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71. Hisao Tsukamoto, Hidetoshi Yoshimura, and Satoshi Toki: Metabolism of Drugs. VI.* The Metabolic Fate of Methylhexabital (5-Cyclohexenyl-3,5-dimethylbarbituric Acid). (2).[3] On the Chromic Oxidation of Methylhexabital and Normethylhexabital (5-Cyclohexenyl-5-methylbarbituric Acid).

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In the earlier papers in this series,[1,2] it was reported that a metabolite of ethylhexabital (EHB, 5-cyclohexenyl-5-ethylbarbituric acid) isolated from the urine of rabbits receiving EHB was identical with the oxidation product of EHB with chromium trioxide and its structure was confirmed as 5-(3′-oxocyclohex-1′-enyl)-5-ethylbarbituric acid. By analogy with this, the present studies on the metabolic fate of methylhexabital J. P. (MHB, 5-cyclohexenyl-3,5-dimethylbarbituric acid) was undertaken and the results in outline were reported in the previous communication.[3]

It is expected that one of the methylene groups in the cyclohexenyl ring of MHB will be oxidized to a carbonyl and the oxidized compound will possibly be obtained by a chromic oxidation of MHB as well as EHB.

It is shown in this paper that the oxidation reactions of MHB and nor-MHB (5-cyclohexenyl-5-methylbarbituric acid) are studied in parallel with the *in vivo* metabolism of MHB[4] and the structures of the oxidation products are established by analogy with EHB.[2]

To a suspension of powdered MHB in acetic anhydride was added dropwise a solution of chromium trioxide in acetic anhydride at 35° under stirring. Colorless plates (Ia), m.p. 160~161°, and colorless needles (Ib), m.p. 240~241°(decomp.), were obtained from the reaction mixture; yield about 28% and 2%, respectively.

Elementary analyses of the two products were in accord with 5-cyclohexenonyl-3,5-dimethylbarbituric acid and therefore it was considered that these were probably isomeric substances. The formation in a theoretical yield of a 2,4-dinitrophenylhydrazone as reddish orange crystals, m.p. 228~230°(docomp.), from (Ia) established that it was a ketone, but a dinitrophenylhydrazone could not be obtained from (Ib) under the same conditions.

However, as will be mentioned in the following paper[5] of this series, the ultraviolet and infrared absorption spectra indicated that these oxidation products might be α,β-unsaturated ketones. It seems reasonable that (Ib) will not be able to form 2,4-dinitrophenylhydrazone because of the steric hindrance and the position of the carbonyl is presumably the 6′-position in the cyclohexenyl ring which was close to the methyl radical in the 5-position of the barbituric acid ring.

This presumption was confirmed by the following experiments. The cyclohexenonyl derivatives, (Ia) and (Ib), were converted to the phenol derivatives (IIa) as colorless plates, m.p. 161~162°(decomp.), and (IIb) as colorless plates, m.p. 214~215° (decomp.), respectively, by the dehydrogenation reaction according to the method de-

* Part V: H. Tsukamoto, E. Takabatake, T. Ariyoshi: This Bulletin, **3**, 459(1955).
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1) H. Tsukamoto, E. Takabatake, H. Yoshimura: This Bulletin, **2**, 201(1954).
2) H. Tsukamoto, H. Yoshimura, S. Toki: *Ibid.*, **3**, 239(1955).
3) H. Tsukamoto, H. Yoshimura: *Ibid.*, **3**, 397(1955).
4) Part VII: H. Tsukamoto, H. Yoshimura, S. Toki: *Ibid.*, **4**, 367(1956).
5) Part VIII: H. Tsukamoto, H. Yoshimura, S. Toki: *Ibid.*, **4**, 370(1956).

scribed previously.[2] (IIa) was easily acetylated to the corresponding acetyl compound (V), m.p. 154~155°.

In this case, there were also obtained as the by-products 3,5-dimethylbarbituric acid (III) and phenol (IV), into which (Ia) and (Ib) were split by hydrogen produced during the dehydrogenating procedure. (IIa) and (IIb) were further submitted to an oxidative alkali fusion with potassium hydroxide, sodium hydroxide, or lead peroxide at 230~240° and respectively yielded *m*-hydroxybenzoic acid (VI), colorless needles, m.p. 192~194°, and salicylic acid (VII), colorless needles, m.p. 155~156°.

These experiments indicated that the structures of (IIa) and (IIb) would be 5-*m*-hydroxyphenyl- and 5-*o*-hydroxyphenyl-3,5-dimethylbarbituric acid and accordingly the structure of the oxidation products of MHB, (Ia) and (Ib), was considered to be 5-(3'-oxocyclohex-1'-enyl)- (3-keto-MHB) and 5-(6'-oxocyclohex-1'-enyl)-3,5-dimethylbarbituric acid (6-keto-MHB), respectively. The processes of the foregoing reactions are shown in Chart 1.

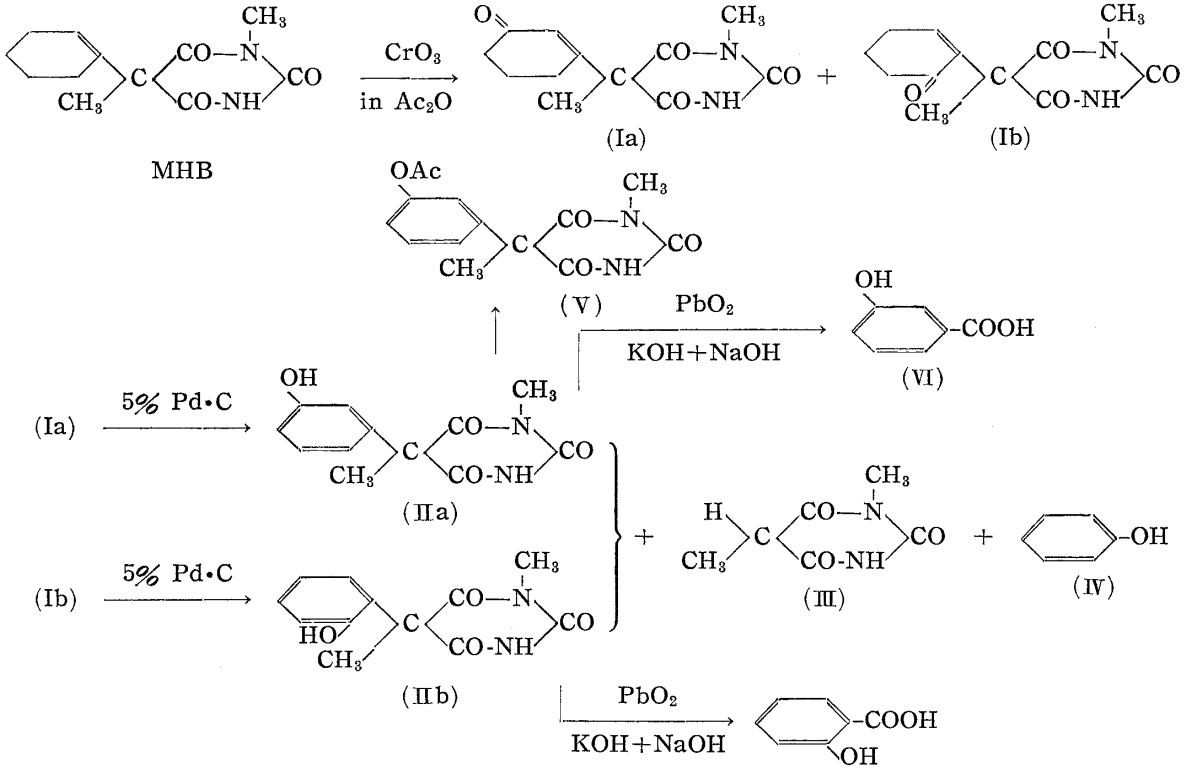

Chart 1.

In the oxidation of nor-MHB, results analogous to the oxidation of MHB were also obtained and the reaction products were colorless plates (I'a), m.p. 215~216°(decomp.), and colorless needles (I'b), m.p. 278~280°(decomp.). The yields were about 28% and 3%, respectively. The formation in a good yield of a 2,4-dinitrophenylhydrazone, m.p. 270~272°(decomp.), from (I'a) established that this substance was a ketone and elementary analyses of (I'a) and of its 2,4-dinitrophenylhydrazone were in fair agreement with the structure in which one of the methylene groups of the cyclohexenyl ring was oxidized to a carbonyl.

Further, when (I'a) was methylated in alkaline solution with dimethyl sulfate during several hours, (I'a) was converted to (Ia). Therefore, the position of the carbonyl is the same as in MHB and the structure of (I'a) must be 5-(3'-oxocyclohex-1'-enyl)-5-methylbarbituric acid (3-keto-nor-MHB).

The structure of (I'b) is not established yet (Chart 2). From these experimental

results, it is shown that barbiturates with a cyclohexenyl ring is principally oxidized to the corresponding 3-keto compounds.

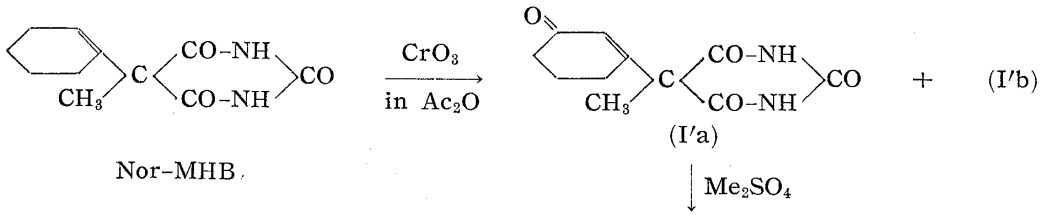

Chart 2.

The authors are indebted to Messrs. T. Hattori, K. Funagoshi, and T. Hōrai for the elementary analyses and also to Dainippon Seiyaku Co. Ltd. for their supplies of MHB and monomethylurea.

Experimental*

CrO_3 Oxidation of MHB—To a stirred suspension of 5 g. of powdered MHB in 40 cc. of Ac_2O was added dropwise a solution of 5.6 g. of CrO_3 in 40 cc. of Ac_2O during 1 hr. and the reaction mixture was further kept at about 35° for 1 hr. under stirring, thereafter allowed to stand overnight. The solvent was distilled off until dryness under a reduced pressure and 50~100 cc. of water was added to the residue. This was extracted repeatedly with AcOEt and, after washing with a small quantity of water, the combined extract was dried over Na_2SO_4. The reddish brown oily substance left after evaporation of the solvent was dissolved in acetone, decolorized through an alumina column, and recrystallized repeatedly from MeOH. About 1.5 g. of colorless plates (Ia), m.p. 160~161°, and 0.1~0.15 g. of colorless needles (Ib), m.p. 240~241°(decomp.), of which the former was more soluble in MeOH than the later, were obtained. Their analytical values were in fair agreement with 5-cyclohexenonyl-3, 5-dimethylbarbituric acid. *Anal.* Calcd. for $C_{12}H_{14}O_4N_2$: C, 57.60; H, 5.61; N, 11.20. Found (Ia) : C, 57.76; H, 5.26; N, 11.42. Found (Ib) : C, 57.75; H, 5.91; N, 11.04.

2,4-Dinitrophenylhydrazone of (Ia) To a solution of (Ia) in MeOH was added a solution of 2,4-dinitrophenylhydrazine hydrochloride in MeOH and the mixture was warmed on a water bath for 1 min. Reddish orange crystals that deposited after cooling were recrystallized from a large qunatity of MeOH to m.p. 228~230°(decomp.). *Anal.* Calcd. for $C_{18}H_{18}O_7N_6$: C, 50.26; H, 4.18; N, 19.53. Found : C, 50.51; H, 3.98; N, 19.13.

Aromatization of (Ia)—This procedure was analogous to EHB,[2] reacting 2 g. of powdered (Ia) with 1.5 g. of 5% Pd-C at 150~155° under a reduced pressure (20 mm. Hg) for 1.5 hrs., and the product was colorless plates (IIa), m.p. 161~162°(decomp.),** which recrystallized from water containing a few drops of MeOH; yield, 1.0 g. The melting point of (IIa) was markedly depressed by admixture with (Ia) and the elementary analysis was in agreement with that of 5-hydroxyphenyl-3, 5-dimethylbarbituric acid. *Anal.* Calcd. for $C_{12}H_{12}O_4N_2 \cdot \frac{1}{2}H_2O$*** : C,56.03; H, 5.06; N, 10.89. Found : C, 56.05; H, 4.90; N, 10.90.

As the product of cleavage by the hydrogen produced on aromatization, two substances were obtained and one of these, a substance (III) that sublimed in the neck of a flask was colorless needles, m.p. 169~170°. Yield, about 0.05 g. to which about 0.1 g. of the same substance obtained from the mother liquor of recrystallization of (IIa) was added. *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.13; N, 17.95. Found : C, 45.80; H, 5.21; N, 17.95.

The melting point was not depressed by admixture with 3, 5-dimethylbarbituric acid, m.p. 169~170°, which was prepared by the condensation of monomethyl diethylmalonate and monomethylurea by the usual method. *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.13; N, 17.95. Found : C, 46.54; H, 5.01; N, 17.61.

The other, a distillable liquid (IV), was a substance with a phenolic odor and crystallized on cooling; yield, about 0.25 g. By the usual method, this was converted to the phenylurethan as colorles needles, m.p. 123~124°, which was identical with the phenolphenylurethan, m.p. 123~124°, by admixture.

Acetylation of (IIa)—A mixture of 0.2 g. of (IIa), 2 cc. of Ac_2O, and 0.2 g. anhyd. AcONa was refluxed for 1 hr. The crystalline product, obtained by pouring the reaction mixture into 15 cc. of water, was recrystallized from 50% MeOH to colorless scaly crystals, m.p. 154~155°. *Anal.* Calcd.

* All melting points are uncorrected.

** It is once moistened at about 110° and then melts at 161~162°.

*** This sample was dried over P_2O_5 for 2 days at room temp. in vacuum.

for $C_{14}H_{14}O_5N_2$: C, 57.93; H, 4.83; N, 9.66. Found: C, 57.63; H, 4.83; N, 9.19.

Aromatization of (IIb)—This was also analogous to the former procedure,[2] reacting 0.75 g. of powdered (Ib) with 0.7 g. of 5% Pd-C at 165~175° for 1.5 hrs. Colorless plates (IIb), m.p. 214~215° (first becoming moist at about 120°) (from MeOH), was isolated as the aromatization product; yield, about 0.6 g. *Anal.* Calcd. for $C_{12}H_{12}O_4N_2 \cdot \frac{1}{2}H_2O$*: C, 56.03; H, 5.06; N, 10.89. Found: C, 56.15; H, 5.39; N, 10.11.

As the by-products, a small amout of 3,5-dimethylbarbituric acid and phenol were also produced.

Alkali Fusion of (IIa)—This was the same procedure as mentioned in the previous report,[2] using 1 g. of (IIa), 3 g. KOH, 2 g. NaOH, 1 cc. water, and 6 g. of PbO_2. Colorless needles (VI), m.p. 192~194° (from water), were obtained from the reaction mixture. Yield, about 0.1 g. This melting point was not depressed on admixture with *m*-hydroxybenzoic acid, m.p. 192~194°.

Alkali Fusion of (IIb)—This was the same procedure as the former using 0.45 g. of (IIb), 3 g. KOH, 2 g. NaOH, 1 cc. water, and 3 g. PbO_2. Colorless needles (VII), m.p. 155~156°, which was purified by sublimation. Yield, 0.05 g. This was identical with salicylic acid, m.p. 155~156°, by admixture.

CrO_3 Oxidation of Nor-MHB—The same procedure as that of MHB was also used in this reaction. As the products, colorless plates (I'a), m.p. 215~216°(decomp.), and colorless needles (I'b), m.p. 278~280°(decomp.), of which the former was more soluble in MeOH than the latter, were obtained. Yield, about 28% and 3%, respectively.

The analytical value of the former was in fair agreement with 5-cyclohexenonyl-5-methylbarbituric acid. *Anal.* Calcd. for $C_{11}H_{12}O_4N_2$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.97; H, 5.15; N, 11.86.

2,4-Dinitrophenylhydrazone of (I'a)—Reddish orange needles, m.p. 270~272°(decomp.), recrystallized from large quantity of MeOH, were obtained by the same procedure as that for (Ia). *Anal.* Calcd. for $C_{17}H_{16}O_7N_6$: C, 49.04; H, 3.84; N, 20.19. Found: C, 48.59; H, 3.86; N, 20.08.

Methylation of (I'a)—To a soluton of 1.0 g. of (I'a) in 3 cc. of 2*N* NaOH was added 0.3 cc. of Me_2SO_4, warmed at 45~50° on a water bath for 10 mins. under shaking, successively added with 2 cc. of 2*N* NaOH and 0.3 cc. of Me_2SO_4, and further kept at 45~50° for 10 mins. After allowing to stand at room temp. for 2 hrs., 10 cc. of water was added to the reaction mixture, unchanged Me_2SO_4 extracted with AcOEt, and alkaline aq. layer was separated. It was acidified with HCl, extracted with AcOEt, and dried over Na_2SO_4. The residue left after evaporation of AcOEt was recrystallized from 50% MeOH. About 0.2 g. of colorless plates, m.p. 159~160°, was obtained and was identified as (Ia) by admixture.

Summary

Chromic oxidation of MHB (5-cyclohexenyl-3,5-dimethylbarbituric acid) and nor-MHB (5-cyclohexenyl-5-methylbarbituric acid) were undertaken in order to compare with the metabolic products of MHB. As the oxidation products of MHB, 5-(3'-oxocyclohex-1'-enyl)- and 5-(6'-oxocyclohex-1'-enyl)-3,5-dimethylbarbituric acid were obtained and principally 5-(3'-oxocyclohex-1'-enyl)-5-methylbarbituric acid was obtained as that of nor-MHB.

Their chemical structures were confirmed by their degradation experiments, in which cyclohexenyl groups were dehydrogenated to phenol groups and further converted to the corresponding hydroxybenzoic acid by an oxidative alkali fusion.

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* This sample was dried over P_2O_5 for two days at room temp. in vacuum.