute sodium bicarbonate solution prior to being dried over fused calcium chloride. After removal of the ether under reduced pressure and cooling, the mixed isomeric benzoates were left as a more or less oily white crystalline paste; yield practically quantitative (95 g.).

Separation of the 1,2-Methylidene Glycerol 1′-Benzoate (V) from the Isomeric 1,1′-Methylidene Glycerol 2-Benzoate (VI).—The above semi-crystalline mass was dissolved in four times its volume of warm ether and cooled to room temperature (18°), when it deposited a network of fine, prismatic needles. These were filtered off by suction but not washed, since they are relatively quite soluble in the solvent at ordinary temperatures. By further cooling the filtrate to 0° a second crop could be filtered off at this temperature. Finally, sufficient solvent was evaporated from the remainder to cause the solution practically to solidify when cooled to −20° with stirring; the cold paste was transferred to a small, previously cooled Büchner funnel and suction applied while the whole was slowly allowed to warm to room temperature. The remaining thin layer of unmelted crystals was added to the two previous crops and the whole allowed to lose any adsorbed ether by standing at a temperature below 15°. Recrystallization from hot ligroin (b. p. 80–90°) gave pure 1,1′-methylidene glycerol 2-

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[17] Adams and Adkins, THIS JOURNAL, 47, 1361 (1925).

benzoate (VI) in the form of long (1–2 cm.) colorless prismatic needles, m. p. 72°, corresponding to the product obtained by Schulz and Tollens.[18] The crystals are very soluble in benzene, and other solvents at 30° and are deposited readily from ether and alcohol as the temperature falls toward 0°; they are insoluble in water and cold ligroin. The yield in the most favorable experiment was approximately 50% of the mixed benzoates.

Anal. Subs., 0.1952: CO_2, 0.4536; H_2O, 0.0988. Calcd. for $C_{11}H_{12}O_4$: C, 63.4; H, 5.81. Found: C, 63.3; H, 5.66%.

The ethereal solution of the remaining isomeric benzoate (V) contained residual traces of pyridine, which was removed by distillation and the residue then fractionated under reduced pressure.

The main product boiled at 172–175° (15 mm.) and undoubtedly was the "oily benzoate" analyzed by Schulz and Tollens; yield, 45% of total mixed benzoates. On long standing at 0° or by solution in methyl alcohol and cooling to −20°, large, colorless, tabular prisms of 1,2-methylidene glycerol 1′-benzoate (V) melting at 26° and possessing the same solubility relations in organic solvents as the first isomer were eventually obtained, though only with considerable difficulty.

Anal. Subs., 0.2047: CO_2, 0.4741; H_2O, 0.1061. Calcd. for $C_{11}H_{12}O_4$: C, 63.4; H, 5.81. Found: C, 63.2; H, 5.52. *Mol. wt.* Subs., 0.4117; ethylene bromide, 40.07; ΔT, 0.566°. Mol. wt., calcd.: 208.1. Found: 213.

Alkaline Hydrolysis of 1,2-Methylidene Glycerol 1′-Benzoate (V) to 1,2-Methylidene Glycerol (VII).—Forty g. of V was added to 110 g. of a 20% potassium hydroxide solution and continuously shaken at 75° for ten to fifteen minutes until the oil resulting from the melting of the crystals had dissolved completely to a clear solution. After cooling the solution, the excess of potassium hydroxide was converted into carbonate by passing in carbon dioxide and the solution completely saturated by adding anhydrous potassium carbonate. The resulting liquid acetal (together with some sodium benzoate thrown out of solution) was extracted by repeated shaking with ether and decantation, the sodium benzoate filtered off and the ether solution dried over solid potassium carbonate. After removal of the ether, distillation under reduced pressure in the presence of a small amount of solid potassium carbonate yielded 15 g. (75%) of crude product. On redistillation pure 1,2-methylidene glycerol (VII) was obtained; b. p. 84–85° (11 mm.); 104° (28 mm.); 195° (760 mm.); $n_D^{20} = 1.4477$ $d_4^{20} = 1.2113$.

Anal. Subs., 0.2061: CO_2, 0.3414; H_2O, 0.1435. Calcd. for $C_4H_8O_3$: C, 46.12; H, 7.75. Found: C, 46.20; H, 7.79. *Mol. wt.* Subs., 0.1049, 0.4312: ethylene bromide, 40.77, 40.77; ΔT, 0.250, 0.954°. Mol. wt., 122, 131.

These values indicate some association due to the free hydroxyl group, extrapolation to zero concentration giving a mol. wt. of 107 (theoretical, 104).

The substance is a slightly viscous, colorless, hygroscopic liquid, soluble in all proportions in ether, alcohol, water and warm benzene. When freshly distilled a very slight odor is noticeable which later disappears. Even on prolonged exposure no odor of formaldehyde is developed, hydrolysis only occurring on boiling with dilute acids (hydrochloric acid, etc.). This behavior is in marked contrast to most glycerin acetals.

When the acetal is mixed with 0.01% by weight of dry hydrogen chloride and heated to 100° for twenty minutes, the refractive index (which is practically unchanged immediately after addition of catalyst) rises from 1.4477 to 1.4540 (20°), thus indicating a large conversion to the 1,1′-isomer (VIII) described below.

Alkaline Hydrolysis of 1,1′-Methylidene Glycerol 2-Benzoate (VI) to 1,1′-Methylidene Glycerol (VIII).—Forty grams of VI hydrolyzed in the same manner as the above corresponding isomer yielded 12 g. (60%) of 1,1′-methylidene glycerol (VIII). Careful distillation of the resulting product gave a slightly viscous, colorless, hygroscopic liquid; b. p. 82° (11 mm.); 100° (28 mm.); 191° (760 mm.); n_D^{20} = 1.4533; d_4^{20} = 1.2256.

Anal. Subs., 0.2037: CO_2, 0.3432; H_2O, 0.1416. Calcd. for $C_4H_8O_3$: C, 46.12; H, 7.75. Found: C, 45.95; H, 7.77. *Mol. wt.* Subs., 0.2009, 0.4074, 0.5116; ethylene bromide, 40.44, 40.44, 40.44; ΔT, 0.498°, 0.936°, 1.114°. Mol. wt., 118, 127, 134. By extrapolation to zero concentration as before, mol. wt. = 107 (theoretical, 104.1).

In odor, solubility in solvents and resistance toward hydrolysis, it closely resembles the 1,2-isomer (VII). On similar treatment with hydrogen chloride, the refractive index, instead of falling as would be expected from a partial conversion into the isomer (VII), gradually rose over a period of twenty-four hours to 1.4583 at 20°, accompanied by discoloration and increase in viscosity, the latter phenomena indicating some more deep-seated change.

Methylation of 1,2-Methylidene Glycerol (VII).—Ten grams of acetal (VII) was dissolved in 43 g. (3 moles) of methyl iodide and the usual methylation procedure followed by slowly adding 35 g. of dry silver oxide during a period of three hours, the mixture being refluxed and well stirred throughout the addition. After extracting with ether and drying over calcium chloride, fractionation of the resulting liquid yielded 8.5 g. (80%) of crude 1,2-methylidene glycerol 1′-methyl ether (IX), b. p. 145–150° (760 mm.). To remove unchanged acetal, glycerol, etc., this was heated with a globule of metallic sodium for a few minutes at 80°, the product filtered and the filtered liquid redistilled. The pure methyl ether was then obtained as a colorless, mobile liquid possessing a pleasant, ethereal odor, soluble in all proportions in ether, alcohol, benzene and water; b. p. 147° (760 mm.); n_D^{20} = 1.4213; d_4^{20} = 1.0788.

Anal. Subs., 0.1988: CO_2, 0.3651; H_2O, 0.1497. Calcd. for $C_5H_{10}O_3$: C, 50.8; H, 8.56. Found: C, 50.1; H, 8.43. *Mol. wt.* Subs., 0.3107; ethylene bromide, 40.50; ΔT, 0.741°. Mol. wt., 122 (theoretical, 118.1).

Methylation of 1,1′-Methylidene Glycerol (VIII).—Ten grams of the acetal was methylated by means of dimethyl sulfate and caustic potash according to the method of Haworth[18] and the resulting methyl ether (X) separated from the reaction mixture by continuous ether extraction over a period of eight hours. Distillation of the extract yielded 6 g. (55%) of crude 1,1′-methylidene glycerol 2-methyl ether, b. p. 150–160° (760 mm.).

Purification with metallic sodium as above and redistillation gave a pure product, b. p., 152° (760 mm.); n_D^{20} = 1.4295, and possessing the same appearance, odor and solubilities as the corresponding isomer (IX).

Anal. Subs., 0.2019: CO_2, 0.3731; H_2O, 0.1521. Calcd. for $C_5H_{10}O_3$: C, 50.80; H, 8.56. Found: C, 50.61; H, 8.43. *Mol. wt.* Subs., 0.2115; ethylene bromide, 43.11; ΔT, 0.508°. Mol. wt., 114 (theoretical, 118.1).

Acid Hydrolysis of 1,2-Methylidene Glycerol 1′-Methyl Ether (IX).—Seven grams of the ether was dissolved in an equal volume of water and 6 drops of concentrated hydrochloric acid added. On refluxing for ten minutes at the boiling point, liberation of formaldehyde commenced and after further refluxing for thirty minutes it was allowed to simmer for two to three hours in a small open Erlenmeyer flask until the evolution ceased. Water was added from time to time to replace that lost by evaporation. The hot solution was then neutralized by adding solid lead carbonate, cooled, filtered and subjected to vacuum distillation. The sole product (b. p. 110° at 13 mm.) was readily recognized as glycerol α-methyl ether by its boiling point and refractive index; n_D^{20} = 1.4445;[3] yield, 3 g. (50%).

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[18] Haworth, *J. Chem. Soc.*, **107**, 8 (1915).

Acid Hydrolysis of 1,1'-Methylidene Glycerol 2-Methyl Ether (X).—Five grams of this ether was hydrolyzed by the same method and yielded 2 g. (45%) of pure glycerol β-methyl ether;[15] b. p. 120° (13 mm.); $n_D^{20} = 1.4480$.

The identity was further confirmed by conversion of the product into 1,1'-*p*-nitrobenzylidene glycerol 2-methyl ether and isolation of the two crystalline isomers, m. p. 42 and 47°, respectively.[19]

Summary

1. The possibility of both optical and geometrical isomerism in the structurally isomeric cyclic acetals of glycerol is pointed out.

2. Advantage is taken of the absence of geometrical isomerism in the methylidene glycerols in order to isolate and determine the structure of the two isomers formed by partition of formaldehyde between the 1,2- and 1,1'-hydroxyl groups of glycerol during cyclic acetal formation.

3. The isolation and identification of the two isomeric methylidene glycerols and of certain of their derivatives are described.

4. The interconversion of the ring systems of the two isomeric acetals has been investigated.

MONTREAL, CANADA

NEW BOOKS

A Textbook of Inorganic Chemistry. Volume VI, Part I. Nitrogen. By EDMUND B. R. PRIDEAUX, M.A., B.Sc. (N. Z.), D.Sc. (Lond.), F.I.C., and HERBERT LAMBOURNE, M.A. (Cantab.), M.Sc. (Lond.), F.I.C. J. B. Lippincott Company, Philadelphia, 1928. xxviii + 242 pp. 25 figs. 15.5 × 23 cm.

This volume deals solely with nitrogen, and in view of the present importance and extensive literature on the subject, naturally presents a problem to the authors as to what they shall include in the 231 pages of text allotted to them.

The fourteen chapters include an introductory chapter on the nitrogen atom, the properties of nitrogen, one on ammonia, hydroxylamine, nitrogen and the halogens, oxy-halogen derivatives, hydrides and their derivatives, hyponitrous acid, the oxides of nitrogen, nitrous acid, nitric acid. nitrogen and sulfur and one on the fixation of nitrogen. Some space might have been saved in the chapter on ammonia by a more judicious selection of graphs. For textbook purposes a satisfactory discussion of the synthetic production of ammonia is presented, including a brief reference to the technical features of the process.

The authors' prefatory intention to avoid "undue detail in physical constants and in the minutiae of chemical processes" has been somewhat overlooked by the later inclusion of such data as the tables of the solubility of nitrogen in water, and in sea water, and the listing of five different equations for the specific heat of ammonia at constant pressure. This

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[19] A full account of this work has been submitted for publication in THIS JOURNAL.