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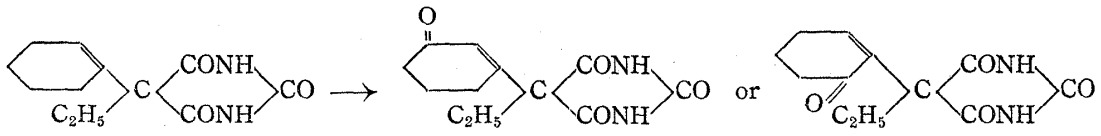
45. Hisao Tsukamoto, Hidetoshi Yoshimura, and Satoshi Toki : Metabolism of Drugs. II. The Metabolic Fate of Ethylhexabital (5-Cyclohexenyl-5-ethylbarbituric Acid). (2).

(*Pharmaceutical Institute, Medical Faculty, University of Kyushu**)

In the previous paper,[1] it was reported that a metabolic product of ethylhexabital (EHB, 5-cyclohexenyl-5-ethylbarbituric acid) was isolated from the urine of rabbits receiving EHB, and its chemical structure was assumed to be either 5-(3′-oxo-1′-cyclohexen-1′-yl)-5-ethylbarbituric acid (Ia) or 5-(6′-oxo-1′-cyclohexen-1′-yl)-5-ethylbarbituric acid (Ib), in which the carbonyl was conjugated to the double bond, as shown :



EHB (Ia) (Ib)

The present investigation was undertaken in order to decide which of these alternative structures would be the most probable. Various methods were employed to synthesize these substances, but were all unsuccessful, presumably due to the presence of the cyclohexenonyl radical. Consequently, it was considered to be advisable to convert the cyclohexenonyl radical to a phenol radical by catalytic aromatization.

When the EHB-M (ethylhexabital metabolite) was heated at 180° with 5% palladium-charcoal under a reduced pressure, it was dehydrogenated to 5-hydroxyphenyl-5-ethylbarbituric acid (III),** m.p. 195~197°(decomp.), which was easily acetylated to the corresponding acetyl compound (IV), m.p. 211°(decomp.), by refluxing with acetic anhydride and anhydrous sodium acetate. In this case, ethylbarbituric acid (V) and phenol (VI) were also obtained as by-products. It is interesting to note that (III) was reductively split into (V) and (VI) by hydrogen produced during the dehydrogenation reaction.

According to the method of Graebe and Kraft,[2] (III) was fused with potassium hydroxide, sodium hydroxide, and lead peroxide at 230~240°. It was then converted to the product (VIII), m.p. 192~194°, which was shown to be *m*-hydroxybenzoic acid by an elemental analysis, and by its failure to depress the melting point of an authentic sample, m.p. 192~194°. In another case, where the temperature of fusion was lower (160~180°), the reaction product was (VII), m.p. 150°(decomp.), which agreed with hydroxyphenylethylmalonic acid in analytical results.

These experiments indicate that the structure of (III) must be 5-(*m*-hydroxyphenyl)-5-ethylbarbituric acid. The processes of the foregoing reactions are shown :

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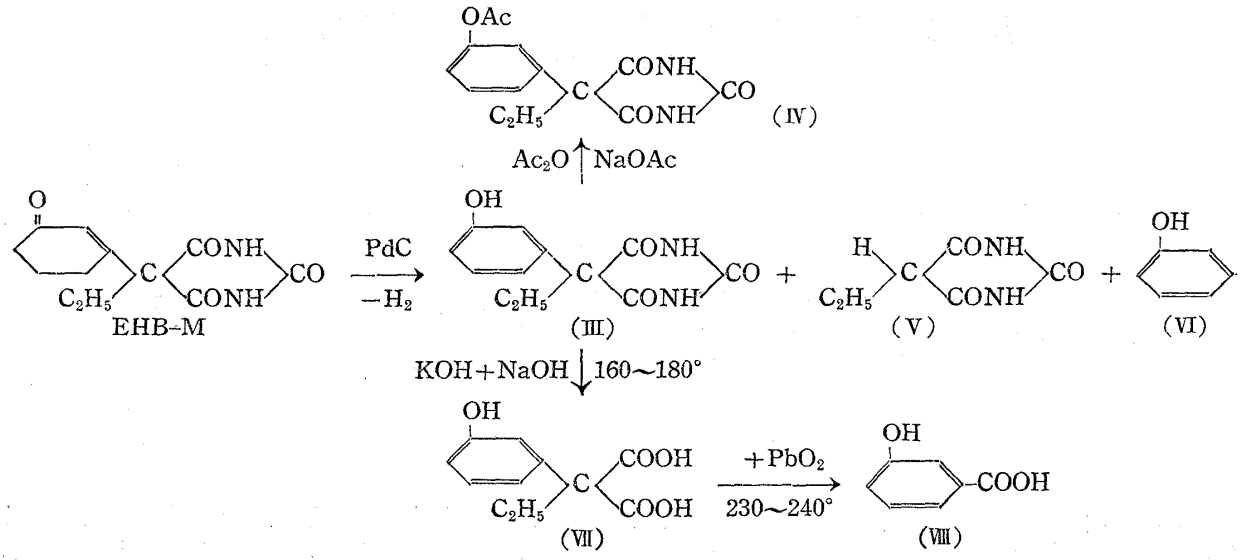
* Katakasu, Fukuoka (塚元久雄, 吉村英敏, 土岐 智).

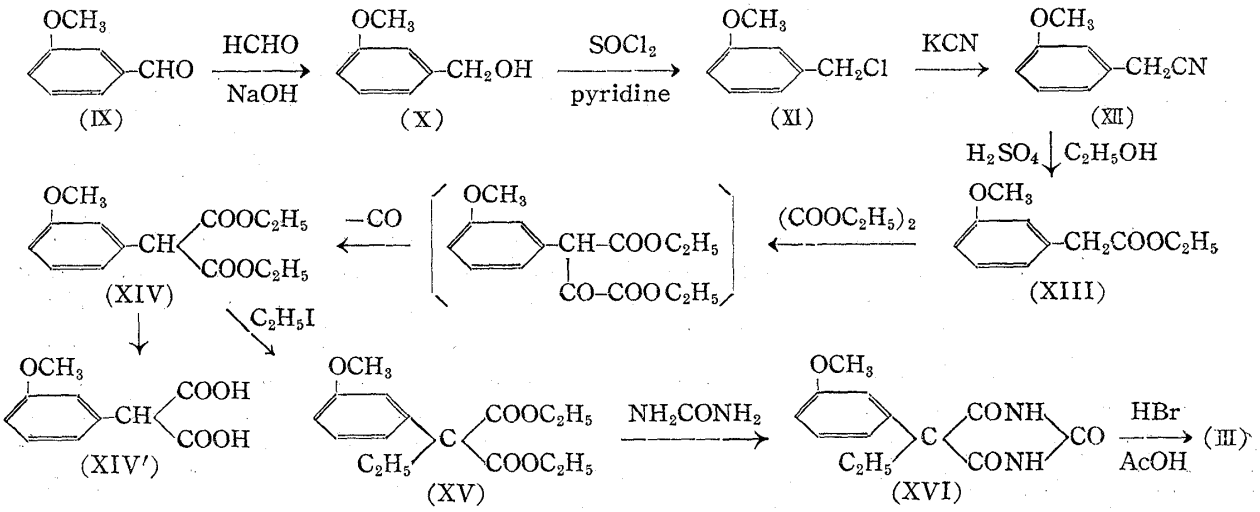
** (III) possesses no hypnotic action.

1) Part I : H. Tsukamoto, E. Takabatake, H. Yoshimura : This Bulletin, **2**, 201(1954).

2) C. Graebe, H. Kraft : Ber., **39**, 797(1906).



Further, 5-(*m*-hydroxyphenyl)-5-ethylbarbituric acid*** was systematically synthesized by analogy with the procedure of phenobarbital synthesis[3,4] as shown and was identified with (III) by showing no depression of the melting point on admixture.



From the above experiments, the dehydrogenated product of EHB-M was confirmed to be 5-(*m*-hydroxyphenyl)-5-ethylbarbituric acid and accordingly the chemical structure of EHB-M would be (Ia) and not (Ib).

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Experimental

Aromatization of EHB-M—When a mixture of 2.5 g. of powdered EHB-M and 1.5 g. of 5% Pd-C[5] in a distillation flask was heated at 180~185° for 1.5 hrs. in an oil bath under a reduced pressure (20 mm. Hg), a colorless liquid (A) distilled out, colorless needles (B) sublimated in the neck of the

*** It was previously reported by Pierce and Rising that this compound was prepared from 5-*m*-aminophenyl-5-ethylbarbituric acid and decomposed at 199.5~200°. cf. J. Am. Chem. Soc., 58, 1361(1936).

3) M. Rising, J. Stieglitz: J. Am. Chem. Soc., **40**, 720(1918).
4) T. Itai: Bull. Natl. Hyg. Lab. Tokyo, **68**, 75(1950).
5) "Org. Syntheses," **26**, 78.

flask, and the greater part of the reaction product (C) remained with the Pd-C in the flask. On cooling, (A) crystallized to colorless needles, m.p. 40°, with a phenolic odor. Yield, 330 mg.

By the usual method, (A) was derived to the 3,5-dinitrobenzoate, m.p. 144°, and the phenylurethane, m.p. 123°. The melting points of both derivatives were not depressed by admixture with the corresponding phenol derivatives. Sublimation of (B) gave colorless needles, m.p. 190°, and this product was not depressed by admixture with ethylbarbituric acid, m.p. 191°, which was prepared according to the method of Fisher and Dilthey.[6] Yield, 40 mg.

(C) was repeatedly extracted with MeOH, and the extract was filtered to remove the catalyst. A viscous residue remained after evaporation of MeOH from the extract. It was dissolved in acetone, chromatographed through an alumina column, and eluted with the same solvent. The residue from the first portion of the eluate solidified when it was boiled for a time with benzene, and was recrystallized from water to colorless plates, m.p. 195~197°(decomp.), which were identified with 5-(*m*-hydroxyphenyl)-5-ethylbarbituric acid by admixture. Yield, 1.2 g. *Anal.* Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.06; H, 4.84; N, 11.29. Found: C, 57.79. H, 4.77; N, 11.00.

From the later portions of the eluate, a small amount of ethylbarbituric acid (30 mg.) was obtained.

Acetylation of (III)—A mixture of 0.3 g. of (III), 3 cc. Ac_2O, and 0.3 g. anhyd. AcONa was refluxed for 1 hr. The crystalline product was obtained by pouring the reaction mixture into 20 cc. of water, and was recrystallized from 50% MeOH to colorless needles, m.p. 211°(decomp.). Yield, theoretical. *Anal.* Calcd. for $C_{14}H_{14}O_5N_2$: C, 57.93; H, 4.83; N, 9.66. Found: C, 58.05; H, 4.69; N, 9.96.

Alkali Fusion of (III)—(i) A mixture of 1 g. of (III), 5 g. KOH, 3 g. NaOH, and 1 cc. of water was heated in a nickel crucible for 1 hr. at 165~170° in an oil bath, and was followed immediately by heating at 230~240° for 1 hr. over a direct flame; 10 g. of PbO_2 was added in small quantities during the latter procedure. After cooling, the reaction mixture was poured into 60 cc. of water, filtered, acidified with conc. HCl, and extracted with ether. The ether extract was shaken with a sat. $NaHCO_3$ solution, the aqueous solution was acidified with HCl, extracted again with ether, and the ether removed from the extract after drying over anhyd. Na_2SO_4, yielding 0.4 g. of yellow brown crystals. After decolorization with charcoal, one more recrystallization from water gave coloress needles (VIII), m.p. 191~193°, which were found to be identical with *m*-hydroxybenzoic acid (m.p. 192~194°) by admixture; yield, 0.1 g. (17%). *Anal.* Calcd. for $C_7H_6O_3$: C, 60.94; H, 4.35. Found: C, 60.67; H, 4.15.

(ii) A mixture of 1 g. of (III), 3 g. KOH, 2 g. NaOH, and 1 cc. of water was heated successively at 180~185° for 1 hr., at 190~195° for 20 mins., and finaly at 195~200° for 10 mins. in an oil bath. After cooling, the reaction mixture was treated as in the preceding experiment (i). A slightly yellow oily substance was obtained and crystallized by boiling with benzene to colorless needles (VII), m.p. 148°; yield, 0.4 g. By recrystallization from benzene containing a few drops of ether, the melting point was raised to 150°(decomp.) and this agreed with hydroxyphenylethylmalonic acid (VII) in analytical value. *Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.36. Found: C, 59.17; H, 5.47.

Preparation of 5-(*m*-Hydroxyphenyl)-5-ethylbarbituric Acid (III)—(1) *m*-Methoxybenzyl alcohol (X) was prepared from *m*-methoxybenzaldehyde (IX)[7] by the crossed Cannizzaro reaction of Davidson and Bogert.[8] $b.p_5$ 119~120.5°, yield, 90%.

(2) *m*-Methoxybenzyl chloride (XI) was prepared by the chlorination of (X) with $SOCl_2$ and pyridine, according to the method of Cornforth and Robinson.[9] $b.p_5$ 92.5~95°; yield, 90%.

(3) *m*-Methoxybenzyl cyanide (XII) was prepared by the same procedure as the preparation of benzyl cyanide.[10] $b.p_5$ 124~128°; yield, 85%.

(4) Ethyl *m*-methoxyphenylacetate (XIII) was prepared by the same procedure as that for ethyl phenylacetate.[11] $b.p_4$ 118~122°; yield, 80%.

(5) Ethyl *m*-Methoxyphenylmalonate (XIV)[12]: To a solution of 1.6 g. of Na in 34 cc. of abs. EtOH, (XIII) was added rapidly through a dropping funnel while stirring vigorously and cooling to 60°. This was washed down with a small quantity of abs. EtOH and was followed immediately by the addition of 10 g. of ethyl oxalate. After keeping at 60° for 2 hrs. under constant stirring, the reaction mixture was allowed to stand overnight. The residue, obtained by evaporation of EtOH, was dissolved in water, and the impurities were removed by extraction with ether.

The aqueous layer was acidified with dil. H_2SO_4, extracted with ether, dried over anhyd. Na_2SO_4,

6) E. Fisher, A. Dilthey: Ann., **335**, 357(1904).
7) "Org. Syntheses," **29**, 64.
8) Davidson, Bogert: J. Am. Chem. Soc.. **57**, 905(1935).
9) J. W. Cornforth, R. Robinson: J. Chem. Soc., **1942**, 684.
10) "Org. Syntheses," Coll. Vol. **1**, 101.
11) *Ibid.*, **1**, 265.
12) *Ibid.*, **2**, 572.

and the ether distilled off. The residual oil, contained in a Claisen flask, was heated at 180~185° under a reduced pressure of about 20~24 mm. Hg in an oil bath and CO evolved. After the evolution of CO ceased (about 3 hrs.), the oil which had distilled was returned to the flask, and the malonate (XIV) was distilled at 150~151°/2 mm. Hg; yield, 8 g. (44.8%).

The free acid (XIV′) was obtained by hydrolysis of the above malonate (XIV) with ethanolic KOH and recrystallized from benzene to colorless scales, m.p. 119°. *Anal.* Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.76. Found: C, 57.10; H, 4.59.

(6) Ethyl *m*-Methoxyphenylethylmalonate (XV): To a solution of 0.8 g. of Na in 25 cc. of abs. EtOH cooled in ice, 8 g. of (XIV) was added dropwise and was followed by the addition of 5.6 g. of EtI while stirring vigorously, after which it was refluxed for 5 hrs. at which time it was stirred slowly in an oil bath (100~105°). After standing overnight, the reaction mixture was poured into 100~150 cc. of water and extracted with ether. The extract was washed with a solution of $Na_2S_2O_3$, dried over anhyd. $CaCl_2$, and the solvent removed. Distillation of the residue *in vacuo* gave 5 g. of colorless oil, $b.p_4$ 161~165°.

(7) 5-(*m*-Methoxyphenyl)-5-ethylbarbituric Acid (XVI): To a constantly agitated cold solution of 0.5 g. of Na in 8 cc. of abs. MeOH and 2.4 g. of urea, 4.5 g. of (XV) was added dropwise and washed down with a small quantity of abs. MeOH. The solution was refluxed for 4 hrs. in an oil bath (100~105°). After cooling, about 100 cc. of water was poured into the reaction mixture, and the impurities were extracted once with ether. An oil was obtained when the aqueous solution was acidified with dil. H_2SO_4. It was cooled in an ice box to induce crystallization. The crystals were filtered, washed with water, dried in a desiccator, and recrystallized from EtOH to colorless prisms, m.p. 167~169°(decomp.); yield, 2.3 g.(55.2%). *Anal.* Calcd. for $C_{13}H_{14}O_4N_2$: C, 59.54; H, 5.34; N, 10.68. Found: C, 59.41; H, 5.62; N, 10.88.

(8) Demethylation of (XVI): A mixture of 0.5 g. of (XVI), 5 cc. AcOH, and 1 cc. of 47% HBr was refluxed for 16 hrs. in an oil bath (120°). After cooling, AcOH and HBr were distilled off *in vacuo* and the remainder was recrystallized from water containing a few drops of EtOH to colorless plates, m.p. 196~198°(decomp.); yield, 0.4 g.(85.1%). The melting point of this material was undepressed by admixture with the aromatization product(III) of EHB-M, m.p. 195~197°. *Anal.* Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.06; H, 4.84; N, 11.29. Found: C, 57.38; H, 4.85; N, 11.31.

The acetyl derivative of this material, m.p. 211°(decomp.), was also undepressed by admixture with the acetyl derivative (IV), m.p. 211°(decomp.), of (III).

Summary

The chemical structure of the metabolic product of ethylhexabital (EHB: 5-cyclohexenyl-5-ethylbarbituric acid) isolated from the urine of rabbits receiving EHB was confirmed to be 5-(3′-oxo-1′-cyclohexen-1′-yl)-5-ethylbarbituric acid by degradation reactions of EHB-metabolite.

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