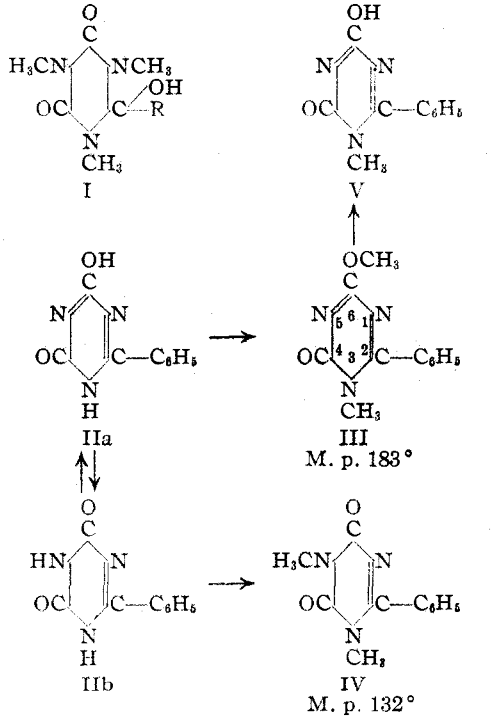
[CONTRIBUTION FROM THE LABORATORIES OF THE MOUNT SINAI HOSPITAL]

Studies on Triazines. II. Lactim–Lactam Isomerism in Substituted Tetrahydrotriazines

BY EDITH BLOCH[1] AND HARRY SOBOTKA

In a previous communication[2] 1,3,5-trimethyl-2-phenyl(or -alkyl)-2-hydroxy-4,6-dioxohexahydrotriazines (I) were described. In order to corroborate this formulation it was attempted to arrive at a common derivative starting from 2-phenyl-4,6-dioxotetrahydrotriazine (II), the cyclization product of benzoyl biuret, a substance studied extensively by Ostrogovich.[3] In his later communications he ascribes mono-enolic structures to this product and to various homologs, as given in formula IIa. However, the result of catalytic hydrogenation seems to favor IIb, as only two hydrogen atoms can be introduced in the methyl homolog, yielding trigenic acid.[4]



The methylation of 2-phenyl-4,6-dioxotetrahydrotriazine with diazomethane in ether yields a mixture of two isomeric substances $C_{11}H_{11}O_2N_3$. One of them crystallizes in fine needles of m. p. 183°, whereas the other forms heavy, stout platelets of m. p. 132° and is generally more soluble in organic solvents and water. At first it was suspected that the two isomers differ from each other like isocyanurates from cyanurates, the former carrying the methyl groups on nitrogen, the latter on oxygen.

The constitution of the lower melting substance (IV) was confirmed by analysis of its decomposition products. After eight hours of digestion in alkaline solution, benzoic acid could be isolated from the mother liquors and methylamine hydrochloride, as well as ammonium chloride from the distillate, the methylamine hydrochloride definitely exceeding 1 equivalent.

Quantitative methoxyl determinations showed the absence of methoxyl in substance IV and the presence of only 1 methoxyl group in substance III. On treatment with dilute acid or alkali, substance III easily loses one methyl group and a monomethyl derivative (V) is formed. We therefore assign structure III with one methoxyl and one methyl imide group to this product. The location of the methyl groups in position 3 and 6 is not proved definitely, but seems more likely than in 4 and 5 or the highly improbable positions 3 and 4 or 5 and 6. The simultaneous occurrence of oxygen and nitrogen bound methyl groups in the molecule of this substance is the more remarkable, since no such "$^1/_3$ or $^2/_3$-isoesters" occur in the case of cyanuric acid. Hantzsch and Bauer[5] claimed the existence of such compounds, but Slotta and Tschesche[6] disproved their results and attribute the non-existence of such "mixed" esters–isoesters to the great trend toward symmetry in the molecule. In the present case there is, however, a far lesser degree of symmetry in the starting material which makes the unequal methylation more plausible. On treatment with diazomethane the monomethyl derivative V yielded again the mixed ester–isoester III in about 80% yield.[7]

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[1] Hernsheim Fellow in Chemistry.

[2] Sobotka and Bloch, THIS JOURNAL, **59**, 2606 (1937).

[3] A. Ostrogovich, *Gazz. chim. ital.*, **39**, 540 (1909); **44**, 562 (1914); **65**, 229 (1935); *Bul. Soc. Stiinte Cluj*, **4**, 521, 528 (1929).

[4] A. Ostrogovich and G. Ostrogovich, *Gazz. chim. ital.*, **66**, 48 (1936).

[5] Hantzsch and Bauer, *Ber.*, **38**, 1005, 1113 (1905).

[6] Slotta and Tschesche, *ibid.*, **60**, 295, 301 (1927).

[7] The methylation of imino nitrogen by diazomethane seems to depend upon its position in a ring between two CO groups, influencing the acidic character of the imino hydrogen. Cyanuric acid [Palazzo and Scelsi, *Gazz. chim. ital.*, **38**, 659 (1908)], phthalimide [Pechmann, *Ber.*, **28**, 859 (1895)], succinimide and the triazines in the present case react, whereas urea, methyl urea, benzoyl

Although the substances I and IV differ from each other only by the elements of methyl alcohol, it was not possible to convert one into the other. Neither the removal of CH_3OH from substance I nor the addition of the elements of water to the double bond in IV could be achieved. Aqueous or alcoholic sulfuric or hydrochloric acids of various concentrations were tried. However, in each case only the starting material could be recovered, even after heating to 100° in concd. sulfuric acid.

The similarity between substances I and IV is exemplified by their behavior on bromination. The tetrabromide $C_{11}H_{11}O_2N_3Br_4$ is very similar in appearance and properties to the substance $C_{12}H_{14}O_2N_3Br_3$ derived from substance I by bromination under identical conditions.[2] They differ from each other by one methyl group and the replacement of one hydrogen atom by bromine. Debromination of the new tetrabromide with alkali, zinc dust, or silver salts does not yield the starting material or any other crystalline substance.

The pharmacological action of these substances is under investigation.

Experimental Part

Benzoyl Biuret.—Forty grams of urea was dissolved in 120 cc. of dry pyridine and refluxed for two hours. The mixture was allowed to cool to about 80° and 38.5 cc. of benzoyl chloride was added dropwise under stirring, until a uniform solution was obtained, which occurs sharply on addition of the last drop. The solution was warmed for thirty minutes on a boiling water-bath, cooled to room temperature and kept in the refrigerator overnight. The resulting solid mass of crystals was extracted three times with 200 cc. of warm chloroform to remove benzamide and dibenzamide, formed as by-products of the reaction. The residue was heated for five minutes with 400 cc. of water and filtered hot through a Büchner funnel. This extraction with water was repeated twice. Then the residue was extracted twice with 200 cc. of hot methyl alcohol and filtered hot as above. After drying, the residue had a melting point of about 220° and was sufficiently pure for the following reaction; yield 11–12 g. After repeated recrystallization from ethyl alcohol the substance melted at 224–225° (all melting points corrected).

From the combined aqueous and alcoholic extracts and mother liquors a mixture of benzoyl urea and little benzoyl biuret was obtained. It was extracted with water in a Soxhlet extractor for forty-eight hours A small amount of pure benzoyl biuret could be obtained from the residue in the thimble by recrystallization from ethyl alcohol. From the aqueous extracts benzoyl urea crystallized, which, after recrystallization from ethyl alcohol, melted at 214–216°; yield *ca.* 25 g.[8]

2-Phenyl-4,6-dioxotetrahydrotriazine (II).—Twelve grams of crude benzoyl biuret was dissolved in a solution of 7.5 g. of potassium hydroxide in 350 cc. of water and after standing for one hour the solution was saturated with carbon dioxide. The monopotassium salt crystallized and was redissolved by addition of more water. The solution was now made just acid to congo by addition of 50% acetic acid. On standing overnight the triazine crystallized in beautiful needles, which after recrystallization from ethyl alcohol melted at 297–300°; yield *ca.* 5 g.[8] The substance could be recovered unchanged after two hours of heating with concentrated sulfuric acid on a boiling water-bath.

Methylation of 2-Phenyl-4,6-dioxotetrahydrotriazine.—A solution of diazomethane in ether (from 8 g. of nitrosomethyl urea) was dried for one hour over pellets of potassium hydroxide and then poured over 3 g. of 2-phenyl-4,6-dioxotetrahydrotriazine, suspended in 500 cc. of dry ether. Slow reaction with gradual evolution of nitrogen occurred. After standing for two days at room temperature, the ether was filtered from a small amount of undissolved material and evaporated *in vacuo* to a volume of about 25 cc. After standing in the refrigerator overnight, the crystalline part was filtered on a Büchner, pressed well, to remove as much of the oily material as possible, then recrystallized twice from benzene: m. p. 183°; yield about 0.8–1.0 g. The ethereal and benzene mother liquors were combined and evaporated to dryness under reduced pressure. The partly oily residue was dissolved in 300 cc. of boiling water. On slow cooling and rubbing a small amount of fine needles appeared, which after recrystallization from benzene melted at 183° and were combined with the first lot; yield about 0.1 g The substance forms long fine white needles, very soluble in methanol, ethanol, hot benzene, soluble in chloroform, ether, glacial acetic acid; little soluble in water and in petrolic ether.

Anal.[9] Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.83; H, 5.07; N, 19.30; OCH_3, 14.30. Found: C, 60.83; H, 5.11; N, 19.50; OCH_3, 14.18.

The aqueous mother liquors were extracted three times with 100 cc. of benzene in a separatory funnel, the combined extracts dried over sodium sulfate and evaporated *in vacuo*. The oily residue crystallized on rubbing with a few drops of petrolic ether. The substance was dissolved in 50 cc. of butanol on a hot water-bath. On cooling it slowly crystallized and after standing for several days was filtered on a Büchner funnel and washed several times with a mixture of 1 part of methyl alcohol and 4 parts of petrolic ether: m. p. 120–125°; yield *ca.* 0.5 g. Examination under the microscope proved that the substance still contained needles of the higher melting isomer. By repeated recrystallization from butanol it was finally obtained pure, in heavy, stout platelets melting at 132°. The substance is very soluble in organic solvents, except petrolic ether, also soluble in water. It is easily soluble in concd. hydrochloric acid and can be reprecipitated on neutralization with 10% ammonia.

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urea, benzoyl biuret and glycine anhydride were found to remain unchanged in dry ether, also in wet ether suspension and in acetone-ether mixtures. For the reaction of amino acids see Kuhn and Brydowna, *Ber.*, **70**, 1333 (1937).

(8) Method adapted from A. Ostrogovich. *Bul. Soc. Stiinte Cluj.* **4**, 521, 528 (1929).

(9) We are indebted to Dr. S. A. Morrell for the methoxyl determinations.

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.83; H, 5.07; N, 19.30; OCH_3, 0. Found: C, 60.86; H, 4.92; N, 19.56; OCH_3, 0.

Monomethyl Derivative (V).—Five-tenths gram of substance III was heated with 2 cc. of normal sodium hydroxide for ten minutes. After cooling the solution was acidified with dilute sulfuric acid; the product separated at once and was recrystallized from dilute methanol or from a large amount of water, as prismatic glistening white needles, of m. p. 278–280°. The same product was also obtained by heating substance III in aqueous or alcoholic hydrochloric acid.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.43; N, 20.49; OCH_3, 0. Found: C, 59.02; H, 4.54; N, 20.22; OCH_3, 0.

Alkali Hydrolysis of Substance IV.—Hydrolysis was carried out in an apparatus similar to that described by Lieber and Smith;[10] 217 mg. of substance III was dissolved in 40 cc. of 25% sodium hydroxide and heated. After the given time intervals the receiver containing a measured amount of acid was changed and the liquid in the distilling flask each time filled up to the original volume The acid was titrated with 0.1 *N* alkali and from the amounts used by the distilled ammonia and methylamine the percentage hydrolysis was computed. It was 36.7, 56.3, 73.0, 83.2, and 84.6% after one, two, four, six, and eight hours, respectively.

After eight hours the alkaline solution was carefully acidified and the resulting precipitate filtered. After recrystallization from alcohol the substance formed shining plates which proved to be identical in melting point and gave no melting point depression with benzoic acid (122°). In order to determine the nature of the distilling amine, 1 g. of substance IV was hydrolyzed for eight hours with 50 cc. of 25% potassium hydroxide and the distillate absorbed in excess hydrochloric acid. The solution was evaporated to dryness and the residue carefully dried in a vacuum desiccator to constant weight; yield 460 mg. The material was extracted in a Soxhlet extractor with absolute alcohol for four hours. The alcoholic extract on evaporation yielded 350 mg. of methylamine hydrochloride. The residue in the thimble consisted of ammonium chloride.

Reaction of Substance IV with Bromine.—Forty-five hundredths gram of substance IV was dissolved in 2 cc. of glacial acetic acid and 2.5 cc. of an 8% solution of bromine in glacial acetic acid added dropwise. The bromide crystallized at once in beautiful red plates, which on filtering and washing with dry ether became yellow, apparently with loss of hydrobromic acid; yield 0.57 g. The substance was recrystallized from hot glacial acetic acid, containing bromine; it is very soluble in methanol, ethanol, soluble in hot chloroform and glacial acetic acid, insoluble in ether; it is readily debrominated by dilute alkali, also by silver salts in aqueous solution or etheric suspension.

Anal. Calcd. for $C_{11}H_{11}O_2N_3Br_4$: C, 24.58; H, 2.04; N, 7.82; Br, 59.59. Found: C, 24.84; H, 2.30; N, 7.73; Br, 59.87.

Summary

2-Phenyl-4,6-dioxotetrahydrotriazine, the cyclization product of benzoyl biuret, yields two isomeric dimethyl derivatives on methylation with diazomethane. The pair represents a case of lactam–lactim tautomerism involving one of the two methyl groups.

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[10] E. Lieber and G. B. L. Smith, THIS JOURNAL, **59**, 2283 (1937).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A New Synthesis of 3,4-Benzpyrene Derivatives

BY LOUIS F. FIESER AND E. B. HERSHBERG[1]

The only synthesis of the powerfully carcinogenic 3,4-benzpyrene heretofore achieved is that of Cook and Hewett,[2] consisting in the application to pyrene of the general method of constructing an additional ring with the use of succinic anhydride. With the technical improvements in the various steps introduced in this Laboratory,[3,4] by Winterstein, Vetter and Schön,[5] and by Vollmann, *et al.*,[6,7] 3,4-benzpyrene can now be prepared fairly readily by this method in over-all yield of about 36%.[3] The succinic anhydride synthesis, however, is not adaptable to the preparation of many derivatives of the important parent hydrocarbon, and the list of compounds thus far obtained by application of the general synthesis or by utilization of the same intermediates includes only the following substances: 4′-methyl-3,4-benzypyrene[3,8] (and its dihydride[3,8]), 3′(?)-methyl-3,4-benzpyrene,[5] 4′-hydroxy-3,4-benzpyrene,[4] 3,4-benzpyrene-3′,4′-dicarboxylic anhydride[9] (and its dihydride[9]), 1′,2′,3′,4′-tetrahydro-3,4-benzpyrene.[3,5,10]

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[1] Lilly Research Fellow.

[2] Cook and Hewett, *J. Chem. Soc.*, 398 (1933).

[3] L. F. Fieser and M. Fieser, THIS JOURNAL, **57**, 782 (1935).

[4] Fieser, Hershberg, Long and Newman, *ibid.*, **59**, 475 (1937).

[5] Winterstein, Vetter and Schön, *Ber.*, **68**, 1079 (1935).

[6] Vollmann, Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937).

[7] For further comments on the synthesis, see Sannié and Poremski, *Bull. soc. chim.*, [5] **3**, 1139 (1936); Rondoni and Corbellini, *Atti accad. Lincei*, VI, **21**, 128 (1935).

[8] Fieser and Newman, THIS JOURNAL, **57**, 1602 (1935).

[9] L. F. Fieser, M. Fieser and E. B. Hershberg, *ibid.*, **58**, 1463 (1936).

[10] The analytical sample of this hydrocarbon prepared with Mrs. Fieser[3] (by Clemmensen reduction) formed faintly yellow plates, m. p. 113°, whereas Winterstein, Vetter and Schön[5] subsequently