mately the same for all, its maximum occurring at about 4×10^{-3} hydrogen-ion concentration when one gram of air-dry gelatin occupies a volume of about 46 cc. Bivalent ionizing acids give much less swelling with a maximum at about the same point, and combine in somewhat greater equivalent amounts.

8. Salt ions do not combine with gelatin, but increase the absorption of alkalies or acids. They markedly decrease swelling and osmotic pressure, probably by decreasing the ionization of acids or alkalies combined with the gelatin. Since salt ions do not appreciably affect the ionization of the dilute highly ionized mineral acids or bases, the hydrogen or hydroxyl ion is not the determining factor when salts are present. The action of buffer mixtures likewise is not determined by the hydrogen-ion concentration.

9. The swelling of gelatin is the result of osmotic pressure within the jelly, with the jelly acting as an imperfectly resisting membrane, the more so when highly swollen. While the osmotic pressure at the optimum concentration of univalent acids and bases is the same, the swelling is much less in alkalies because of the weakened membrane effect. Bivalent sufuric acid gives the same swelling as bivalent calcium or barium hydroxide when swelling is small and the solution is not so great.

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SPIRO-PYRIMIDINES. II. CYCLOHEXANE-1,5-SPIRO-PYRIMIDINES.

BY ARTHUR W. DOX AND LESTER YODER.

Received March 14, 1921.

In the first paper[1] of this series a number of derivatives of cyclobutane-1,5-*spiro*-pyrimidine were described. They may be regarded as variously substituted barbituric acids in which the 5-carbon atom enters into a 4-membered hydrocarbon ring. The method of preparation consists in condensing an α, ω-dibromo-paraffin with ethyl malonate with formation of a cycloparaffin-1,1-dicarboxylic ester; the second ring is closed by condensation of the two carbethoxyl groups with urea according to the well-known veronal synthesis. By this method it should be possible also to obtain other *spiro*-pyrimidines containing 5- and 6-membered hydrocarbon rings. Starting, for example, with 1,5-dibromopentane instead of 1,3-dibromopropane, the above method of synthesis should yield a cyclohexane-1,5-*spiro*-pyrimidine.

[1] Dox and Yoder, THIS JOURNAL, **43**, 677 (1921).

The intermediate product required for this synthesis would therefore be ethyl cyclohexane-1,1-dicarboxylate. This substance has not heretofore been prepared. Haworth and Perkin[1] attempted to prepare it by converting pentamethylene diamine into the corresponding glycol, then into the dibromide, and condensing the latter with ethyl malonate. The supposed 1,5-dibromopentane which they obtained was found, however, to contain about 75% of 1,4-dibromobutane. These mixed bromides were condensed with ethyl malonate, and after saponification the cyclopentane-1,1-dicarboxylic acid was isolated and identified. The cyclohexane-1,1-dicarboxylic ester, which was also present, was not separated until after saponification and loss of carbon dioxide, when hexahydrobenzoic acid was isolated and identified as its decomposition product. Freer and Perkin[2] and Kipping and Perkin[3] did, however, prepare the ethyl esters of methyl- and phenyl-cyclohexane-1,1-dicarboxylic acids from 1,5-dibromohexane and 1-phenyl-1,5-dibromopentane, respectively. These bromo derivatives were obtained from glycols prepared by reduction of the ketone alcohols. No satisfactory method was available at that time for the preparation of α,ω-dibromo-paraffins with more than 3 carbons.

The preparation of 1,5-dibromopentane from pentamethylene diamine attempted by Haworth and Perkin, although theoretically possible, is altogether unsatisfactory in point of yield and purity of the product. Another method introduced more recently by Von Braun[4] has proved far more successful. It consists in distilling benzoyl-piperidine with phosphorus pentabromide, the products being 1,5-dibromopentane and benzonitrile. After removal of the phosphorus oxybromide, von Braun separated the dibromopentane from benzonitrile by heating the mixture for several hours with fuming hydrobromic acid at 120° to 130° to hydrolyze the nitrile. He then distilled the dibromopentane and removed benzoic acid from it by washing the distillate with dil. alkali. From this product, the Perkin condensation with ethyl malonate should yield ethyl cyclohexane-1,1-dicarboxylate.

Experimental.

Preparation of 1,5-dibromopentane.—Inasmuch as some slight improvements were introduced into von Braun's method, the procedure we followed will be outlined briefly. Instead of phosphorus pentabromide which is rather inconvenient to handle, it was found that the addition of the theoretical amount of bromine to a mixture of phosphorus tribromide and benzoyl-piperidine answered the purpose equally well.

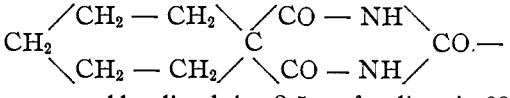
[1] Haworth and Perkin, *J. Chem. Soc.*, **65**, 86–105 (1894).
[2] Freer and Perkin, *ibid.*, **53**, 202–22 (1888).
[3] Kipping and Perkin, *ibid.*, **57**, 304–23 (1890).
[4] Von Braun, *Ber.*, **37**, 3210–13 (1904).

In a distilling flask, molecular proportions of phosphorus tribromide and benzoyl-piperidine were carefully mixed while the material was cooled with tap water. The benzoyl-piperidine gradually dissolved to give a clear reddish solution. To this mixture the molecular proportion of bromine was slowly added, while the product was cooled as before. Then the contents of the flask were distilled slowly under diminishead pressure until the distillate began to solidify in the condenser. The distillate was poured on ice to decompose the phosphorus oxybromide. At this point it is importnat to use a rather liberal supply of ice, otherwise the reaction, which begins very slowly, may suddenly develop sufficient heat to cause the mixture to boil violently. After two hours, the oily layer is separated and shaken several times with water. Von Braun separated the mixture of dibromopentane and benzonitrile by hydrolyzing the letter with hydrobromic acid. We found that the separation can be effected much more easily by shaking three or four times in the cold with conc. sulfuric acid, which removes the benzonitrile completely. The remaining dibromopentane was then shaken with dil. sodium carbonate solution and finally dehydrated with calcium chloride. After two distillations, a product was obtained which boiled at a temperature between 87° and 90° at 5 mm. pressure. Von Braun reports a boiling point of 220° to 222° at ordinary pressure and 104° to 105° at 14 mm. The yield from 71 g. of crude benzoyl-piperidine was 62 g. or 72%.

Ethyl cyclohexane-1,1-dicarboxylate.—In condensing the 1,5-dibromopentane with ethyl malonate, the procedure previously outlined[1] was followed.

Sodium ethyl malonate, prepared by dissolving 13.1 g. of sodium in 300 cc. of absolute alcohol and adding 45.7 g. of ethyl malonate, was added from a dropping funnel to 65.6 g. of 1,5-dibromopentane contained in a flask surrounded by a bath of water at 80°. The mixture was then heated on the steam-bath for 2 hours, at the end of which time it was nearly neutral to litmus. The greater part of the alcohol was next distilled. It contained some volatile bromine derivative as evidenced by the odor and the turbidity produced by dilution with water, probably bromo-amylene. Water was added to the residue, whereupon the sodium bromide dissolved and a yellow oil separated. The latter was washed with water, dried with calcium chloride and distilled at 5 mm. pressure. A small amount of unchanged ethyl malonate and dibromopentane came over in the first fraction; then, between 105° and 110°, the cyclohexane-1,1-dicarboxylic ester distilled. A viscous, high boiling residue was probably heptane-1,1,7,7-tetracarboxylic ester. The latter was not examined further. Redistillation of the fraction collected between 105° and 110° gave 20 g. of a product boiling at 105° to 106° at 5 mm. pressure. This was used for the preparation of the *spiro*-pyrimidines.

Cyclohexane-1,5-*spiro*-2,4,6-triketo-hexahydro-pyrimidine,



Sodium ethylate, prepared by dissolving 3.5 g. of sodium in 60 cc. of alcohol, was added to 10.5 g. of ethyl cyclohexane-1,1-dicarboxylate and 4.5 g. of urea, and the mixture heated in the autoclave at 105° for 4.5 hours. The insoluble white product, consisting of the sodium salt of the ureide and sodium carbonate, was collected on a filter, dissolved in a small volume

[1] Dox and Yoder, *loc. cit.*

of water, and acidified with hydrochloric acid. White, lustrous, scaly crystals separated. These were purified by recrystallization from alcohol. In crystalline form and physical appearance the product closely resembled the corresponding cyclobutane derivative described in the previous paper. It is sparingly soluble in water, more soluble in dil. alkali and in alcohol, but unlike the cyclobutane derivative it is tasteless. It melted at 281°. The yield was 2.5 g. or 28%.

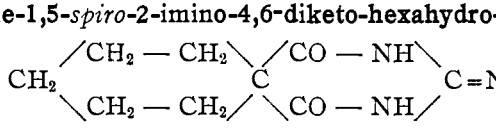
Subs., 0.2, 0.2: cc. 0.1 *N* acid, 20.4, 19.9. Calc. for $C_9H_{12}N_2O_3$: N, 14.28. Found: 14.28, 13.98.

It is of interest to note that a *spiro* derivative of somewhat similar structure was prepared by Thole and Thorpe[1] by condensation of cyclohexanone with cyano-acetamide and subsequent hydrolysis and loss of carbon dioxide. They designate it cyclohexane-1,1-diacetimide. It is in reality cyclohexane-1,4-*spiro*-2,6-diketo-piperidine. It differs from our product in that the heterocycle is a pyridine instead of a pyrimidine ring.

Amide of cyclohexane-1,1-dicarboxylic acid.—The smallness of the yield of *spiro*-pyrimidine led us to search for by-products in the mother liquor from the crude sodium salt obtained in the above preparation. The strong decomposition of the urea into ammonia suggested the possibility that an amide might have been formed. The mother liquor was accordingly evaporated under a jet of air until it had reached a pasty consistency. Hydrochloric acid was then added in slight excess. A yellow oil separated, which partially solidified on standing. The oily mass was spread out on a porous plate to absorb the oil, then recrystallized from water and finally from alcohol. This gave white slender needles. The substance is sparingly soluble in water, readily soluble in alcohol, and is tasteless. It melts at 237°. The yield was 2 g. of the pure substance.

Analysis. Subs. 0.2, 0.2: cc. 0.1 *N* acid, 23.5, 23.4. Calc. for $C_8H_{14}N_2O_2$: N, 16.47. Found: 16.45, 16.38.

Cyclohexane-1,5-*spiro*-2-imino-4,6-diketo-hexahydro-pyrimidine,



The reaction mixture, consisting of 2 g. of sodium dissolved in 40 cc. of absolute alcohol, 4.7 g. of ester and 2.6 g. of guanidine carbonate, was heated for 4.5 hours at 105°. The insoluble sodium salt of the product was filtered off, dissolved in water and the solution acidified with acetic acid. The white precipitate thus formed was dissolved in ammonia and finally obtained in microscopic crystals by evaporation of the ammonia. The product was dried at 100°. It is insoluble in water and alcohol, soluble in alkalies and in strong acids. It is tasteless and has no melting point. The yield was 3 g. or 68%.

Subs., 0.2, 0.2: cc. 0.1 *N* acid, 30.3, 30.7. Calc. for $C_9H_{13}N_3O_2$: N, 21.54. Found 21.21, 21.49.

[1] Thole and Thorp, *J. Chem. Soc.*, 99, 445 (1911).

Summary.

Ethyl cyclohexane-1,1-dicarboxylate was prepared by condensation of 1,5-dibromopentane with ethyl malonate. This condenses with urea and with guanidine to form derivatives of cyclohexane-1,5-*spiro*-pyrimidine. The cyclohexane-*spiro*-pyrimidines are very similar in properties to the corresponding cyclobutane-*spiro*-pyrimidines described in our previous paper.

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[CONTRIBUTION FROM THE MAYO FOUNDATION CLINIC.]

THE ORTHO-DIETHYLAMINO-CYCLOHEXANOL ESTER OF PARA-AMINOBENZOIC ACID.

BY A. E. OSTERBERG AND E. C. KENDALL.

Received March 28, 1921.

Amino alcohol esters of aromatic acids are known to possess physiological properties, chief among which is that of producing local anesthesia. The anesthetic effect of the diethylamino ethyl ester of *p*-aminobenzoic acid, (procaine), is ascribed in part to the linkage, $-O-\overset{H_2}{C}-\overset{H_2}{C}-N$ = [1], the maximum being produced when the oxygen is bound directly to the carbonyl of an aromatic acid.

Cyclohexanol resembles more definitely an aliphatic alcohol than an aromatic phenol. Similarly the properties of *o*-amino-cyclohexanol are those of an aliphatic amino alcohol. In discussing the properties of this substance with Professor Julius Steiglitz he suggested the possibility of its use in the preparation of esters of the above type.

With the idea of maintaining those linkages to which physiological action is ascribed but at the same time materially enhancing its molecular weight we have prepared a homolog of procaine, the *o*-diethylamino-cyclohexanol ester of *p*-aminobenzoic acid. The physiological properties of this compound together with those of derivatives of this ester containing substituents in the cyclohexane ring are being studied and will be reported elsewhere. This report concerns only the synthesis of the *o*-diethylamino-cyclohexanol ester of *p*-aminobenzoic acid.

Preparation of *o*-Diethylamino-cyclohexanol.

Fifty-four g. of *o*-chloro-cyclohexanol is treated with twice the theoretical amount of diethylamine at 150° in a sealed tube for several hours. To the reaction product is added 25 g. of sodium carbonate and a small amount of water, and the excess of diethylamine and water boiled off. The residue is extracted with absolute alcohol. After removal of the

[1] O. Kamm, THIS JOURNAL, **42**, 1030–3 (1920).