Summary

1-(β-D-Ribofuranosyl)urea (Ⅶ) was synthesized *via.* 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl isocyanate (Ⅱ) and 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)urea (Ⅴ). One of the intermediate, Ⅴ, which is an important starting material for the synthesis of ribonucleosides, was obtained in a yield of 75.0% by direct ammonolysis at 0° of the reaction mixture of 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride and silver isocyanate. The structure of Ⅴ was confirmed by converting it to (β-D-ribofuranosyl)thymine.

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68. Tyunosin Ukita, Mitsuaki Yoshida, Akira Hamada, and Yoshio Kato*2 : The Syntheses of Glycosylbarbiturate.*3

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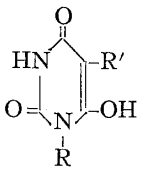
In our previous paper,[1] it was shown that the 5-phenylcarbamoylbarbituric acids (I) revealed a remarkable inhibitory activity against the multiplication of the rat ascites hepatoma (AH 130) cells *in vitro* and also *in vivo* test of Ehrlich ascites carcinoma in mice. However, the assays of the anti-tumor activities were made difficult on account of the poor solubility in water of this series of compounds. It was, therefore, desired to modify the structures of these compounds to be more soluble without decrease in the activities.



I R : H, CH_3, C_6H_5
R′ : $CONHC_6H_5$
Ⅱ R : glycosyl
R′ : suitable substituents

Chart 1.

As the first step of this type of research, in this paper, syntheses of 1-β-D-glucopyranosyl- (Ⅵ) and 1-β-D-ribofuranosylbarbituric acid (X) were attempted. Of these glycosides, the latter compound (X), especially, seemed to be interesting in biochemical point of view, because it has a structure of 6-hydroxyuridine, the synthesis and properties of which have never been reported.

As for the synthesis of glycosylbarbituric acids, Goodman, *et al.*[2] reported on the condensation of 2,4,6-trimethoxypyrimidine and 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide by Hilbert-Johnson's method,[3] but they failed to obtain the desired condensation product. Bergmann, *et al.*[4] treated 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea with malonic acid in acetic anhydride, but the product was found to be N,N′-bis-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylcarbamoyl)malondiamide instead of

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*3 From the thesis of Yoshio Kato for the degree of Doctor of Pharmaceutical Sciences, University of Tokyo (1962).

1) T. Ukita, Y. Kato, M. Hori, H. Nishizawa : This Bulletin, 8, 1021 (1960).
2) I. Goodman, P. Newmark : J. Am. Chem. Soc., **79**, 6446 (1957).
3) G.E. Hilbert and T.B. Johnson : *Ibid.*, **52**, 2001, 4489 (1930).
4) T.B. Johnson, W. Bergmann : *Ibid.*, **60**, 1916 (1938).

the desired glucosylbarbituric acid derivatives. Bodendorf[5] reported that the condensation of 5,5-diethylbarbituric acid and 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl bromide in alkaline acetone afforded 1,3-bis(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5,5-diethylbarbituric acid, however, he failed to isolate pure 1,3-bis(β-D-glucopyranosyl)-5,5-diethylbarbituric acid by subsequent deacetylation of the above product with sodium methoxide. On the other hand, 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea was condensed with diethylmalonyl chloride in pyridine by Helferich[6] to obtain a product which gave corresponding data in elemental analysis to 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5,5-diethylbarbituric acid but there was no evidence to substantiate this structural assignment.

The present authors followed the Helferich's method and treated 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea (Ⅳ) with malonyl chloride in pyridine, but the product, m.p. 196.5° (decomp.), was not the desired one but was identical with N,N′-bis(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylcarbamoyl)malondiamide (Ⅴ), which had been obtained by Bergmann by the condensation of Ⅳ and malonic acid in acetic anhydride. The compound (Ⅴ) synthesized by Bergmann's procedure also melted at 196.4°*4 and its admixture with the above product showed no depression of the melting point.

This compound was treated with diluted aqueous alkali and the reaction mixture was separated by Dowex-1 (Cl^-) ion exchange chromatography into two products. The one, which was not adsorbed on the resin, melted at 206~207° (decomp.) and was identified as glucosylurea (Ⅲ). The other product adsorbed on the resin was eluted with 0.01*N* hydrochloric acid-0.02*M* sodium chloride, and was isolated as a sodium salt in white powder. In paper chromatography in four solvents and paper electrophoresis at pH. 9.0, this product gave single spot which absorbed ultraviolet ray and gave a positive reaction with the periodate benzidine reagent. The elemental analysis of this substance well coincided with that of sodium 1-(β-D-glucopyranosyl)barbiturate (Ⅵ) having three moles of water. The compound (Ⅵ) consumed 3.98 moles of periodate and had ultraviolet spectra (Fig. 1a) in acid and alkaline pH typical of the 1-substituted barbiturates. Accordingly, the structure of this compound must be represented by Ⅵ.

Since the ratio of Ⅲ and Ⅵ obtained from Ⅴ was 1.0 : 0.82, each one mole of these compounds should be produced from one mole of Ⅴ, that is, on alkaline deacetylation,

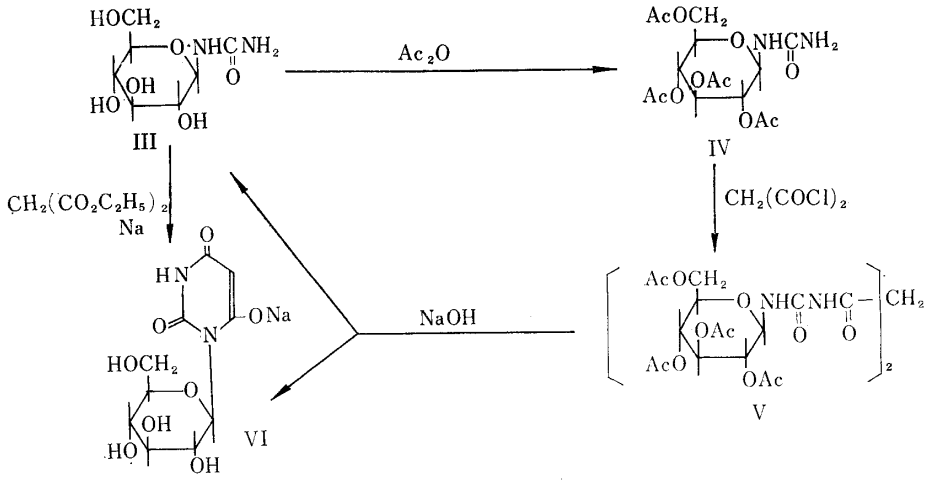

Chart 2.

*4 The melting point reported by Bergmann for this compound is 206~207°, but on careful heating in the determination of the melting point, this compound melted at 196.5° with decomposition.

5) K. Bodendorf : Arch. Pharm., **282**, 78 (1944).

6) B. Helferich, W. Kosche : Ber., **59**, 69 (1926).

V underwent a cleavage at one of the two malonamide linkage to form the barbituric acid ring by cyclization, and to liberate the glucopyranosylurea.

The compound (VI) was also obtained in a poor yield of 1.89% by the condensation of diethyl malonate and glucosylurea (III) in ethanolic sodium ethoxide according to the general method in barbituric acid synthesis.

In order to synthesize 1-(β-D-ribofuranosyl)barbituric acid, 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)urea (VII), which was reported in the previous paper,[7] was reacted with malonyl chloride in pyridine as the preceding case of glucosyl derivatives. The reaction mixture, however, gave a resinous product and the desired condensation product could not be isolated. The ribosylurea (VII) was then heated with malonic acid in acetic anhydride to give a yellow powder.

From the yellow powder, by alumina chromatography, a white powdery substance was isolated in 40.3% yield. This substance was homogeneous in silica gel thin-layer chromatography and the elemental analysis and molecular weight well agreed with a structure of N,N'-bis(2,3,5-tri-O-benzoyl-β-D-ribofuranosylcarbamoyl)malondiamide (VIII). This compound (VIII) strongly absorbed ultraviolet ray at 296 mμ in alkaline ethanolic solution as in the case of V.

By silicic acid column chromatography, the above yellow powder gave, besides VIII, a small amount of second product as a white powder. The elemental analysis and ultraviolet absorption spectra, which were similar to those of 1-methyl-5-acetylbarbituric acid, of the second product supported that the compound should have a structure of 1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-5-acetylbarbituric acid (IX).

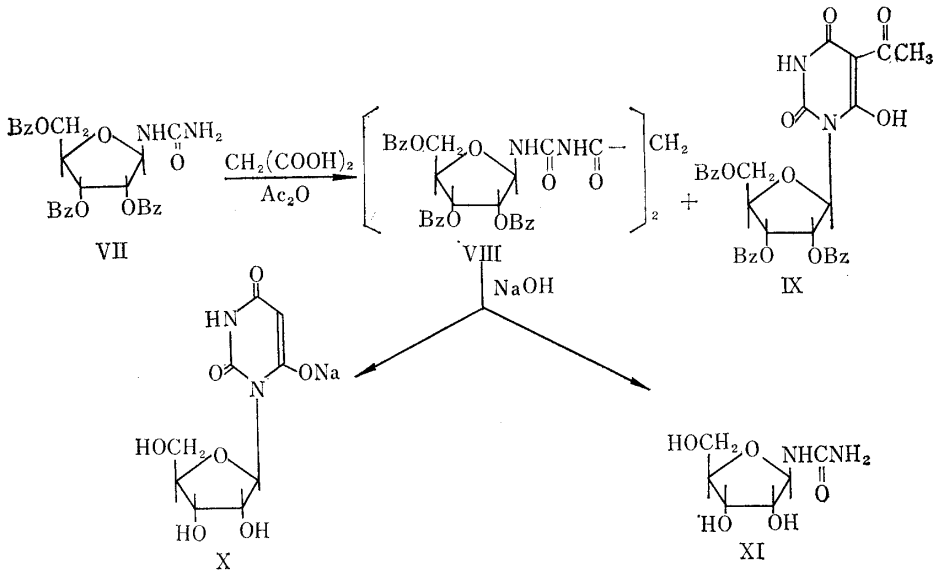

Chart 3.

The yellow powder was then treated with 2% aq. sodium hydroxide, and the products were separated by DEAE-cellulose column. One of the components, which was not adsorbed on the ion exchange cellulose, was proved by paper chromatography to be β-(D-ribofuranosyl)urea (XI). From the fraction adsorbed on the ion exchange cellulose and colored with the Ehrlich's reagent, a product (X) was isolated in 37% yield (calculated from VII). The elemental analysis of X well coincided with the molecular formula : $C_9H_{11}O_7N_2Na \cdot H_2O$, X gave an electrophoretic mobility of $M_{DNP\text{-}glycine}$ =0.87 and pKa values of 3.6 and 12.4 and consumed 2.4 moles of periodate in 24 hours without

7) T. Ukita, M. Yoshida : This Bulletin, **12**, 454 (1964).

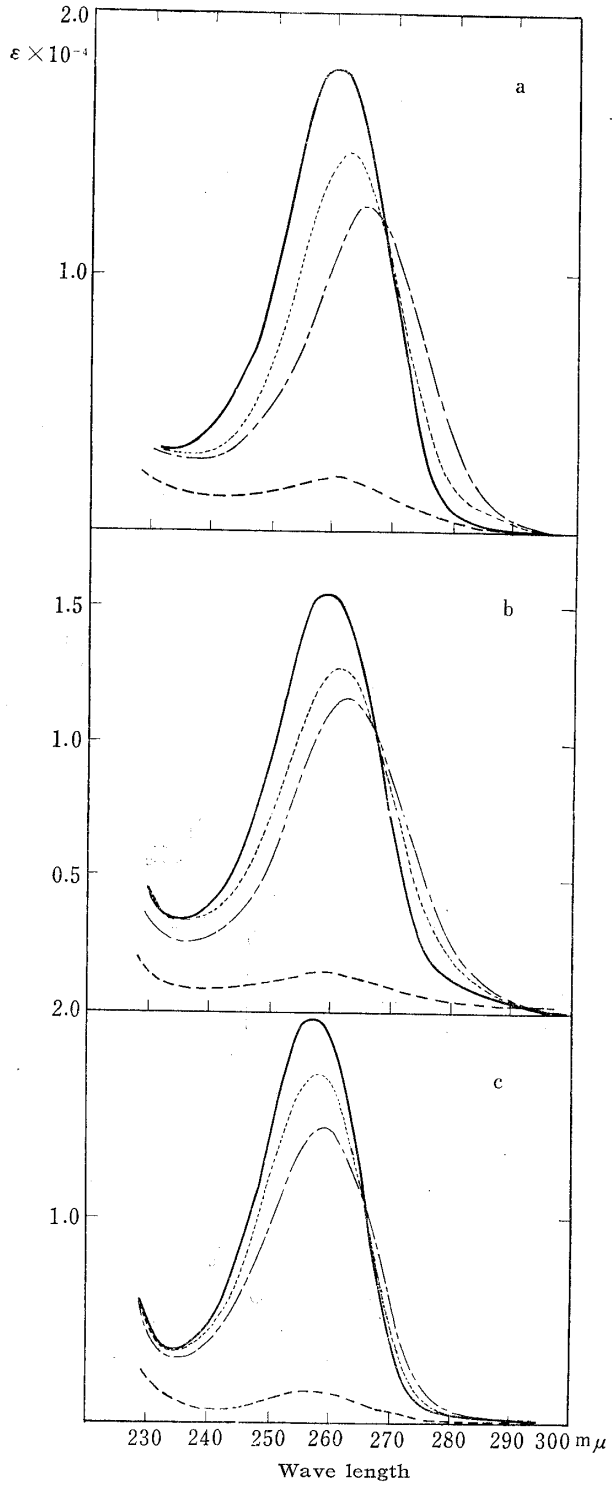

Fig. 1. Ultraviolet Spectra of 1-Substituted Barbiturates

a: 1-(β-D-Glucopyranosyl)barbituric acid
b: 1-(β-D-Ribofuranosyl)barbituric acid
c: 1-Methylbarbituric acid
—•—•— pH, 13.9
····· pH, 13.0
———— pH, 6.0~9.0
– – – – – pH, 1.3

liberation of formic acid. The ultraviolet spectra (Fig. 1b) of this product (X) were similar to that of 1-methylbarbituric acid. Thus, the product (X) should have a structure of sodium 1-(D-ribofuranosyl)barbiturate. On partial acetylation of X with acetic anhydride, a product was obtained, which showed absorption maximum at 278 mμ, and was paper chromatographically identical with a hydrolysis product of IX.

The anomeric centers in 1-D-glucopyranosyl- (VI), 1-D-ribofuranosylbarbiturate (X) and 1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-5-acetylbarbituric acid (IX) could most probably be assigned to be β-configurations. The assignment is supported by the following facts that the starting materials, IV and VII, were β-glycosides, that there was little probability of anomerization during the formation of VIII and IX from VII and the alkaline treatment of V and VIII, thus by the treatment, β-D-glycosylureas were obtained as side products and that β-D-ribofuranosylthymine was obtained from 1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-3-(2-methyl-3-methoxyacryloyl)urea by an alkaline cyclization.[7]

The above results represent that in the syntheses of glycosylbarbituric acids, VI and X, the reactions commonly proceeded through intermediate compounds, V and VIII, which by alkaline treatment gave each one mole of the desired compounds and glycosylureas, III and XI, respectively.

Experimental*5

Paper chromatography was carried out ascendingly on Toyo Roshi No. 53 paper. The solvents used were 1) BuOH-AcOH-H_2O (4:1:5), 2) iso-PrOH-conc. NH_4OH-H_2O (28:1:10), 3) BuOH-EtOH-H_2O (4:1:5), 4) iso-PrOH-conc. NH_4OH-H_2O (7:1:2), and 5) iso-BuOH-saturated with H_2O. The Rf value for these

*5 All melting points are uncorrected.

solvents are represented by Rf_1, Rf_2, Rf_3, Rf_4, and Rf_5, respectively. Paper electrophoresis was performed on Toyo Roshi No. 53 paper at 400 v./23 cm. for 40~60 min. using a buffer solution of BuOH–AcOH–pyridine–H_2O (20:2:10:968) and adjusted to pH 9.0 with NH_4OH. The mobility is represented by M_x taking x as the standard.

N,N′-Bis(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylcarbamoyl)malondiamide (V)——To an ice cooled solution of malonyl chloride (5.58 g.) in anhyd. $CHCl_3$ (30 ml.) was added dropwise 100 ml. of anhyd. $CHCl_3$ solution of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea (IV)*6 (16.2 g.) mixed with 6.56 g. of pyridine under stirring with in 40 min. After additional stirring at 0° for 1 hr., the mixture was washed with 10% $KHSO_4$, 5% $NaHCO_3$ and H_2O successively. The $CHCl_3$ layer was dried over Na_2SO_4 and the solvent was evaporated to dryness. The residual black powder (9.6 g.) was dissolved in a small volume of hot EtOH and the solution was passed through a column of Al_2O_3 (Merk) and eluted with hot EtOH. From the effluent appeared colorless needles which were recrystallized from EtOH. By washing the column with $CHCl_3$, additional amount of the product was obtained. The total yield amounted to 6.7 g., 38.5%, m.p. 196.5° (decomp.). *Anal.* Calcd. for $C_{33}H_{44}O_{22}N_4$: C, 46.55; H, 5.19; N, 6.64. CH_3CO, 8.0. mol. wt., 848.7. Found : C, 46.02; H, 5.03; N, 6.42. CH_3CO, 8.0. mol. wt., 849 (by Akiya-Berger's method,[9] solvent : dichloromethane). $[\alpha]_D^{25.5}$ −41.3° (c=1.445, $CHCl_3$). UV λ_{max}^{EtOH} mμ (ε) : 295 (7735).

Sodium 1-(β-D-Glucopyranosyl)barbiturate (VI)——a) By alkaline treatment of V : A solution of V (424 mg.) in 0.1*N* NaOH (20 ml.) was warmed on a water bath at 85° for 5 min. The pH was adjusted to 7.0 with dil. HCl under ice-cooling and the neutral solution was poured onto a Dowex-1 (Cl^-) (50~100 mesh) column (2.5×17.0 cm.) and the column was washed with H_2O until the washings gave no periodate-benzidine reaction. Then column was eluted with 0.01*N* HCl–0.02*M* NaCl solution under cooling and the fraction which showed UV absorption were combined and deanionized with Ag_2CO_3. The precipitate was filtered and the filtrate was decationized by adding Dowex-50 (H^+) and filtered. The filtrate was passed through an IRC-50 (Na^+) column (1.4×13.5 cm.) to convert the product into Na salt. The effluent was concentrated *in vacuo* below 35°, and the Na salt of the compound was precipitated with abs. EtOH. The white powder thus obtained, after drying, weighed 144 mg. (78.7%). *Anal.* Calcd, for $C_{10}H_{13}O_8N_2Na \cdot 3H_2O$: C, 32.75; H, 5.24; N, 7.65. Found : C, 33.06; H, 5.58; N, 7.36. $[\alpha]_D^{26.5}$ +1.83° (c=0.937, H_2O). Rf_1=0.13, Rf_2=0.35, Rf_3=0.07, and Rf_4=0.46. $M_{DNP-glycine}$ =0.87 $\lambda_{max}^{pH\ 11.2}$ mμ (ε) : 260 (17840). This compound consumed 3.98 moles of periodate at room temperature in 4 hr.*7

The above aqueous washings were combined, concentrated *in vacuo* to about 20 ml. and deionized by successive treatment with Dowex-50 (H^+) and Dowex-1 (OH^-). This deionized solution was concentrated to dryness and the residue was dissolved in a small quantity of H_2O. On addition of abs. EtOH, white powder which weighed 105 mg. (95.4%) precipitated. Recrystallization from dil. EtOH furnished white prisms, m.p. 206~207° (decomp.) which on admixture with the authentic specimen of 1-(β-D-glucopyranosyl)urea (III) showed no depression of the melting point.

b) By cyclization of III with diethyl malonate : To a hot ethanolic solution of III (2.22 g., 0.01 mole) was added 50 ml. of abs. EtOH containing diethyl malonate (1.60 g., 0.01 mole) and Na (23 mg., 0.01 mole). The mixture was refluxed in an oil bath for 1 hr. and the solvent was removed by distillation. A pale brown precipitate was collected after cooling and washed with abs. EtOH. It was then dissolved in a small amount of H_2O and applied on Dowex-1 (Cl^-) column and eluted as described in the above experiment. From the combined fraction which showed UV absorption, 58 mg. (1.85%) of VI was obtained.

N,N′-Bis(2,3,5-tri-O-benzoyl-β-D-ribofuranosylcarbamoyl)malondiamide (VIII) and 1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-5-acetylbarbituric Acid (IX)——Malonic acid (61 mg.) was dissolved in Ac_2O (1.0 ml.) under warming. To the solution was added 290 mg. of VII and the mixture was heated at 100° for 50 min. After cooling, the remaining Ac_2O was decomposed by adding H_2O and the solid mass that appeared was crashed, filtered and washed with H_2O. The yellow powder, thus obtained, was dried over P_2O_5 *in vacuo*, and weighed 320 mg.

The powder was dissolved in $CHCl_3$, the solution was submitted to an alumina column (0.9×10 cm.) and eluted with $CHCl_3$. The first 10 ml. of the effluent was discarded and the next 30 ml. was taken. On evaporation of the solvent, white powder was obtained in a yield of 125 mg. (40.3%). This product

*6 This compound was reported to have a melting point of 85~100° by Helferich[6] and 95° by Sano.[8] In our experiment, a crystal having melting point of 157.5~158.5° (A) was obtained besides the one having melting point of 94~100° (B), and the crystal (B) was convertible to A when stored in desiccator or crystallized slowly from MeOH. The dimorphism between A and B was confirmed by elemental analysis, number of acetyl groups, optical rotations ($[\alpha]_D^{31}$ −13.15 (A), −13.90 (B) (in pyridine)), IR spectra and the same properties of N-acetyl derivatives derived from A and B. A mixture of equal amount of A and B showed a melting point of 157.5~158.5°, the same as A.

*7 Under similar condition N-methylbarbituric acid and methyl glucopyranoside consumed 2 moles of periodate respectively.

8) T. Naito, M. Hirata, T. Kawakami, M. Sano : This Bulletin, **9**, 703 (1961).
9) S. Akiya : Yakugaku Zasshi, **57**, 967 (1937).

gave a single spot on silica gel thin-layer chromatography (solvents : $CHCl_3$–MeOH (1:1) and Et_2O). The spot was detected by heating with conc. H_2SO_4 but not by spraying with *p*-dimethylaminobenzaldehyde.*8 The product was dried over P_2O_5 *in vacuo*. *Anal.* Calcd. for $C_{57}H_{48}O_{12}N_4$: C, 63.55; H, 4.48; N, 5.31. mol. wt., 1076.9. Found : C, 62.85; H, 4.55; N, 4.90. mol. wt., 1075. (Akiya-Berger's method,[9] solvent: dichloroethane–MeOH (20:1)). UV mμ (ε) : λ_{max}^{EtOH} 237 (73800), $\lambda_{max}^{2\%\,Et_3N\text{-}EtOH}$ 237 (73800), 296 (37000).

On treatment with *N* NaOH, this compound was decomposed into X and ribosylurea, which was identified with authentic XI[7] by paper chromatography.

The above yellow powder (340 mg.) was applied to silicic acid (Mallinckrodt) column (1.5×25 cm.), the column was eluted with $CHCl_3$ and each 5 ml. of the effluents were collected. The fractions (tube Nos. 28~32) containing a product which gave an absorption maximum at 274 mμ and gave a negative test with the Ehrlich's reagent were combined and concentrated *in vacuo*. The residual white powder (IX) was dried over P_2O_5. *Anal.* Calcd. for $C_{32}H_{26}O_{11}N_2$: C, 62.53; H, 4.27; N, 4.46. Found : C, 62.54; H, 4.90; N, 4.88. UV : λ_{max}^{EtOH} mμ (ε) 232 (36900), 274 (18400).

The absorption maximum of this compound was similar to those of 1-methyl-5-acetylbarbituric acid, thus IX should have a structure of 1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-5-acetylbarbituric acid.

Sodium 1-(β-D-Ribofuranosyl)barbiturate (6-Hydroxyuridine Sodium Salt) (X)——The yellow powder, which was obtained from 2.9 g. of VII and 610 mg. of malonic acid by the procedure described above, was suspended in 40 ml. of 2% NaOH solution and stirred overnight at room temperature to furnish a yellow clear solution. The solution was decationized with Dowex-50 (H^+) resin and the BzOH that precipitated was filtered through the same resin bed. The remaining BzOH in the filtrate was extracted with Et_2O. The acidic aqueous solution was rapidly adjusted to pH 7.5~8.0 with Et_3N and concentrated under reduced pressure below 35°. The concentrated solution was applied to a DEAE-cellulose column (bicarbonate form, 1.8×45 cm.) and the column was washed with 100 ml. of H_2O and the column was gradiently eluted as follows : the mixing vessel contained 300 ml. of 0.001*M* triethylammonium bicarbonate (pH, 7.5) and the reservoir contained 300 ml. of 0.1*M* triethylammonium bicarbonate buffer (pH, 7.5) and each 10 ml. fractions were taken. The fractions (tube Nos. 68~78) which had UV absorption at 259 mμ and colored orange with the Ehrlich's reagent were combined and concentrated *in vacuo* to ca. 4 ml. keeping the solution at alkaline pH (7.0~8.0) by adding of Et_3N. The residue was decationized with Dowex-50 (H^+) resin and passed through a bed of IRC-50 (Na^+) resin. The effluent was again concentrated under reduced pressure. A white powder was precipitated by adding EtOH to the concentrate in a yield of 320 mg. (37% from VII under conception that VIII was intermediate). *Anal.* Calcd. for $C_9H_{11}O_7N_2Na\cdot H_2O$: C, 36.01; H, 5.71; N, 9.33. Found : C, 36.12; H, 5.06; N, 8.77. UV mμ (ε): $\lambda_{max}^{pH\,1.0}$ 257 (1170), $\lambda_{max}^{pH\,6.0}$ 259 (15200), $\lambda_{max}^{pH\,13.0}$ 263 (11200). pKa : 3.6 and 12.4 (spectrophotometrically determined). $[\alpha]_D^{14}$ +3.21° (c=0.82, H_2O). Rf_3=0.27 and Rf_4=0.34. $M_{DNP\text{-}glycine}$=0.87. This compound consumed 2.40 moles of periodate at 2~3° in 24 hr. without liberation of HCOOH. (N-Phenylbarbituric acid consumed 1.50 moles of reagent under similar condition).

This compound (X) is unstable in acidic solution : In 0.1*N* HCl within 2~3 min., a part of the compound converted to a product (XII) which is electrophoretically neutral (at pH 9.0), gave no color with the Ehrlich's reagent and gave an absorption maximum at 252 mμ at pH 7.0 but gave the same Rf value as X (solvent : 4), and consumed periodate.*10

The above aqueous washings of DEAE-cellulose column were examined by paper chromatography and paper electrophoresis, and the result was that the washings were consisted of XI as a major and XII as a minor component.

The compound (X) was dissolved in pyridine, Ac_2O was added to the solution and the mixture was kept for 30 min. at room temperature. The mixture, on paper chromatography, gave a spot of Rf_4: 0.62 and the aqueous extract of the spot had absorption maximum at 278 mμ similar to 1-methyl-5-acetylbarbituric acid. The Rf value and absorption spectra were coincided with those of hydrolysis product of IX with 5% NaOH.

*8 Barbituric acid derivatives colored orange[10] and urea derivatives colored yellow[11] with the Ehrlich's reagent, but malonic acid, diethyl malonate, 5-substituted barbituric acid and N,N'-disubstituted urea did not color with this reagent.

*10 In the above purification of X, when (Dowex-1 Cl^-) was used instead of DEAE-cellulose and 0.01*N* HCl-0.02*M* NaCl solution was employed as the eluting solvent, a considerable amount of the compound (XII) appeared over a wide range of the fractions eluted. The fractions were combined, deanionized with Ag_2CO_3 and treated as above case of glucosylbarbituric acid to furnish a white powder. *Anal.* Calcd. for $C_9H_{11}O_7N_2Na\cdot 2H_2O$ (this formula is identical with that of X) : C, 33.98; H, 4.75; N, 8.81. Found : C, 33.83; H, 4.16; N, 8.72. UV mμ : $\lambda_{max}^{pH\,6.0}$ 252, $\lambda_{max}^{pH\,13.0}$ 255.

10) A. Weischenk : Ber., **34**, 1685 (1901).

11) R. M. Fink, R. E. Cline, C. Mcgaughey, K. Fink : Anal. Chem., **28**, 4 (1956).

The authors are indebted to Takeda Chemical Industries Co., Ltd. for their kind supply of the starting materials for the present syntheses and to Dr. M. Sano of Central Research Laboratory, Daiichi Seiyaku Co., Ltd. for a gift of standard sample for identification. Thanks are also due to the Central Analysis Room of this Faculty for carring out the elemental analysis and optical measurements.

Summary

By condensation of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)urea (Ⅳ)with malonyl chloride in pyridine, N,N′-bis(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylcarbamoyl)-malondiamide (Ⅴ) was obtained. This compound, when treated with alkali, afforded each one mole of 1-(β-D-glucopyranosyl)urea and sodium 1-(β-D-glucopyranosyl)barbiturate (Ⅵ). Condensation of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)urea (Ⅶ) with malonic acid in acetic anhydride gave N,N′-bis(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-carbamoyl)malondiamide (Ⅷ) with a small amount of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-5-acetylbarbituric acid (Ⅸ). On alkaline treatment, Ⅷ afforded sodium 1-(β-D-ribofuranosyl)barbiturate (Ⅹ) and 1-(β-D-ribofuranosyl)urea (Ⅺ). The overall yield of Ⅵ and Ⅹ from Ⅳ and Ⅶ were 30.3% and 37% respectively. The stucture of the glycosylbarbiturates, Ⅵ and Ⅹ, were discussed and their properties were described.

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69. Keijiro Takagi, Yutaka Kasuya, and Kazuo Watanabe: Studies on the Drugs for Peptic Ulcer. A Reliable Method for Producing Stress Ulcer in Rats.

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For studying the remedies for peptic ulcer, we estimate their effectiveness on the experimental peptic ulcer of animals. In this field Shay's procedure[1] is the well established convenient method, but this is not enough for the research of complicated causative factors of peptic ulcer. Complexity of the etiology of gastric ulcer made many researchers to find a variety of experimental procedures to produce this lesion on animals.[1~11]

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1) H. Shay, S. A. Komarov, S. S. Fels, D. Meranze, H. Siplet: Gastroenterology, **5**, 43 (1945).
2) H. Selye: Nature, **138**, 32 (1936).
3) A. Robert, J. E. Nezamis: Proc. Soc. Exp. Biol. Med., **99**, 443 (1958).
4) M. Levrat, R. Lambert: Gastroenterology, **37**, 421 (1959).
5) J. Watt, C. W. M. Wilson: *Ibid.*, **37**, 8 (1959).
6) S. Bonfils, G. Rossi. G. Liefooghe, A. Lambling: Rev. Franc. Clin. Biol., **4**, 888 (1959).
7) J. D. Dahl, R. K. Blaisdell, E. Beutler: Proc. Soc. Exp. Biol. Med., **101**, 622 (1959).
8) C. R. Thomas, C. L. Dorolle, C. R. Effron, G. Volunter, M. Meyer, J. M. Chaumontet, D. Larue: Arzneim. Forsch., **10**, 589 (1960).
9) H. Selye, P. Jean, M. Cantin: Proc. Soc. Exp. Biol. Med., **103**, 444 (1960).
10) D. A. Brodie: Gastroenterology, **43**, 107 (1962).
11) T. Toriumi: Tokyo Jikeikai Med. J., **71**, 1876 (1956).