

**Formic Acid Reduction. III.¹⁾ Barbituric Acid Derivatives. New
5-Methylation Reaction of Barbituric Acid Derivatives
with Formate and Course of the Reaction**

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(Received June 19, 1967)

It has been found that after heating with a reagent, given by $5\text{HCO}_2\text{H} \cdot 2\text{N}(\text{C}_2\text{H}_5)_3$, several barbituric acid derivatives were methylated at the 5-position. The reaction was revealed to proceed through an intermediate, 5,5'-methylidynebis (barbituric acid), which had been previously known as the usual reaction product obtained by heating with formic acid. The reaction course was found to involve an interesting aspect that the reagent carries out a saturation of the carbon-carbon double bond at the 5-position followed by a reductive fission of the bond.

The salt-like compounds of formic acid, represented by general formula $5\text{HCO}_2\text{H} \cdot 2\text{NR}_3$, are liquid of constant high boiling point, and have been previously studied in this laboratory as reducing agents effective for certain reduction reactions.^{1,3)} Using $5\text{HCO}_2\text{H} \cdot 2\text{N}(\text{C}_2\text{H}_5)_3$, bp 95° (15 mmHg), which is hereafter called as TEAF (abbreviated from triethylammonium formate), it has now been found that 5-methylation of barbituric acid, its N-methyl derivatives and 2-thio-substituted analog can be effected with this reagent. In the literature^{4,5)} the reactions with formic acid alone have been reported to give 5,5'-methylidynebis(barbituric acid)s. The 5-methylation was, however, revealed to proceed through this 5,5'-methylidyne compound as an intermediate. The finding of such original reaction appeared to merit an investigation on the pathway of the reaction. Studies on this aspect have introduced interesting intermediate reaction which leads to the saturation of carbon-carbon double bond at the 5-position followed by reductive fission of the single bond.

I. 5-Methylation of Barbituric Acids by Heating with Triethylammonium Formate (TEAF)

There have been a number of papers on the reactions of barbituric acids with formic acid^{4,5)} or its derivatives such as ammonium formate,^{5,6)} formamide⁶⁻⁸⁾ and ethyl orthoformate.⁷⁾ In these reactions, 5-hydroxymethylene-, 5-aminomethylene- or 5-ethoxymethylenebarbituric acids are obtainable in some cases and in other cases 5,5'-methylidynebis(barbituric acid)s are formed presumably by further condensation of the primary product with the starting barbituric acid.

In contrast to the above facts, it has been found in this laboratory that a variety of barbituric acid derivatives, when heated with TEAF, were converted into the corresponding 5-methyl compounds in good yields. As substrate, barbituric acid (I), 1-methylbarbituric acid (II), 1,3-dimethylbarbituric acid (III), and 2-thiobarbituric acid (IV) were used. These compounds were heated along with TEAF (12 molar equiv. as HCO_2H). At about 100° , the

1) Part II: K. Ito, *Yakugaku Zasshi*, **86**, 1166 (1966).

2) Location: *Oshika, Shizuoka*.

3) M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **12**, 677 (1964); M. Sekiya, K. Ito, A. Hara, and J. Suzuki, *ibid.*, **15**, 802 (1967); M. Sekiya, Y. Harada, and K. Tanaka, *ibid.*, **15**, 833 (1967).

4) H. Gysling and G. Schwarzenwach, *Helv. Chim. Acta*, **32**, 1484 (1949).

5) M. Ridi, *Gazz. Chim. Ital.*, **79**, 175 (1949); *C.A.*, **44**, 117 (1950).

6) P. Papini and R. Cimmarusti, *Gazz. Chim. Ital.*, **77**, 142 (1947). [*C.A.*, **42**, 1286 (1948)].

7) J.W. Clark-Lewis and M.J. Thompson, *J. Chem. Soc.*, **1959**, 2401.

8) H. Brederick, R. Gompper, F. Effenberger, K.H. Popp, and G. Simchem, *Ber.*, **94**, 1241 (1961).

mixture colored either yellow or orange according to the substrate, and during continuous heating at 135–145° for 3–4 hours the color then disappeared gradually, while evolution of carbon dioxide was observed. By treatment of the reaction solution, from I, II, III and IV, triethylammonium 5-methylbarbiturate (Vs), 1,5-dimethylbarbituric acid (VI), 1,3,5-trimethyldialuric acid (VII) and triethylammonium 5-methyl-2-thiobarbiturate (VIII_s) were obtained respectively in 72–80% yields as shown in Chart 1.

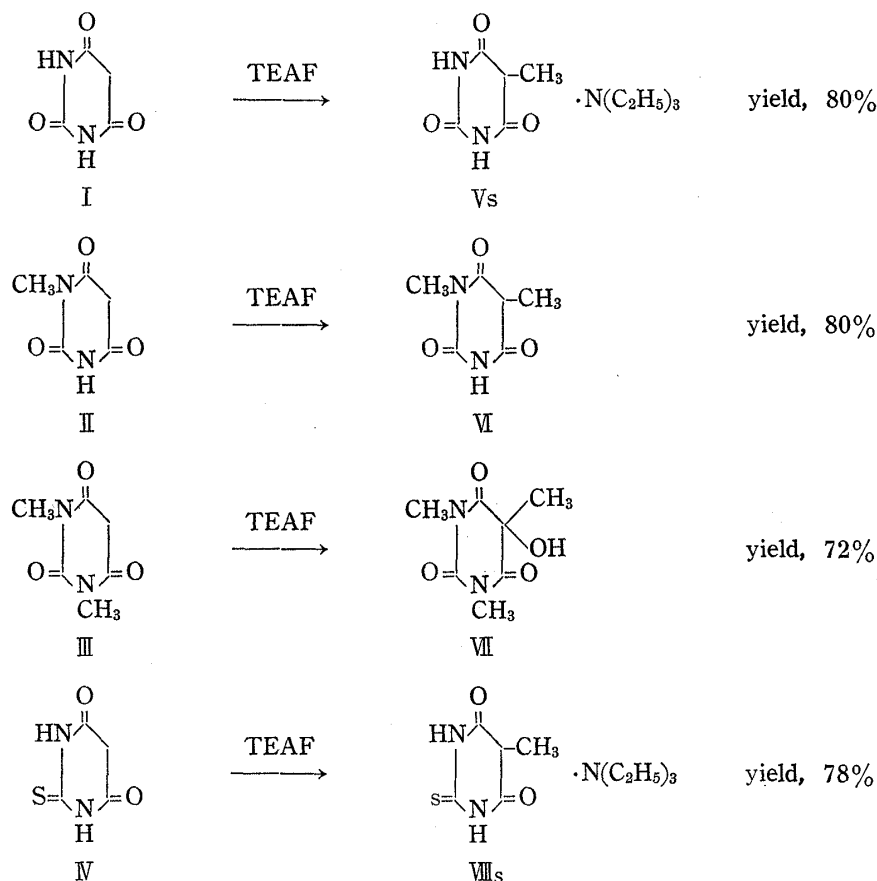


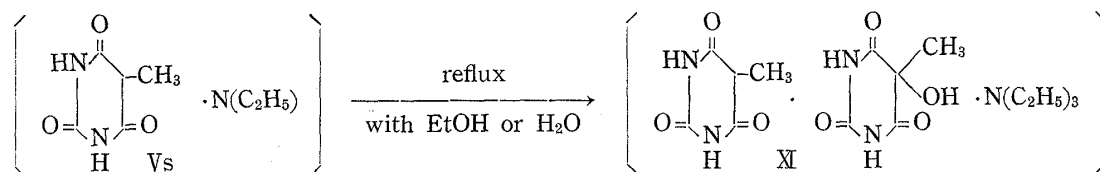
Chart 1

The reaction appeared to proceed specifically with TEAF or other trialkylammonium formates, but not with formic acid. On heating V with formic acid no reaction other than the previously reported formation^{4,5)} of 5,5'-methylidynebis(barbituric acid) occurred even under rather severe conditions.

In Chart 1 the formation of VII from III, different from the others, is considered to be due to the extreme instability of the expected product, 1,3,5-trimethylbarbituric acid, on oxidation in atmosphere. A similar observation has been reported⁹⁾ that the dialuric acid was isolated in the case of the catalytic hydrogenation of 1,3-dimethyl-5-anilinomethylenebarbituric acid over palladised calcium carbonate. Furthermore 1,3,5-trimethylbarbituric acid was confirmed spectrophotometrically as the real direct product in the reaction. Immediately after the reaction, an ultraviolet spectrum measurement of the reaction solution provided the appearance of an intense absorption at 272 mμ, which was different from that of VII ($\lambda_{\text{max}}^{\text{MeOH}}$: 231 mμ), and this observation would be indicative of the presence of the expected 1,3,5-trimethylbarbituric acid from analogy with the absorptions of 5-alkyl-substituted analogs, such as 5-benzyl-1,3-dimethylbarbituric acid⁹⁾ ($\lambda_{\text{max}}^{\text{MeOH}}$: 268 mμ) and 5-phenethyl-1,3-dimethylbarbituric acid⁹⁾ ($\lambda_{\text{max}}^{\text{MeOH}}$: 270 mμ).

9) Preparation of these compounds will be reported in the succeeding paper of this series (Part IV).

Among 5-methyl-substituted products of the reaction described above, 5-methylbarbituric acid (V) and 5-methyl-2-thiobarbituric acid (VIII) were obtained in the form of triethylammonium salt, probably owing to their stronger acidities. Both of the triethylammonium salts, Vs and VIIIs, has not been known. The former was shown to be labile on oxidation, but the latter was not so sensitive. The compound Vs was crystallized from ethanol-chloroform to needles of mp 202—204° (decomp.), which was identical with one prepared from an authentic 5-methylbarbituric acid. However, when heated with ethanol or water for longer period, the crystals were converted into plates of mp 198—200° (decomp.), which we gave the empirical formula $C_{16}H_{27}O_7N_5$, and which was ascribed as a new complex-compound (XI) composed of 5-methylbarbituric acid (V), 5-methyldialuric acid (XII) and triethylamine in proportion of one mole each. Data for the assignment are described below.



To an aqueous solution of XI an excess of hydrochloric acid was added to neutralize the triethylamine component of XI, the precipitate immediately formed were proved to be identical with V (yield 78.5%). The mother liquor was lyophilized and then extracted with chloroform. The chloroform-soluble component and the insoluble component were proved to be identical with triethylamine hydrochloride (yield 77%) and XII (yield 86%) respectively. From these facts the units composing the complex seemed to be V, XII and triethylamine. The complex itself did not undergo further conversion on refluxing with ethanol or water for longer period, this showing it to be a stable complex and not a mixture. The content of V in the complex was determined spectrophotometrically. Aqueous solution of either V or its triethylammonium salt, Vs was shown to have an absorption maximum at 269 m μ with values of log ϵ , 4.25 and 4.35, respectively, while XII gave absorption in far ultraviolet region, no absorbance being observed at 269 m μ . In an ultraviolet spectrum of an aqueous solution of the complex (XI) an absorption maxima at 269 m μ was observed bearing an evidence for the existence of Vs, and its molar absorption for $C_{16}H_{27}O_7N_5$ showed log ϵ =4.28. This showed its content to be one mole in the complex, $C_{16}H_{27}O_7N_5$.

II. 5,5'-Methyldynebis(barbituric acid)s as Intermediates in the 5-Methylation of Barbituric Acids

As mentioned in the foregoing section, the 5-methylation of barbituric acids (I, II, III, and IV) gave a colored solution or a colored precipitate at the earlier stage of the reaction. After interruption of the reaction at this stage, treatment of the reaction mixture gave the corresponding 5,5'-methyldynebis(barbituric acid) as triethylammonium salt (XIIIs, XIVs, XVs, and XVIs), in 80—87% yield, as shown in Chart 2.

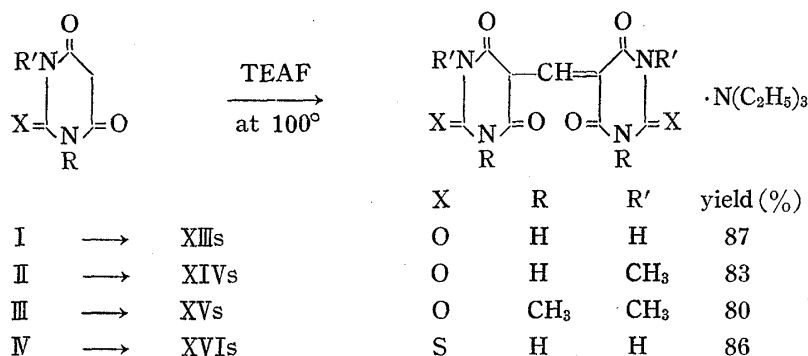
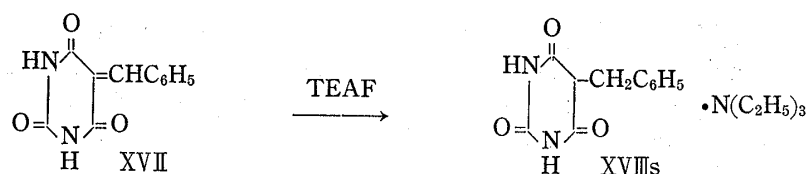


Chart 2



This type of the reaction was found to proceed readily with a variety of other 5-arylmethylenebarbituric acid analogs. Although the extensive work will be published in the succeeding paper of this series, saturation of carbon-carbon double bond at the 5-position by interaction of TEAF may be adopted in general.

It was therefore considered that the formation of 5-methylbarbituric acid from 5,5'-methylidynebis(barbituric acid) would be initiated by saturation of its methylidyne bridge forming 5,5'-methylenebis(barbituric acid) (XIX), although the detection of this intermediate in the reaction was hardly feasible. After preparing XIX by another route, we intended to subject it to heating with TEAF with the expectation that this possible reaction would be the stage succeeding to the formation of the 5,5'-methylene compound. Compound XIX was prepared by catalytic hydrogenation of an aqueous solution of XIII over palladium-on-charcoal catalyst, on referring to the paper⁴) reported by Gysling. An attempt to carry out heating XIX along with TEAF fulfilled the above expectation, the reaction proceeded to give 5-methyl compound Vs in 83% yield estimated from 2 molar equivalent formation.

Based on the above findings it was considered that XIX would be an intermediate in the conversion from 5,5'-methylidyne compound to 5-methylbarbituric acid. However, pathway for the conversion from 5,5'-methylene compound to 2 molar equivalent of 5-methylbarbituric acid was still a problem to be solved.

It was noticeable that during the course of the above demonstrated reaction with XIX appearance of yellow color was observed. After interruption of the reaction at this stage a measurement of ultraviolet absorption spectrum of the diluted reaction solution gave the absorbance at 269 $m\mu$ which was identical with the absorption maximum of the 5,5'-methylidyne compound (XIII). This observation implied that XIII is an intermediate existing in the course of the reaction. Thus, we propose the following pathway, involving reductive fission at the methylene bond, in consideration that the intermediate, 5,5'-methylidyne compound (XIII), must be derived from barbituric acid (I).

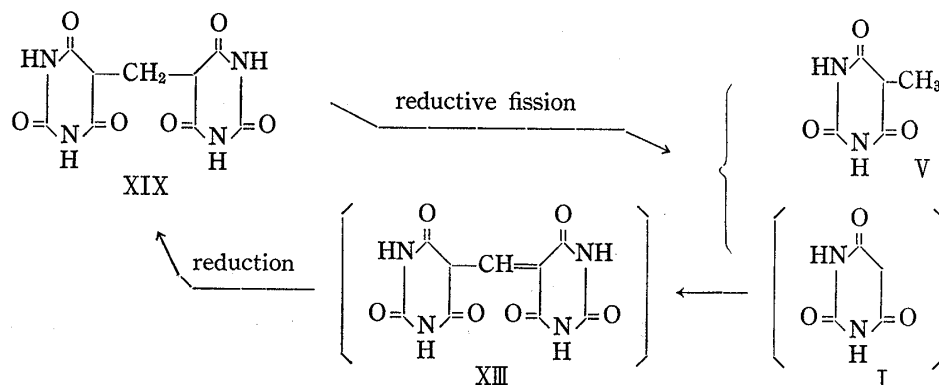
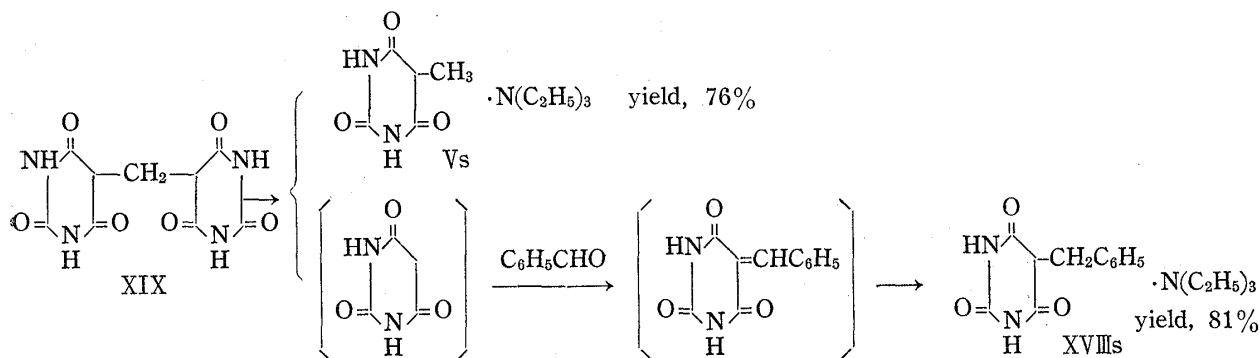


Chart 3

Two molar equivalent formation of Vs from XIX may be caused by restoration of XIX from I, which is thought to be formed as a product by the likely reductive fission. Although this fission stage seemed peculiar, since such a type of reaction has not been known till now, the above proposal was corroborated by the following experiment.

An attempt to carry out the TEAF reaction of XIX in the presence of benzaldehyde was made with the expectation to obtain 5-benzylbarbituric acid (XVIII), by trapping the

intermediate, barbituric acid (I), with benzaldehyde. While, as mentioned at the beginning of this section, the formation of XVIII occurred by the TEAF reaction of 5-benzylidenebarbituric acid (XVII), it was also ascertained beforehand that the nearly quantitative formation of the same was readily brought about also by heating a mixture of I and benzaldehyde with TEAF. The attempt was successful to result in the formation of XVIIIs and Vs in reasonable yields.



This trapping reaction could be said to bear a direct evidence for the intermediate stage of the reductive fission and thus to strengthen the proposed pathway (Chart 3) for the conversion from XIX to V.

It could therefore be concluded that the whole pathway for the formation of 5-methylbarbituric acid (V), from barbituric acid (I), by the reaction with TEAF is as shown in the following scheme. And the analogous reactions of the other barbituric acid derivatives could be considered to take pathways similar to it.

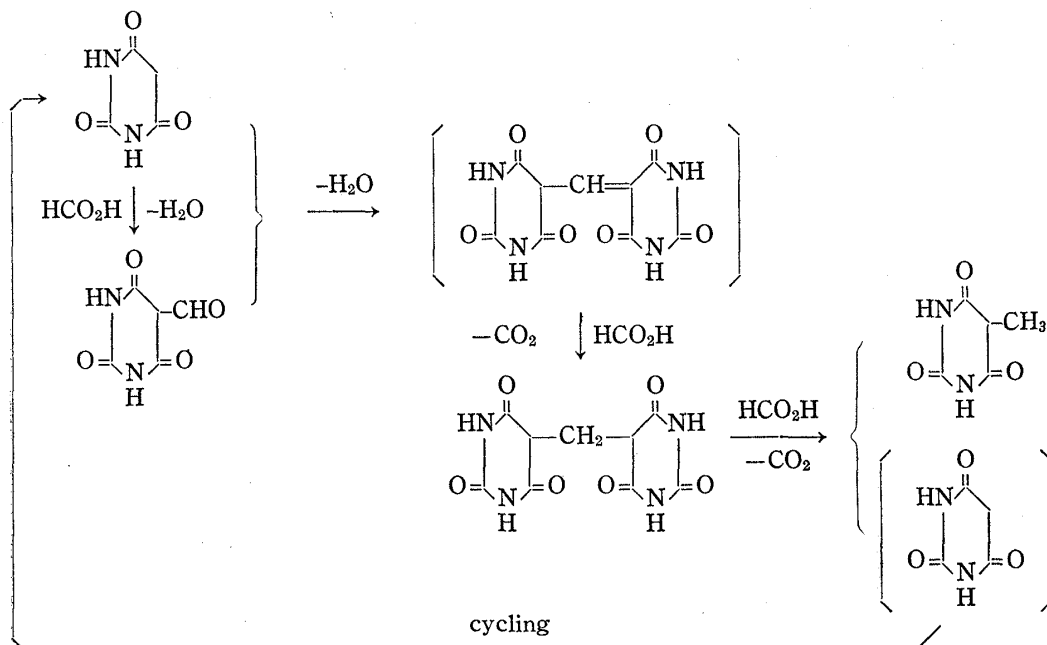


Chart 4

Experimental

5-Methylbarbituric Acids from Barbituric Acids. General Procedure—To 62.2 g (0.72 mole as HCO_2H) of TEAF 0.06 mole each of barbituric acids, *i.e.* barbituric acid (I), 1-methylbarbituric acid (II), 1,3-dimethylbarbituric acid (III), and 2-thiobarbituric acid (IV), was added. The mixture was heated with constant stirring and a constant stream of air free from CO_2 was passed in order to check transfer of emitting CO_2 by $Ba(OH)_2$ solution. At about 90–110° the primary mixture first turned to a homogeneous liquid and

colored either yellow or orange according to the substrate, in some cases giving a colored precipitate. The temperature was raised and maintained at 135–145°, while emission of CO₂ was observed and the color disappeared gradually. After complete disappearance of the color and subsidence of the CO₂ emission, the clear reaction solution was concentrated under reduced pressure to remove triethylamine and excess of TEAF. To the resulting residue acetone or CHCl₃-ether was added for crystallization. After allowing to stand overnight, the crystals were filtrated and washed and were shown to be nearly pure by UV spectrophotometric determination. The followings are identification of the products obtained by the above procedures.

Triethylammonium 5-Methylbarbiturate (Vs): Obtained from I. Yield, 80%. A quick way of recrystallization from EtOH gave needles, mp 202–204° (decomp.). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ : 269. *Anal.* Calcd. for C₁₁H₂₁O₃N₃ [C₅H₉O₃N₂·N(C₂H₅)₃]: C, 54.30; H, 8.70; N, 17.27. Found: C, 53.85; H, 8.56; N, 17.27. The IR spectrum was identical with that of the specimen prepared from 5-methylbarbituric acid¹⁰ and triethylamine.

1,5-Dimethylbarbituric Acid (VI): Obtained from II. Yield, 80%. Needles (from EtOH), mp 169–170°, lit.¹¹ mp 169–170°. UV $\lambda_{\text{max}}^{\text{MeOH}}$ m μ : 262. *Anal.* Calcd. for C₆H₈O₃N₂: C, 46.16; H, 5.16; N, 17.94. Found: C, 46.06; H, 5.23; N, 17.61.

1,3,5-Trimethyldialuric Acid (VII): Obtained from III. Yield, 72%. Needles (from benzene), mp 107°, lit.⁷ mp 107°. UV $\lambda_{\text{max}}^{\text{MeOH}}$ m μ : 231. IR ν_{Nujol} cm⁻¹: 3480 (OH). *Anal.* Calcd. for C₇H₁₀O₄N₂: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.21; H, 5.43; N, 15.24.

Triethylammonium 5-Methyl-2-thiobarbiturate (VIII_s): Obtained from IV. Yield, 78%. Prisms (from EtOH), mp 196–197° (decomp.). UV $\lambda_{\text{max}}^{\text{MeOH}}$ m μ : 244, 275.5. *Anal.* Calcd. for C₁₁H₂₁O₂N₃S [C₅H₆O₂N₂S·N(C₂H₅)₃]: C, 50.94; H, 8.16; N, 16.20; S, 12.36. Found: C, 50.85; H, 7.99; N, 16.18; S, 12.37. Free 5-methyl-2-thiobarbituric acid was obtained by addition of HCl to the aqueous solution. Needles (from H₂O), mp 249–252°, lit.¹² mp ca. 244° (decomp.). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ m μ : 274. *Anal.* Calcd. for C₅H₆O₂N₂S: C, 37.96; H, 3.82; N, 17.71; S, 20.27. Found: C, 37.75; H, 3.90; N, 17.53; S, 20.05.

The Complex Compound (XI) from Triethylammonium 5-Methylbarbiturate (Vs)—After heating an alcoholic or aqueous solution of Vs for a relatively long period, crystals which were deposited in the cool were collected and recrystallized from EtOH-CHCl₃ to plates, mp 198–200° (decomp.). This complex compound, XI, 0.7 g was obtained from 1.0 g of Vs. *Anal.* Calcd. for C₁₆H₂₇O₇N₅ [C₅H₉O₃N₂·C₅H₆O₄N₂·N(C₂H₅)₃]: C, 47.87; H, 6.78; N, 17.45. Found: C, 47.72; H, 6.95; N, 17.48.

When a solution of 2.4 g of XI dissolved in 6 ml of H₂O was acidified with conc. HCl, a precipitate was obtained, which was identified as 5-methylbarbituric acid by noting the exact correspondence of the infrared spectrum with the spectrum of an authentic sample and no depression was observed in the melting point on admixture with the same sample. Yield, 0.67 g (78.5%). Fine needles (from H₂O), mp 199–202°, lit.¹⁰ mp 203°. The foregoing mother liquor was lyophilized and the resulting residue was extracted with CHCl₃. Evaporation of the CHCl₃ solution gave triethylammonium chloride, which weighed 0.70 g (87%) after recrystallization from EtOH. The infrared spectrum was identical with an authentic sample. Recrystallization of the unextracted residue from EtOH gave 5-methyldialuric acid, weighing 0.8 g (86%), mp 225–228°, lit.¹⁰ mp 228–230°, undepressed on admixture with an authentic sample prepared.¹⁰ The infrared spectrum was also identical with that of the authentic sample. *Anal.* Calcd. for C₅H₆O₄N₂: C, 37.98; H, 3.83; N, 17.72. Found: C, 38.16; H, 3.98; N, 18.16.

The complex compound itself did not undergo further conversion on refluxing its ethanolic or aqueous solution for further long period.

The ultraviolet spectrum of the material in an aqueous solution showed an absorption maxima at 269 m μ (log ϵ 4.28). This absorbance is consistent with that of triethylammonium 5-methylbarbiturate [269 m μ (log ϵ 4.25)], bearing an evidence of the existence of it and the molar absorptivity well corresponded to that of the content of one molar equivalent in the complex. Another unit, 5-methyldialuric acid or its salt showed absorption in far ultraviolet region.

5,5'-Methyldynebis (barbituric acid)s from Barbituric Acids. General Procedure—A mixture of 62.2 g (0.72 mole as HCO₂H) of TEAF and 0.06 mole each of barbituric acids, I, II, III and IV, was heated with stirring. At the temperature above 90° the primary mixture first turned to a homogeneous liquid and took on color. By maintaining at about 110°, II and III gave yellow or orange-yellow solutions, and I and IV gave yellow and red-orange precipitate respectively. The mixtures were submitted to concentration under reduced pressure for the runs with II and III, and to filtration on cool for the runs with I and IV, to give the reaction products. The resulting crystalline residue and the precipitates were washed with CHCl₃ or acetone, and dried. These materials were identified as triethylammonium salts of 5,5'-methyldynebis(barbituric acid)s and shown to be nearly pure by UV spectrophotometric determination. The followings are identifications of the products.

10) B. Dumas and H.G. Biggs, *J. Biol. Chem.*, **237**, 2306 (1962).

11) H. Tsukamoto, H. Yoshimura, and S. Toki, *Chem. Pharm. Bull.* (Tokyo), **4**, 364 (1956).

12) J. Wheeler, *Am. Chem. J.*, **32**, 352 (1904).

5,5'-Methylidynebis(barbituric acid) (XIII): Obtained from I as triethylammonium salt (XIIIs). Yield, 87%. Orange-yellow prisms (from H_2O), mp 265—267° (decomp.). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ $m\mu$: 234, 411. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{21}\text{O}_6\text{N}_5$ [$\text{C}_9\text{H}_6\text{O}_4\text{N}_4 \cdot \text{N}(\text{C}_2\text{H}_5)_3$]: C, 49.04; H, 5.76; N, 19.07. Found: C, 48.62; H, 5.91; N, 18.68. Free XIII liberated by addition of aqueous HCl to the aqueous solution, yellow fine crystals, mp 316—318° (decomp.), lit.⁵⁾ mp >300°. *Anal.* Calcd. for $\text{C}_9\text{H}_6\text{O}_4\text{N}_4$: C, 40.61; H, 2.27; N, 21.05. Found: C, 40.84; H, 2.27; N, 21.39. Both infrared spectra of the free acid and the salt were identical with those of the free acid and its salt which were prepared by the known method.⁵⁾

5,5'-Methylidynebis(1-methylbarbituric acid) (XIV): Obtained from II as triethylammonium salt (XIVs). Yield, 83%. Orange-yellow prisms (from EtOH), mp 196—198° (decomp.). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ $m\mu$: 236, 414. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{25}\text{O}_6\text{N}_5$ [$\text{C}_{11}\text{H}_{10}\text{O}_6\text{N}_4 \cdot \text{N}(\text{C}_2\text{H}_5)_3$]: C, 51.64; H, 6.37; N, 17.71. Found: C, 51.69; H, 6.49; N, 17.66. The free acid, yellow needles, mp 266—268° (decomp.). *Anal.* Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_6\text{N}_4$: C, 44.90; H, 3.43; N, 19.04. Found: C, 44.90; H, 3.47; N, 19.28. For identity of this unknown substance free acid was prepared by another way according to the method⁵⁾ using HCO_2H as reagent, in which a mixture of II and HCO_2H was refluxed to give crystals, mp 266—267° (decomp.). The infrared spectra of this material and its triethylammonium salt were identical with those of the materials obtained above.

5,5'-Methylidynebis(1,3-dimethylbarbituric acid) (XV): Obtained from III as triethylammonium salt (XVs). Yield, 80%. Orange-yellow prisms (from CHCl_3 -ether), mp 183—184° (decomp.). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ $m\mu$: 237, 418. *Anal.* Calcd. for $\text{C}_{19}\text{H}_{29}\text{O}_6\text{N}_5$ [$\text{C}_{13}\text{H}_{14}\text{O}_6\text{N}_4 \cdot \text{N}(\text{C}_2\text{H}_5)_3$]: C, 53.89; H, 6.90; N, 16.54. Found: C, 53.84; H, 6.90; N, 16.69. The infrared spectrum was identical with that of the specimen obtained from the free acid, which was prepared by the known method,⁵⁾ by treating it with aqueous triethylamine.

5,5'-Methylidynebis(2-thiobarbituric acid) (XVI): Obtained from IV as triethylammonium salt (XVIs). Yield, 86%. Red-orange plates (from H_2O), mp 258—260° (decomp.). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ $m\mu$: 241, 264, 301, 454. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{21}\text{O}_4\text{N}_5\text{S}_2$ [$\text{C}_9\text{H}_6\text{O}_4\text{N}_4\text{S}_2 \cdot \text{N}(\text{C}_2\text{H}_5)_3$]: C, 45.09; H, 5.30; N, 17.53; S, 16.05. Found: C, 45.06; H, 5.08; N, 17.33; S, 15.83. The infrared spectrum was identical with that of the specimen obtained from the free acid, which was prepared by the known method,¹³⁾ by treating it with aqueous triethylamine.

5-Methylbarbituric Acids from 5,5'-Methylidynebis(barbituric acid)s. General Procedure—A mixture of 20.7 g (0.24 mole as HCO_2H) of TEAF and 0.01 mole each of triethylammonium salts of 5,5'-methylidynebis (barbituric acid)s, XIIIs, XIVs, XVs and XVIs, was heated at 135—145°, while considerable emission of CO_2 was observed by checking transfer of stream of air free from CO_2 and the color of the substrate disappeared gradually. After complete disappearance of the color, by the same treatment of the resulting clear solution as that for the TEAF reaction of barbituric acids described in the beginning of Experimental gave the 5-methylbarbituric acid in the following yields: Vs from XIIIs in 85%, VI from XIVs in 84%, VII from XVs in 73%, and VIIIs from XVIs in 85%. The identities of these products were made by comparison of the melting points and the infrared spectra with those obtained in the above, where exact correspondences were observed.

5,5'-Methylenebis(barbituric acid) (XIX)—A solution of 11 g of XIIIs dissolved in 350 ml of H_2O was catalytically hydrogenated over 1.1 g of palladium-on-charcoal containing 0.11 g of Pd, under ordinary pressure. Hydrogen uptake was stopped and the color of the solution disappeared when 2 molar equiv. of hydrogen was absorbed. After removal of the catalyst, the solution was acidified with HCl whereupon white precipitate was obtained. Yield, 76 g (94%). Recrystallization from H_2O gave needles, mp 279—282° (decomp.), lit.⁴⁾ mp >300°. *Anal.* Calcd. for $\text{C}_9\text{H}_8\text{O}_6\text{N}_4$: C, 40.30; H, 3.01; N, 20.89. Found: C, 40.48; H, 3.17; N, 20.74.

TEAF Reaction of 5,5'-Methylenebis(barbituric acid) (XIX)—A mixture of 62.4 g (0.72 mole as HCO_2H) of TEAF and 8.0 g (0.03 mole) of XIX was heated with constant stirring, the colorless solution took on yellow color at about 100° and considerable emission of CO_2 set in. At this time measurement of ultraviolet spectrum of a part of the reaction solution in H_2O gave the absorbance at 269 $m\mu$, which was identical with the absorption maximum of XIIIs, temperature was raised at 130—140° and maintained until the emission of CO_2 was nearly stopped, while the yellow color disappeared gradually. Then, excess of TEAF was removed by distillation under reduced pressure and the residue was crystallized by washing with acetone, then the crystals were collected. Yield, 12.1 g (83%). Recrystallization from EtOH gave needles, mp 202—204° (decomp.). The infrared spectrum and the melting point were identical with those of Vs obtained in the foregoing.

5-Benzylbarbituric Acid (XVIII)—a) A mixture of 25.9 g (0.3 mole as HCO_2H) of TEAF and 5.4 g (0.025 mole) of 5-benzylidenobarbituric acid (XVII) was heated with constant stirring. A rapid reaction took place at about 100° with considerable emission of CO_2 . The temperature was maintained for 30 min until the color of XVII disappeared. The major part of the triethylammonium salt, XVIIIs was deposited in the cool and collected by filtration. Further amount of the same compound was obtained by concentration of the filtrate. Yield, 7.3 g (91%). This material, showing the nearly same melting point as that of the pure crystals, was recrystallized from H_2O to needles, mp 222—224°. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ $m\mu$: 267. *Anal.* Calcd.

13) H. Zenno, *Yakugaku Zasshi*, 73, 1063 (1953).

for $C_{17}H_{25}O_3N_3$: C, 63.92; H, 7.98; N, 13.16. Found: C, 64.02; H, 7.93; N, 13.02. By addition of aqueous HCl to the aqueous solution, XVIII was precipitated. Recrystallization from EtOH gave needles, mp 210—212°, lit.,¹⁴ mp 206°. *Anal.* Calcd. for $C_{11}H_{10}O_3N_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.55; H, 4.64; N, 12.90. This material was identified by comparison of the infrared spectrum and by mixed melting point test with the specimen, which was obtained by catalytic hydrogenation procedure of a solution of XVII dissolved in aqueous triethylamine over palladium-on-charcoal catalyst.

b) By heating a mixture of 25.9 g of TEAF, 3.2 g (0.025 mole) of I and 3 g (0.028 mole) of benzaldehyde, the reaction took place similarly. The reaction mixture was treated by the same procedure as in a). Yield of XVIIIs, 7.1 g (89%). The material, mp 222—223°, was identified by comparison of the infrared spectrum with the specimen obtained in a).

TEAF Reaction of 5,5'-Methylenebis(barbituric acid) (XIX) in the Presence of Benzaldehyde—A mixture of 41.5 g (0.48 mole as HCO_2H) of TEAF, 5.4 g (0.02 mole) of XIX and 3.2 g (0.03 mole) of benzaldehyde was heated with constant stirring at about 100—110°, while with emission of CO_2 , the mixture turned to homogeneous yellow solution and then the color gradually disappeared. The reaction was completed by raising the temperature at about 120°. Crystals deposited in the cool were collected by filtration and removal of a part of TEAF gave the same crystals. Yield, 5.3 g (82%). This material, which showed mp 220—224° (decomp.) after recrystallization from H_2O , was identified as triethylammonium 5-benzylbarbiturate by noting the exact correspondence of the infrared spectrum with the spectrum of XVIIIs. The foregoing filtrate was thoroughly concentrated and the resulting residue was crystallized by addition of acetone. The crystals were collected by filtration, washed with acetone and recrystallized from EtOH. Yield, 3.7 g (76%). This material, mp 201—203° (decomp.) was identified as triethylammonium 5-methylbarbiturate by noting the exact correspondence of the infrared spectrum with the spectrum of Vs.

Acknowledgement The authors thank Prof. S. Ueo of Kyoto University for his interest and encouragement. Elemental analyses and spectrophotometric analyses were performed by Mr. K. Narita and Mrs. K. Yamamoto of this college, to whom thanks are due. Authors are indebted to Mr. J. Suzuki for his technical assistance in the present experimental work.

14) R. Conrad, *Ber.*, **34**, 1340 (1901).