Oxidation of *trans*-2-Oxo-9-decalincarboxaldehyde (VIa)——1.4 ml. of 8*N* chromic acid solution was rapidly added under stirring to a solution of 100 mg. of crude VIa in 20 ml. of Me_2CO (freshly distilled on $KMnO_4$) at room temperature and stirring was continued for 10 min. The reaction mixture was treated with 2 ml. of MeOH and 50 ml. of H_2O and the mixture was stirred for half an hour. The reaction mixture was extracted with $CHCl_3$ and the organic layer was washed with H_2O, dried, and evaporated *in vacuo*.

The residue (115.5 mg.) was dissolved in 10 ml. of 2*N* NaOH and extracted with $CHCl_3$. The H_2O layer was acidified with conc. HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The crystalline residue (92.2 mg.) was recrystallized from Et_2O to give 81.5 mg. (75%) of *trans*-2-oxo-9-decalincarboxylic acid (X), m.p. 118.5～120°, as plates.

We are very grateful to Dr. K. Takeda, Director of this laboratory for his constant encouragement. Our thanks are also due to the members of the analytical and the physicochemical department of this laboratory for analytical and optical data.

Summary

trans-9-Methyl- (XIa) and -9-aminomethyl-2-decalones (VIII) were prepared from the parent *trans*-2-oxo-9-decalincarbonitrile (I) by a series of reductions and were characterized.

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48. Yoshihisa Mizuno, Morio Ikehara, and Kyoichi A. Watanabe*1 : Potential Antimetabolites. VI.*2 An Improved Synthesis of 2-β-D-Ribofuranosyl-as-triazine-3,5(2*H*,4*H*)-dione (6-Azauridine).

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6-Azauridine (VI) is one of the most promising anticancer agents among a number of antimetabolites examined.[1] Chemical preparation of the nucleoside was already reported by Handschumacher,[2] Prystas *et al.*,[3] and authors.[4] Prystas' method which is the latest one consists in inhibition of ribosidation on nitrogen 4 of *as*-triazine-3,5-(2*H*,4*H*)-dione by introducing catalytically replaciable diphenylmethyl group on the nitrogen. Authors' method consists in protecting the same nitrogen from the ribosidation by introducing easily replaciable group, viz., methylmercapto group on position 5 of 1,2,4-triazine. The azauridine was prepared by us by way of azacytidine (V).[4]

Now, an alternative and more improved procedure to prepare the nucleoside was devised on the ground of the finding that methylmercapto group attached to position 5 of *as*-triazine-3(2*H*)-one quite easily replaced by nucleophilic reagent such as hydroxyl group,[5] leaving the rest of molecule intact. Thus, mild acid hydrolysis of 2-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-5-methylmercapto-*as*-triazine-3(2*H*)-one (III) gave rise

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*1 Kita 12-jo, Nishi 5-chome, Sapporo (水野義久, 池原森男, 渡辺恭一).
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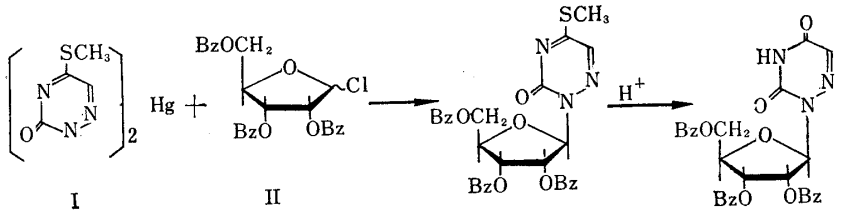
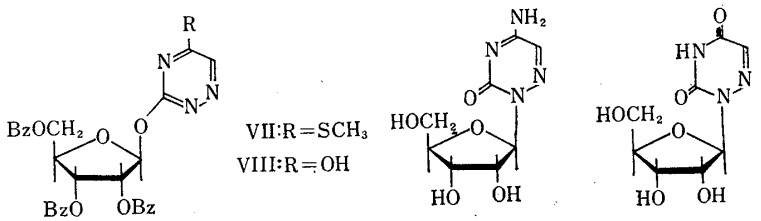
to 2-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-*as*-triazine-3,5(2*H*,4*H*)-dione (IV) in almost a quantitative yield.

For the preparative purposes, III was not isolated in pure state, instead crude reaction mixture of condensation of mercuri salt of 5-methylmercapto-*as*-triazine-3(2*H*)-one (I) with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride (II), which was found to contain two O-glycosides VII and VIII along with N-glycosides III and IV, was treated with 80 per cent acetic acid. By this treatment the O-glycosides were hydrolyzed to *as*-triazine-3,5(2*H*,4*H*)-dione (6-azauracil) and 2,3,5-tri-O-benzoyl-D-ribofuranose, while N-glycoside III was converted into IV, which means the treatment made easier the separation of the desired nucleoside IV by using alumina chromatographic technique.



I II III IV

Bz=C_6H_5CO



VII: R=SCH_3
VIII: R=OH

V VI

Debenzoylation of IV with methanolic ammonia according to Handschumacher's procedure seemed to be unsuitable for the preparative purposes, because not only debenzoylation was incomplete but also a considerable decomposition of the nucleoside was always observed under the condition described by him.[2] Catalytic debenzoylation of IV with sodium methoxide gave a good result to afford 2-β-D-ribofuranosyl-*as*-triazine-3,5(2*H*,4*H*)-dione (6-azauridine) (VI).

Among several substituents on position 5 examined, methylmercapto group was found to give the most desirable result. Thus, acetyl-6-azacytosinemercury failed to give the corresponding nucleoside according to the usual procedure.

Experimental

Tri-O-benzoyl-6-azauridine (IV) from Methylmercapto Derivative (III)——The methylmercapto derivative (III) (0.482 g., 0.82 mmol.) was dissolved in 80% aqueous AcOH in a tightly closed flask, and kept standing at room temperature for two days. When the flask was opened a strong odor of methylmercaptan was observed. The mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 20 cc. of toluene and evaporated *in vacuo* to remove AcOH, then crystallized from EtOH; yield, 429 mg. (94%), m.p. 180~183°. Two recrystallizations from EtOH gave white needles (356 mg., 78%), m.p. 186~187° (Prystaš, Gut and Šorm report m.p. 190°[3]). *Anal.* Calcd. for $C_{29}H_{23}O_9N_3$: C, 62.48; H, 4.16; N, 7.54. Found: C, 62.60; H, 4.32; N, 7.60.

Preparative Procedure——A solution of 10.08 g, (0.02 mol.) of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose in 280 cc. of dry ether was saturated with dry hydrogen chloride at 0°. After a week in an ice-box, the ether was removed and the residue was dissolved in 70 cc. of anhydrous benzene which was removed *in vacuo*. This procedure was repeated twice. The residue thus obtained was again dissolved in 70 cc. of benzene and addded with stirring to a previously prepared suspension of mercury

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salt of di(5-methylmercapto-*as*-triazine-3(2*H*)-one) (I)[4] in benzene, which had been prepared by suspending I in 750 cc. of dry benzene in three necked flask equipped with a stirrer and condenser and distilled about 200 cc. of benzene. After addition of the foregoing chloro sugar solution further 120 cc. of benzene was distilled off. The reaction mixture was then refluxed with stirring for 1 hr.

Pale yellow suspension resulted and was filtered. The filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 120 cc. of $CHCl_3$ and the solution was extracted twice with an equal volume of 30% aqueous KI solution, twice with 5% sodium versenate solution, once with 0.1*N* HCl and finally three times with water. After drying over anhydrous Na_2SO_4, $CHCl_3$ was evaporated to dryness *in vacuo*. Reddish syrup remained, weighed 10.5 g., was then dissolved in 315 cc. of 80% aqueous AcOH. After standing for two days at room temperature in a sealed flask, the solvent was distilled off under reduced pressure. The residue was dissolved in 100 cc. of toluene and the solvent was evaporated to dryness *in vacuo* to remove AcOH. The procedure was repeated until removal of a trace of AcOH was complete.

The desired compound IV was isolated by means of alumina chromatography. One hundred gram of acid washed alumina (Merck reagent grade) was packed into a column (4.5 $cm^2 \times 21$ cm.). The foregoing residue was dissolved in 50 cc. of benzene and put onto the column. The column was washed with 400 cc. of benzene at a flow rate of 100 cc. per 40 min. The eluate contained 2.25 g. of 2,3,5-tri-O-benzoyl-D-ribofuranose, which was crystallized from EtOH, m.p. 102~103°. The compound gave negative test for nitrogen. *Anal.* Calcd. for $C_{26}H_{22}O_3$: C, 67.53; H, 4,76. Found : C, 68.01; H, 4.61 (Ness, Diehl and Fletcher report m.p. 102~104° for 2,3,5-tri-O-benzoyl-β-D-ribofuranose.[5]).

Then the column was washed with 400 cc. of 10% AcOEt in benzene. IV was eluted by the treatment. The residue obtained after evaporation of the solvent was crystallized from EtOH, white needles, m.p. 181~184°, yield, 2.35 g., 20.6% on the basis of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribose. Mixed melting point with an authentic specimen did not depress.

6-Azauridine (VI)——A mixture of tri-O-benzoyl-6-azauridine (IV) (163 mg., 0.293 mmol.), absolute MeOH (9.0 cc.) and 0.8*N* NaOMe in MeOH (0.5 cc., 0.4 mmol.) was refluxed gently for 2 hr. After cooling, 9.0 cc. of H_2O was added to the colorless mixture and pH value was adjusted to 7.2 with Amberite IR-120 (H^+). The resine was filtered and washed with H_2O (9.0 cc. × 2). The combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was then azeotropically dried with 9.0 cc. of dry benzene for several times until white crystals were obtained. The crystalline material was washed with Et_2O, and then recrystallized from EtOH-Et_2O, white needles, m.p. 161°, 61 mg., 86% (Šorm and Keilova report m.p. 160°[1]). Ultraviolet absorption spectrum was identical with that of 6-azauridine obtained from 6-azacytidine (V).[4]

5-Acetamido-*as*-triazine-3(2*H*)-one(4-N-Acetyl-6-azacytosine)——A mixture of 6-azacytosine[5] (2.24 g.) and acetic anhydride (50 cc.) was refluxed for half an hour. Acetic anhydride was removed under reduced pressure. The residue was recrystallized from glacial AcOH to give 4.2 g. of needles, m.p. 275°. From elementary analysis and infrared absorption spectra, the compound is the monoacetate with one mole of acetic acid which could not be removed by heating to 110° at 2 mm. Hg for 8 hour. *Anal.* Calcd. for $C_5H_6O_2N_4 \cdot C_2H_4O_2$: C, 39.25; H, 4.71; N, 26.16. Found : C, 38.77; H, 4.79; N, 26.40. IR ν_{max}^{KBr} cm^{-1}: 1587 (antisym. COO^-), 1300 (sym. COO^-) which disappeared in the sample recrystallized from water and dried at 110°, 10^{-4} mm. Hg.

One gram of the compound ($C_5H_6O_2N_4 \cdot C_2H_4O_2$) was recrystallized from 26 cc. of hot water, m.p. >275°. Mixed melting point with the monoacetate (m.p. 275°), 232~240°. *Anal.* Calcd. for $C_5H_6O_2N_4$: C, 38.96; H, 3.99; N, 36.33. Found : C, 38.76; H, 3.91; N, 36.63.

Mercury salt of 4-N-Acetyl-6-azacytosine——4-N-Acetyl-6-azacytosine monoacetate (2.14 g., 0.01 mol.) was dissolved in cold 200 cc. of 0.2*N* NaOH. To this solution was added 2.72 g. (0.01 mol.) of $HgCl_2$ in 30 cc. of EtOH with vigorous stirring. White precipitates began to separate when about half of $HgCl_2$ was added. The precipitates, collected by centrifugation, were suspended in 100 cc. of H_2O and boiled for 15 min., then filtered and washed with EtOH. White powder of mercury salt of 6-azacytosine, did not decompose below 280°, was obtained. Yield, 3.45 g., 98%. *Anal.* Calcd. for $C_5H_4O_2N_4Hg$: C, 17.05; H, 1.13; N, 15.19. Found : C, 17.23; H, 1.53; N, 15.89.

An Attempted Synthesis of 6-Azauridine by Using Mercury Salt of 4-N-Acetyl-6-azacytosine—— Mercury salt of 4-N-acetyl-6-azacytosine (2.12 g., 6 mmol.) was added to 150 cc. of dry xylene. The vigorously stirred suspension was dried by azeotropic distillation of approximately two thirds of the solvent. Benzene solution (90 cc.) of 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride (prepared from 3.0 g. of 2,3,5-tri-O-benzoyl-1-O-acetyl-D-ribofuranose) was added to the previously dried suspension of mercury salt of 4-N-acetyl-6-azacytosine. At reflux temperature the reaction mixture gradually darkened and finally a black suspension resulted (2 hr.). Removal of xylene under reduced pressure gave a resinous residue. As worked up as usual, 40 mg. of solid material was obtained which was found to be a mixture of 6-azacytidine (V), 6-azauridine (VI), partially benzoylated nucleosides and 6-azauracil by paper chromatographic and ultraviolet absorption analysis.

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Attempt of synthesis of 6-azauridine (VI) by way of 6-azacytidine (V) by employing mercury salt of 4-N-acetyl-6-azacytosine was abandoned.

Summary

Our previous method of prepraring azapyrimidine nucleosides is suitable for the preparation of 2-*β*-D-ribofuranosyl-5-amino-*as*-triazine-3(2*H*)-one (6-azacytidine) (V). For the preparation of 2-*β*-D-ribofuranosyl-*as*-triazine-3,5(2*H*,4*H*)-dione (6-azauridine) (VI), however, an alternative route by way of 2-(2′,3′,5′-tri-O-benzoyl-*β*-D-ribofuranosyl)-5-methylmercapto-*as*-triazine-3(2*H*)-one (III) was found to be more convenient than the previous one. The procedure was also improved.

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49. Kunio Nakagawa and Teruji Tsuji : Oxidation with Nickel Peroxide. II.*1 Oxidation of Amines.

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In the preceding paper, it was proved that a variety of alcohols could be converted to the corresponding carbonyl compounds by treatment with nickel peroxide in organic solvents.

Further studies were now undertaken on the oxidation of aromatic and aliphatic amines. Some monosubstituted anilines were readily oxidized to give the corresponding symmetrical azo-compounds with nickel peroxide in benzene solution. On the other hand, benzylamine and its derivatives bearing a substituent in the benzene ring could be easily oxidized by the same oxidant to give the corresponding nitriles in good yields regardless of position and kind of a substituent. Alkylamines also underwent the same oxidation and gave the corresponding nitriles.

Oxidation of Anilines

Oxidation of anilines has already been reported by other investigators using chlorcalk, manganese dioxide, phenyl iodosoacetate and lead tetraacetate.[1-4]

However, the only solid oxidant so far employed and reported with a detailed procedure was manganese dioxide, and so it seemed interesting to compare the oxidizing power of nickel peroxide with that of manganese dioxide.

In the present series of experiments, nickel peroxide was added to the benzene solution of anilines and the heterogeneous mixture was allowed to react under efficient stirring at room temperature or under refluxing. These reactions were conducted by employing nickel peroxide 1.2 times as much as the theoretical amount based on the available oxygen-contents which were determined by means of iodometry, and there

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