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2,5-Dicarbonyl Sugars: New Intermediates for Synthesising Heterocyclic Rings. I. Synthesis of 4(1*H*)-Pyridazinone Derivatives from Dicarbonyl Sugars[1]

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2,5-Dicarbonyl sugars (5-keto-D-fructose and 2,5-diketo-D-gluconate) prepared by bacterial oxidation, react with hydrazine hydrate to give 4(1*H*)-pyridazinone derivatives. Treatment of 5-keto-D-fructose (D-*threo*-2,5-hexodiulose) (I) with hydrazine hydrate yields 3,6-dihydroxymethyl-4(1*H*)-pyridazinone (III), which is identical with the reaction product of kojic acid with hydrazine. Treatment of 2,5-diketo-D-gluconate (D-*threo*-2,5-hexodiulosonate (II) with hydrazine hydrate yields a mixture of 3-hydroxymethyl-4(1H)-pyridazinone-6-carboxylic acid (IV) and 6-hydroxymethyl-4(1*H*)-pyridazinone-3-carboxylic acid (V), whose structures can be established by chemical and spectroscopic methods. The mechanisms of their formation are also discussed.

A large number of heterocyclic compounds have been reported from saccharide derivatives, with the aim of finding their utilities for abundant and relatively inexpensive resources, or of studying the chemistry and biological activity of the heterocyclic compounds prepared, or of elucidating the chemical structures of various sugars and of using them as intermediates in the synthesis of amino sugar derivatives.

We are now going to describe a synthesis of 4(1*H*)-pyridazinone derivatives from 2,5-dicarbonyl hexose or hexonic acid, *i.e.* 5-keto-D-fructose (D-*threo*-2,5-hexodiulose) and 2,5-diketo-D-gluconate (D-*threo*-2,5-hexodiulosonate).

5-Keto-D-fructose (I) was formed from D-fructose,[3a-c] L-sorbose,[3a-c] and D-sorbitol[3d] by many of the members of *Acetobacter* and synthesized from D-fructose and L-sorbose by chemical oxidation.[4]

2,5-Diketo-D-gluconate (II) was formed from D-glucose, D-gluconate and 2-keto-D-gluconate by some microbes belonging to genus *Acetobacter* or *Pseudomonas*.[5a,b]

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3) *a*) O. Terada, K. Tomizawa and S. Kinoshita, *J. Agr. Chem. Soc. Japan*, **35**, 127 (1961); *b*) O. Terada, K. Tomizawa and S. Kinoshita, *J. Agr. Chem. Soc. Japan*, **35**, 131 (1961); *c*) O. Terada, K. Tomizawa and S. Kinoshita, *J. Agr. Chem. Soc. Japan*, **35**, 178 (1961); *d*) M. Kulhanek and Z. Sevcikova, *Folia Microbiologia*, **7**, 288 (1962).

4) G.C. Whiting and R.A. Coggins, *Chemistry and Industry*, **1963**, 1925.

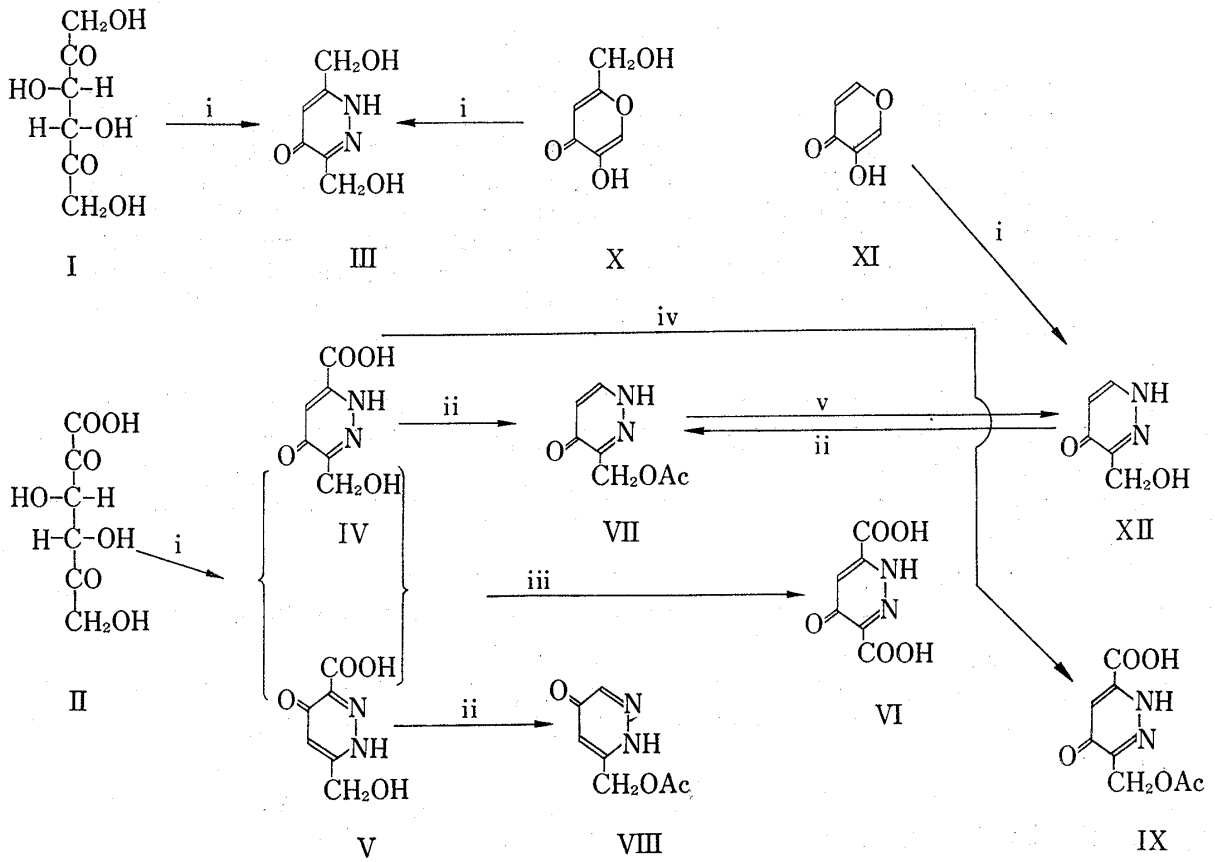
5) *a*) H. Katznelson, S.W. Tanenbaum and E.L. Tatum, *J. Biol. Chem.*, **204**, 43 (1953); *b*) Y, Wakisaka, *Agr. Biol. Chem.*, **28**, 819 (1964).

The production of these dicarbonyl sugars have been gradually improving to a large and efficient production.[6a,b] There are apparently only few references on the reaction of these sugars, in which bis-arylhydrazones of them have been reported on the purpose of elucidating their structures.[5b,7] Application of these sugars easily available for the syntheses of heterocycles have been made only in the syntheses of γ-pyrone derivatives such as kojic acid and comenic acid.[8a,b]

When a mixture of equimolar quantities of I and hydrazine hydrate in methanol was heated under reflux, 3,6-dihydroxymethyl-4(1*H*)-pyridazinone (III) was obtained in a quantities yield, which was identical with the major product obtained by the reaction of kojic acid with hydrazine hydrate.[9a,b]

The compound (II) reacted with hydrazine hydrate yielding a mixture of 3-hydroxymethyl-4(1*H*)-pyridazinone-6-carboxylic acid (IV) and 6-hydroxymethyl-4(1*H*)-pyridazinone-3-carboxylic acid (V), in 53% and 5% yields, respectively. The separation of IV from V was successful through fractional recrystallization of crude reaction product from water, in which IV is almost insoluble.

The structure of IV and V were confirmed by their chemical and spectroscopic behavior.



reagents: i, N_2H_4; ii, Ac_2O; iii, $KMnO_4$; iv, pyridine–Ac_2O; v, HCl

Chart 1

6) *a*) S. Ōga, K. Asano and K. Imada, U.S. Patent 3654316 (1972); *b*) K. Asano, K. Imada, S. Ōga and K. Satō, Japan Patent 45-24391 (1970).
7) *a*) O. Terada, K. Tomizawa, S. Suzuki and S. Kinoshita, *Bull. Agr. Chem. Soc. Japan*, **24**, 535 (1960); *b*) F. Micheel and K. Horn, *Ann.*, **515**, 1 (1934).
8) *a*) S. Ōga, K. Imada and K. Asano, *Agr. Biol. Chem.*, **31**, 1511 (1958); *b*) S. Ōga, K. Imada and K. Asano, The Annual Meeting of Agricultural Chemical Society of Japan, Tokyo, April 1971.
9) *a*) A.F. Thomas and A. Marxer, *Helv. Chim. Acta*, **41**, 1898 (1958); *b*) I. Ichimoto, K. Fujii and C. Tatsumi, *Agr. Biol. Chem.*, **31**, 979 (1967).

Oxidation of IV and V with permanganate afforded the known 4(1*H*)-pyriazinone-3,6-dicarboxylic acid (VI),[9a] which was identical with VI prepared from III. Acetylation of IV with pyridine and acetic anhydride at room temperature, gave 3-acetoxymethyl-4(1*H*)-pyridazinone-6-carboxylic acid (IX).

However, acetylation of IV and V with acetic anhydride on heating afforded the known 3-acetoxymethyl-4(1*H*)-pyridazinone (VII) and the unknown 6-acetoxymethyl-4(1*H*)-pyridazinone (VIII) respectively, accompanied with carbon dioxide liberation. Hydrolysis of VII with dilute HCl gave 3-hydroxymethyl-4(1*H*)-pyridazinone (XII)[9b] which was identical with XII prepared from pyrocomenic acid (XI).

The assigned structure of VIII was confirmed by the elemental analysis and spectral data. The compound (VIII) showed absorption bands due to the acetoxymethyl group at (1380, 1440 and 1750 cm^{-1}) and no absorption bands due to a tertiary amide in the infrared (IR) spectrum.

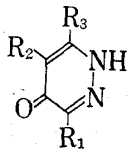
The nuclear magnetic resonance (NMR) spectrum showed two singlets (δ 5.00 and δ 2.12 assigned to $-CH_2O-$ and $-COCH_3$, respectively), and two doublets (δ 6.27 and δ 7.92 assigned to 5- and 3-position of pyridazine ring protons, respectively), whose coupling constant (J) were 3 cps each other, which were consistent with authentic 6-methyl-4(1*H*)-pyridazinone.[9b]

The ultraviolet (UV) absorption of IV and V were in good agreement with that expected on the basis of that of parent compound.[9a,b]

The NMR data of IV, V and related compounds are shown in Table I.

The structure of reaction products from II with hydrazine hydrate were thus elucidated.

Table I. NMR Spectra of 4(1*H*)-Pyridazinone Derivatives



Compounds	R_1	δ	R_2	δ	R_3	δ
III	CH_2OH	4.42(s)	H	6.22(s)	CH_2OH	4.42(s)
IV	CH_2OH	4.48(s)	H	6.72(s)	COOH	
V	COOH		H	6.95(s)	CH_2OH	4.62(s)
VII	CH_2O	5.05(s)	H	6.33(d)	H	8.24(d)
	$\dot{C}OCH_3$	2.10(s)		J=8		J=8
VIII	H	7.92(d)	H	6.27(d)	CH_2O	5.00(s)
		J=3		J=3	$\dot{C}OCH_3$	2.12(s)
XII	CH_2OH	4.44(s)	H	6.25(d)	H	8.16(d)
				J=8		J=8
XX	CH_2OH	4.48(s)	H	6.72(s)	$COOCH_2$	4.38(q)
					$\dot{C}H_3$	1.35(t)
						J=7.5

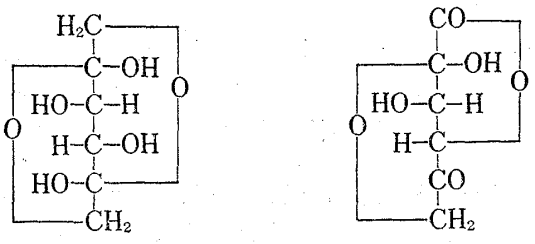
The spectra were obtained at 60 Mc, on Hitachi-20B spectrometer, in DMSO-d_6 (1 drop, D_2O) containing tetramethylsilane (TMS) as an internal standard. Chemical shifts are quoted as (ppm) downfield from TMS (0.00 ppm). Abbreviations used are s=singlet, d=doublet, t=triplet, q=quartet.

There are apparently only few references in the literature reporting the preparation of simple 4(1*H*)-pyridazinone derivatives. These include the reaction of hydrazine with γ-pyrone derivatives such as kojic acid and pyrocomenic acid.[9a,b]

However, also a pyrazole derivatives is obtained by these reaction. Since 5-keto-D-fructose gives kojic acid upon the thermal conversion,[8a] it may be considered that the first step of the reaction of I with hydrazine must therefore be the formation of kojic acid, after which the reaction with hydrazine occurs. This assumption, however, can be excluded by the fact that during the reaction, pyrazole derivatives were not detected on the thin-layer

chromatography.[9b] Thus, it may be expected that there are another mechanisms and intermediates for the reaction. Several attempts to obtain an intermediate from the reaction mixture, failed. Apparently this intermediate is too unstable to submit separation from the mixture formed by any techniques we have been able to devise to data.

For this reason, the reaction mechanism of II with hydrazine hydrate was investigated. As is analogized from the structure of I, which was suggested by Englard, *et al.*[10] existing as the double pyranose rings in the boat form, a possible structure of 2,5-diketo-D-gluconic acid appears to be II'.



I' II'

Fig. 1. Hemiacetal Forms of 5-Keto-D-fructose and 2,5-Diketo-D-gluconic Acid

I': 5-keto-D-fructose
II': 2,5-diketo-D-gluconic acid

The reaction of an equimolar quantities of calcium salt of II and hydrazine hydrate in water at 0° for 1 week, gave a precipitate of calcium salt of IV, in 50% yield. However, when the mother liquor was acidified with HCl and then heated at 95° for 2 hr, both comenic acid and small amount of V were obtained. It must be assumed that 1 mole of hydrazine was not enough to react with 1 mole of II and consequently the rest of II was converted into comenic acid on heating.[8b] For this reason, the reaction of 1 mole of II with 2 mole of hydrazine hydrate was carried out under the same conditions.

A white precipitate was formed in a good yield. The structure (XV) of the product was established by the microanalytical result, spectroscopic evidence and chemical behaviors. The IR spectrum showed band at 1600 and 1400 cm^{-1} assigned to COO^- and a shoulder at 1610 cm^{-1} assigned to C=N group. In the NMR spectrum (Fig. 2a), no absorption showed at δ 7.00 to δ 8.00 attributable to pyridazinone ring proton. The NMR spectrum showed two doublet (J=3.8 cps) at δ 4.12, δ 4.35 and singlet at δ 3.80 assigned respectively to γ-, β-, and ε-proton (integral ratio; 2: 2: 4), which were almost agree with those of sodium 5-keto-D-gluconate.[11] The minor components were observed in δ 4.70 and δ 5.20.

The product XV can be considered as an intermediate in the formation of IV and V, because when warmed with dil. HCl, it gave a mixture of IV and an another intermediate, liberating 1 mole of hydrazine[12] per 1 mole of XV. The latter intermediate, purified with column chromatography, seems to be fairly stable. Thin-layer chromatography showed that heat treatment of an aqueous solution of this intermediate under acidic or neutral conditions, gave V and a small amount of IV. (IV; Rf=0.26, V; Rf=0.42). The liberation of hydrazine appears to be necessary to explain the reaction mechanism, because due to this matter, keto-monohydrazones, having an active carbonyl group, are formed, by which dehydration and cyclization may probably be carried out.

On the basis of these data, apparent course of this reaction may be proposed as follows (see Chart 2).

First, the nucleophilic attack of hydrazine would take place exclusively at 5-position of II, since 2-position of II is stabilized by formation of pyranose ring.[13] Then, pyranose ring opening would take place to form an intermediate (XIV), which lead to the key intermediate (XV) by the action of excess hydrazine. With liberating hydrazine, XV give two possible

10) S. Englard, G. Avigad and L. Prosky, *J. Biol. Chem.*, **240**, 2302 (1965).
11) C.Y. Chen, H. Yamamoto and T. Kwan, *Chem. Pharm. Bull.* (Tokyo), **18**, 815 (1970).
12) The reaction mixture was neutralized with NaOH solution and then distilled. The distillate was determined by KIO_3 method.
13) This matter is substantiated by the reaction of II with arylhydrazine. A part of this reaction was presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1973.

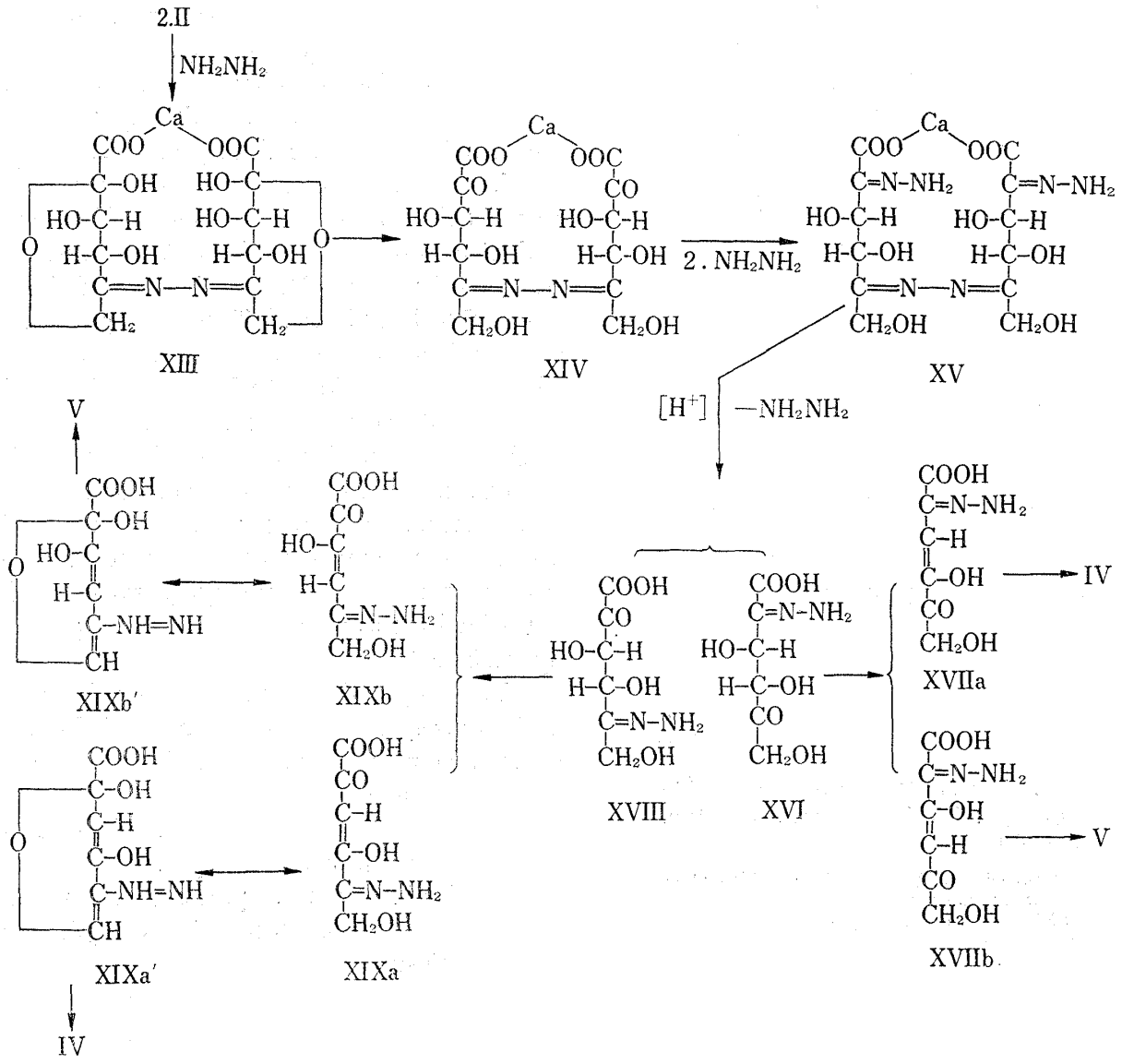


Chart 2

hydrazone (XVI and XVIII). The assumed compound (XVI) would be spontaneously converted into IV and V *via* XVIIa and XVIIb respectively. As for the yields, V was obtained in much less yield than was IV, which suggests that XVIIa is more contributable than XVIIb due to the mesomeric effect.

The assumed compound (XVI) must be unstable and all the possible ring structure seems to result in a highly strained molecule and it is therefore likely that it will be spontaneously converted into IV and V accompanied with dehydration.

The compound (XV) is affected remarkably by [H+], even [H+] of acidic solvent using in thin-layer chromatography. In the NMR spectrum, acidification of a XV solution (D_2O) with DCl, caused two singlets to appear (at δ 7.33 and δ 4.58, assigned respectively to ring proton of IV and CH_2 OH of IV) and two doublet to disappear (at δ 4.12 and at δ 4.35, assigned respectively to γ and β protons of XV) and caused minor peaks around HDO peak to appear (see Fig. 2). In Fig. 2b, a broad singlet at δ 3.4—3.7 seems to be remainder of ε proton of XV.

The intermediate, purified with column chromatography (described before), did not crystallise even on prolonged deep-cooling. Attempt to use several solvents for crystallization also failed. However, this can be considered as a mixture of XIXa',b', on the basis of its

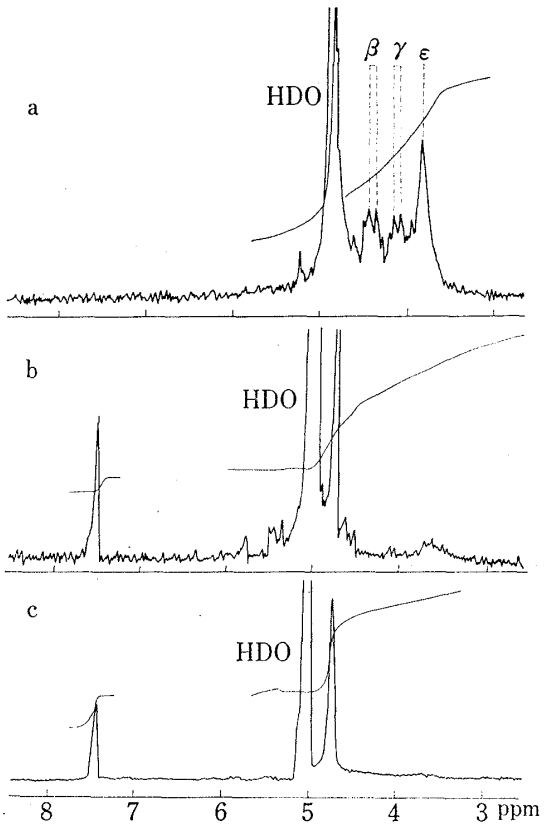


Fig. 2. The NMR Spectra of (a); XV in D_2O, (b); XV in D_2O–DCl, (c); IV in D_2O–DCl

sample: 50 mg, D_2O: 0.5 ml, 20%DCl: 0.01 ml
temp.: at room temp.
a: XV in D_2O, b: XV in D_2O–DCl after 5 hr, c: IV in D_2O–DCl

elementary analysis, NMR spectrum and formation of IV and V on heating.

Due to the stability of ring structure, enol-forms (XIXa′ and XIXb′) may be hardly converted into IV and V, respectively.

The NMR spectrum showed a couple of two doublets at δ 3.88, at δ 4.00 (J=3 cps) and at δ 4.40, at δ 4.70 (J=3.5 cps) assigned respectively to C6–H, C4–H of XIXb′ and C6–H, C3–H of XIXa′. These interpretations are based on studies of some enol-forms of II which are most likely to be formed in acidic media.[8b] At present paper, XIXa′ and XIXb′ might be assumed products, since the UV spectral data cannot be obtained for the sake of a mixture. However, the existence of such assumed compounds may be explained from the structure of mono phenylhydrazone of II obtained by the reaction of II with phenylhydrazine.[13]

The proposed scheme may also be assumed to apply to the formation of II from I. It must be more simple, since the structure of I is symmetrical.

The formation of 4(1*H*)-pyridazinone derivatives from dicarbonyl sugars can be accounted for in terms of hydrazone formation, keto–monohydrazone formation, dehydration and ring closure.

Experimental

All melting points were uncorrected. IR, UV and NMR spectra were recorded on a Hitachi EPI-G 2 spectrometer, Hitachi 124 spectrometer and Hitachi 20-B spectrometer, respectively. Thin-layer chromatography was carried out on Silica gel G. The solvent system used was upper layer of mixed solvents composed of *n*-butanol, formic acid and water (4.0: 1.5: 1.0). Spray reagents used were 2% ferric sulfate solution for the detection of IV and V and comenic acid, and alkaline $AgNO_3$ reagent[14] for I, II and hydrazones of II. With the ferric sulfate reagent 4(1*H*)-pyridazinone derivatives and comenic acid gave a yellow and wine red color, respectively.

The compounds (I and II) were prepared by fermentation and purification described in ref. 6*a*,*b* respectively, and II was used as calcium salt because of its stability.

3,6-Dihydroxymethyl-4(1*H*)-pyridazinone (III)——Hydrazine hydrate (98%, 0.27 ml) was added to a suspension of I (1 g) in MeOH (50 ml). The mixture was heated under reflux for 1 hr and then evaporated to dryness under reduced pressure. The yellow residue was crystallized from MeOH to yield I (0.8 g) as crude crystals. Recrystallization from H_2O–MeOH (1: 1) afforded the white fine needles, mp 221° (decomp.) which were identical (mixed mp and IR spectrum) with authentic material.[9a]

3-Hydroxymethyl-4(1*H*)-pyridazinone-6-carboxylic Acid (IV) and 6-Hydroxymethyl-4(1*H*)-pyridazinone-3-carboxylic Acid (V)——(a) To a solution of calcium salt of II (22.9 g) in 100 ml of a buffer (pyridine: acetic acid: water=2: 1: 2) was added hydrazine hydrate (98%, 5.1 ml). The reaction mixture was heated at 90° for 90 min and then evaporated to dryness under reduced pressure. The residue was dissolved in hot water, decationated with Amberlite IR 120 (H-type), and concentrated to almost dryness to give a crude crystal mass. Recrystallization from hot water gave IV (9.0 g), mp 219° (decomp.). *Anal.* Calcd.

14) W.E. Trevelyan, D.P. Proctor and J.S. Harrison, *Nature*, **166**, 144 (1950).

for $C_6H_6O_4N_2$: C, 42.30; H, 3.53; N, 16.48. Found: C, 42.15; H, 3.60; N, 16.31. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO), 3300 (OH and or NH), 1580, 1550 and 1525 (4(1*H*)-pyridazinone ring mode).[9b] UV $\lambda_{max}^{H_2O}$ mμ(log ε): 263 (3.58), 208 (3.94); λ_{max}^{MeOH} mμ(log ε): 278 (4.02), 205 (4.17); $\lambda_{max}^{2N\ HCl}$ mμ(log ε): 263 (3.58), 208 (3.94); $\lambda_{max}^{2N\ NaOH}$ mμ (log ε): 257 (4.12), 222 (3.82).

The filtrate obtained by removal of crude crystal mass, was concentrated to dryness under reduced pressure and the residue was recrystallized from MeOH to afford V (0.85 g) as white hexagonals, mp 206.5° (decomp.). *Anal.* Calcd. for $C_6H_6O_4N_2$: C, 42.30; H, 3.53; N, 16.48. Found: C, 41.94; H, 3.52; N, 16.31. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO), 3310 (OH and or NH), 1620, 1580 and 1505 (4(1*H*)-pyridazinone ring mode).[9b] UV $\lambda_{max}^{H_2O}$ mμ(log ε): 267 (4.02), 194 (4.21); $\lambda_{max}^{2N\ HCl}$ mμ(log ε): 258 (3.91), 210 (4.16).

(b) Calcium salt of II (22.9 g) was dissolved in distilled water (200 ml) and passed through an Amberlite IR 120 (H-type) column which was then washed with water until the eluate became neutral. The combined eluate was evaporated under reduced pressure to give a heavy syrup. The syrup was dissolved in a buffer solution described in (a) and hydrazine hydrate (10.2 g) was added. The reaction mixture was allowed to stand for 7 days at 5°, affording a precipitate of brownish needles. Recrystallization from H_2O–MeOH gave hydrazine salt of IV as white needles (10.5 g), mp 230° (decomp.). *Anal.* Calcd. for $C_6H_{10}O_4N_4$: C, 35.92; H, 5.45; N, 27.60. Found: C, 36.00; H, 4.95; N, 27.70. Treatment of this crystals with dil. H_2SO_4 gave IV.

(c) Hydrazine hydrate (98%, 5.1 ml) was added dropwise under stirring to a solution of calcium salt of II (22.9 g) in water (200 ml). The reaction mixture was allowed to stand for 7 days at 0° to give a precipitate of faintly yellow hexagonal. The aqueous solution of the precipitate was heated with conc. HCl (5 ml) and then concentrated to syrup to give white needles (8.5 g) which were identical with those of the product prepared by (a).

The mother liquor from the separation of the precipitate mentioned above was acidified with conc. HCl (5 ml) and heated at 95° for 2 hr. Thin-layer chromatography of the reaction mixture on a silica gel plate showed three products which were identical, in their *Rf* value with IV, V and comenic acid. The reaction mixture was then concentrated to dryness under reduced pressure. Resulting residue (red brown mass) was chromatographed on avicel (*n*-butanol: formic acid: water=4.0: 1.5: 1.0, upper layer) to separate three fractions, which were treated each other to give IV, V and comenic acid (0.2, 0.5 and 2.4 g, respectively). Comenic acid, recrystallized from water, was identical (IR spectrum and mixed mp) with authentic sample.[8b]

(d) Hydrazine hydrate (98%, 10.2 ml) was added to a solution of calcium salt of II (22.9 g) under same condition as that of (b). The mixture was allowed to stand for 7 days at 0° to give a precipitate of white powder, which was collected, washed with water and dried on P_2O_5 in room temperature, mp 245° (decomp.). *Anal.* Calcd. for $C_{12}H_{26}O_{10}N_6Ca \cdot 4H_2O$: C, 27.80; H, 5.02; N, 16.20; Ca, 7.73. Found: C, 28.25; H, 5.15; N, 16.23; Ca, 8.02. IR ν_{max}^{KBr} cm^{-1}: 3280 (OH and NH), 1600 and 1390 (COO^-). UV $\lambda_{max}^{H_2O}$ mμ(log ε): 244—254 (3.99). Thin-layer chromatographic behaviors on a silica gel plate:

solvent system: *n*-BuOH: HCOOH: H_2O=4.0: 1.5: 1.0 (upper layer).
ascending development in dark room: *Rf*=0.18 (brown with $AgNO_3$).
ascending development under day light: *Rf*=0.18 (brown with $AgNO_3$).
Rf=0.26 (yellow with Fe##).

A spot at *Rf*=0.26 was in a good agreement with that of IV.

A suspension of the product (5.2 g) in water (100 ml) was heated at 65° for 1 hr, acidified with conc. HCl (3 ml) and cooled at 5° to give a crude crystalline mass which was composed of IV and small amount of V on the thin-layer chromatographic observation. Recrystallization from water gave white needles (1.8 g) with mixed mp and IR spectrum identical with those of IV prepared by method (a).

The filtrate obtained by removal of a crude crystalline mass was evaporated under reduced pressure until the weight of the residual yellow heavy syrup became constant. The product was eluted through avicel with mixed solvent described in (c) to afford faintly yellow syrup (2.25 g). *Anal.* Calcd. for $C_6H_8O_5N_2 \cdot H_2O$: C, 34.95; H, 4.85; N, 13.60. Found: C, 35.05; H, 4.60; N, 13.50. The product was dissolved in water, adjusted to pH 1.5 with dil. HCl, and heated at 95° for 3 hr. Resulting brown solution was concentrated to almost dryness to give a crude crystalline mass which was composed of V and a small amount of IV on the thin-layer chromatographic observation. Recrystallization from hot water gave white hexagonals (0.5 g), with mixed mp and IR spectrum identical with those of V prepared by method (a). On the other hand, the product was dissolved in water, adjusted to pH 7.0 with dil. NaOH solution, and heated at 95° for 3 hr. Treatment of the resulting brown solution afforded V (0.3 g) and IV (0.06 g) which were separated by fractional recrystallization with water.

4(1*H*)-Pyridazinone-3,6-dicarboxylic Acid (VI) from IV and V——A solution of potassium permanganate (3 g) in water (100 ml) was added dropwise to a rapidly stirring solution of IV (0.8 g) in water (50 ml), and the whole was kept at 75°. The reaction mixture was filtered to remove manganese dioxide. The filtrate was concentrated *in vacuo* to give VI as crude crystals, mp 207.5°, which were identical in all respects (mixed mp and IR spectrum) with authentic sample.[9a]

Oxidation of V (0.4 g) with potassium permanganate (1.5 g) was carried out as above IV. The product (0.1 g) was identical (mixed mp and IR spectrum) with VI obtained from IV.

3-Acetoxymethyl-4(1*H*)-pyridazinone (VII) from IV——A mixture of IV (5 g) and acetic anhydride (80 ml) was heated under reflux for 90 min. The reaction mixture was then evaporated *in vacuo* to almost dryness. Recrystallization from MeOH gave pure VII (2.4 g) as colorless needles, mp 207.5° (decomp.), which were identical (mixed mp and IR spectrum) with authentic sample.[9b]

6-Acetoxymethyl-4(1*H*)-pyridazinone (VIII) from V——Similarly, V (0.3 g) was treated with an excess acetic anhydride to yield VIII (0.2 g). Recrystallization from MeOH afforded VIII as colorless needles, mp 211.5° (decomp.). *Anal.* Calcd. for $C_7H_8O_3N_2$: C, 49.54; H, 5.00; N, 17.03. Found: C, 49.89; H, 5.11; N, 17.05. IR ν_{max}^{KBr} cm^{-1}: 1750 (CO). UV $\lambda_{max}^{H_2O}$ mμ(log ε): 267 (4.11).

3-Acetoxymethyl-4(1*H*)-pyridazinone-6-carboxylic Acid (IX)——A mixture of IV (5 g), acetic anhydride (50 ml) and pyridine (50 ml) was allowed to stand for 2 days at room temperature. The reaction mixture was then evaporated to almost dryness. Recrystallization from MeOH afforded pure IX (2.5 g) as white fine needles, mp 199.5° (decomp.). *Anal.* Calcd. for $C_8H_8N_2O_5$: C, 45.30; H, 3.97; N, 13.20. Found: C, 45.70; H, 3.93; N, 13.00. IR ν_{max}^{KBr}: 1720 (CO). Hydrolysis of IX with dil. HCl on heating for 1 hr afforded IV.

Ethyl Ester of 3-Hydroxymethyl-4(1*H*)-pyridazinone-6-carboxylic Acid (XX)——The compound (IV) (5 g) was heated under reflux for 1 hr with EtOH (160 ml) containing HCl (5 g). Evaporation of the solvent left a solid which was recrystallized from hot water to give ethyl ester of IV (4.9 g) as white needles, mp 196° (decomp.). *Anal.* Calcd. for $C_8H_{10}O_4N_2$: C, 48.30; H, 5.00; N, 14.27. Found: C, 48.49; H, 5.05; N, 14.14. IR ν_{max}^{KBr} cm^{-1}: 1735 (CO). UV λ_{max}^{EtOH} mμ(log ε): 280 (4.07), 213 (4.21).

3-Hydroxymethyl-4(1*H*)-pyridazinone (XII)——The compound (VII) (1 g) was heated with 10% HCl (100 ml). The reaction mixture was neutralized with KOH solution. Evaporation to dryness *in vacuo* left a solid which was recrystallized three times from 50% MeOH to give XII (0.5 g) as white needles, mp 212° (decomp.), which were identical (mixed mp and IR spectrum) with authentic sample.[9b]

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