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Formic Acid Reduction. V.[1] Barbituric Acid Derivatives. Reaction of 5-(3-Indolylmethylene)barbituric Acid with the Formate

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Investigation on the thermal TEAF reaction with 5-(3-indolylmethylene)barbituric acid is described in view of the courses of the product formations. With such a compound, not only the previously reported reduction of its methylidyne but also the succeeding reductive fission of the resulting methylene was revealed to occur in the reaction.

In the previous paper[3] of this series, we drew the conclusion for the course of the TEAF[4] reaction converting to 5-methylbarbituric acids from 5,5′-methylenebis(barbituric acid)s that the reaction is initiated by reductive fission of the methylene carbon bond connecting to 5-carbon of barbituric acids. However, this reductive fission stage appeared proper to such methylene bond bridged between two active carbons as those of the 5-positions of barbituric acids, because 5-arylmethylene barbituric acids and analogous compounds, on heating along with TEAF even at higher temperature, were shown to be unchangeable, not suffering reductive fission of their methylene groups. On survey of literature on reductive fission of methylene carbon bond, there has been reported no more than the formation[5] of 1-methyl-2-naphthol and 2-naphthol from 1,1′-methylenebis(2-hydroxynaphthalene) by means of reduction with zinc in basic medium.

In relation to the previous reported reactions[1,3] of the barbituric acid derivatives, with the purpose of verifying the presumable reductive fission of the methylene bond bridged between two active carbons other than 5-positions of barbituric acids, we were tempted to carry out TEAF reaction with 5-(3-indolylmethylene)barbituric acid (I) in the expectation that reduction of its methylidyne to methylene and succeedingly reductive fission of the resulting methylene might occur, as 3-position of indole has been known to behave as active methylene. Undoubtedly, the hydrogenated methylene compound, 5-(3-indolylmethyl)barbituric acid seemed more preferable as the substrate for the reaction, as considered to suffer reductive fission of its methylene, however, attempts to prepare it by catalytic hydrogenation of I were unsuccessful, because of the strong resistance even under a variety of hydrogenation conditions.

Compound I,[6] was prepared from 3-formylindole and barbituric acid and subjected to the TEAF reduction, in which reaction proceeded, on heating with TEAF, with considerable evolution of carbon dioxide, which set in at about 80°, and was ended within 1.5—2 hr at 130—140°. Treatment of the reaction mixture gave the three products shown in Chart 1.

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[1] Part IV: M. Sekiya and C. Yanaihara, *Chem. Pharm. Bull.* (Tokyo), **17**, 747 (1969).
[2] Location: *Oshika, Shizuoka.*
[3] M. Sekiya, and C. Yanaihara, *Chem. Pharm. Bull.* (Tokyo), **17**, 738 (1969).
[4] An abbreviated name of the reagent given by $5HCO_2H \cdot 2N(C_2H_5)_3$.
[5] K. Fries and E. Hubner, *Ber.*, **39**, 439 (1906); Sir R. Robinson and F. Weygand, *J. Chem. Soc.*, **1941**, 386.
[6] R.B. Van Order and H.G. Lindwall, *J. Org. Chem.*, **10**, 128 (1945).

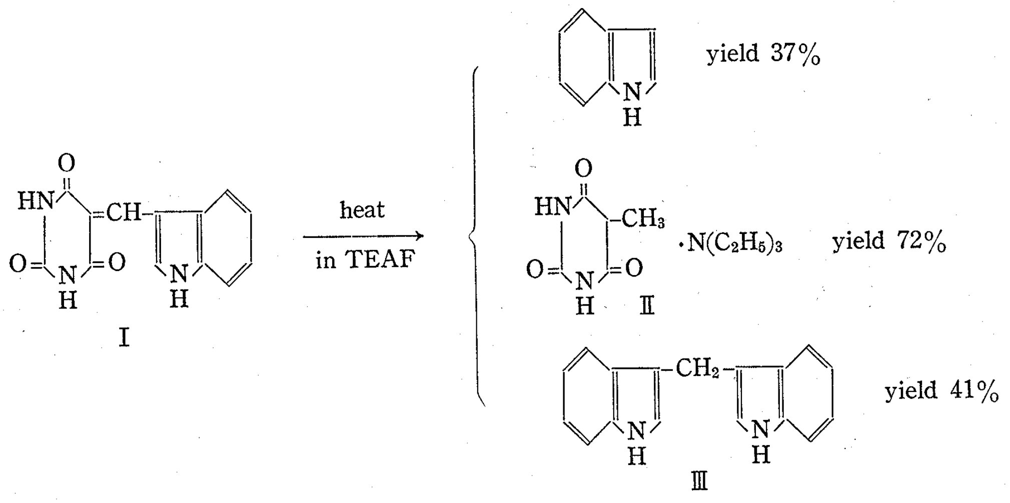

Chart 1

Taking the formation of indole and triethylammonium 5-methylbarbiturate (II) in consideration, our expectation, the reduction of the methylidyne bond and succeeding reductive fission of the resulting methylene bond, appeared to be illustrated, however, evidences of this course had to be made, because of arising confusion from the yields of the products and from the formation of 3,3′-methylenebisindole (III).

For course of the formation of indole and II, possibility other than the above course was first considered. One would be offered, that is initiated by the hydrolysis stage which might be induced by a contaminating little amount of water of TEAF to give 5-formylbarbituric acid and indole. By succeeding reduction with TEAF the former might have a possibility of giving II. The possibility of the above hydrolysis was examined by means of heating I along with 80% acetic acid alone or in the presence of triethylamine at 140—150° for 4 hr and with 2N HCl at the refluxing temperature for 3 hr, however no reaction occurred in every run, resulting in almost theoretical recovery of I. Thus, the possibility of the hydrolysis would be excluded.

Second, to make course of the formation of III clear is a problem. A possibility of the formation from indole itself was excluded, because heating it with TEAF under the condition that prevail in the course of the reaction with I resulted in theoretical recovery. We then presumed the formation to occur, as shown in the following Chart 2, through a replacement reaction (A) between I and indole, followed by succeeding conversion (B) of 3,3′-methylidynebisindole (IV) to III and that (C) of barbituric acid (V) to II. The last conversion from V to II is the known TEAF reaction which has been reported in the preceding paper.[1]

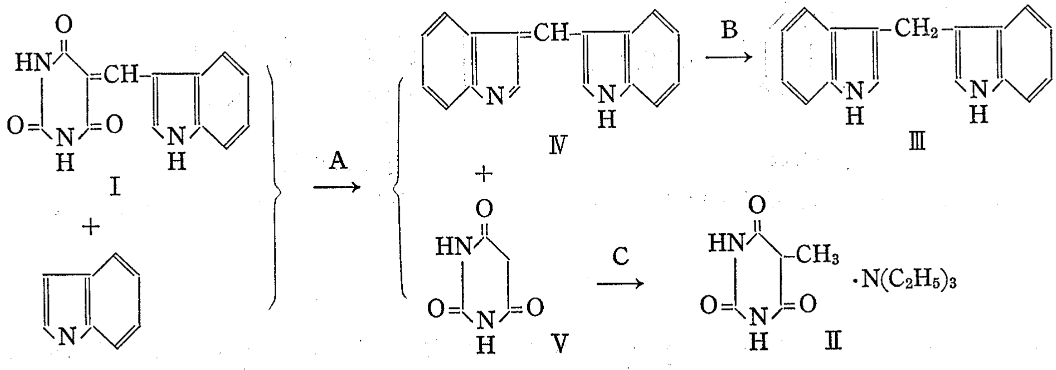

Chart 2

The above conjecture was well realized as in the following. The replacement reaction A was substantiated in the way, where a suspension of I in a solution of a large excess of indole dissolved in a constant boiling mixture of acetic acid and triethylamine, bp 74° (16 mmHg), was heated at about 100°. By treatment of the reaction mixture the products, V and tri-3-indolylmethane were obtained. The latter product has been known⁽⁷⁾ to be formed readily by the reaction between IV and indole, therefore this formation is considered as a secondary conversion of IV with excess of indole. Thus, the above demonstrated reaction can be said to be well in accord with the presumable conversion A in the TEAF reaction. The conversion B from IV to III was also certainly actualized to proceed smoothly with evolution of carbon dioxide when hydrochloride of IV prepared by the known method⁽⁷⁾ was heated along with TEAF at 130—140°. Thus, it would be safely said that the whole stages shown in Chart 2 were realized by the way of the above demonstrations actually to occur in the reaction of I with TEAF. Therefore, courses of the formations of the three compounds II, III and indole in the reaction (Chart 1) were safely considered to take place according to the following Chart 3. Finally, the TEAF reaction of I was revealed to involve the reduction of its methylidyne and the succeeding reductive fission of the resulting methylene at the bond connecting to indole.

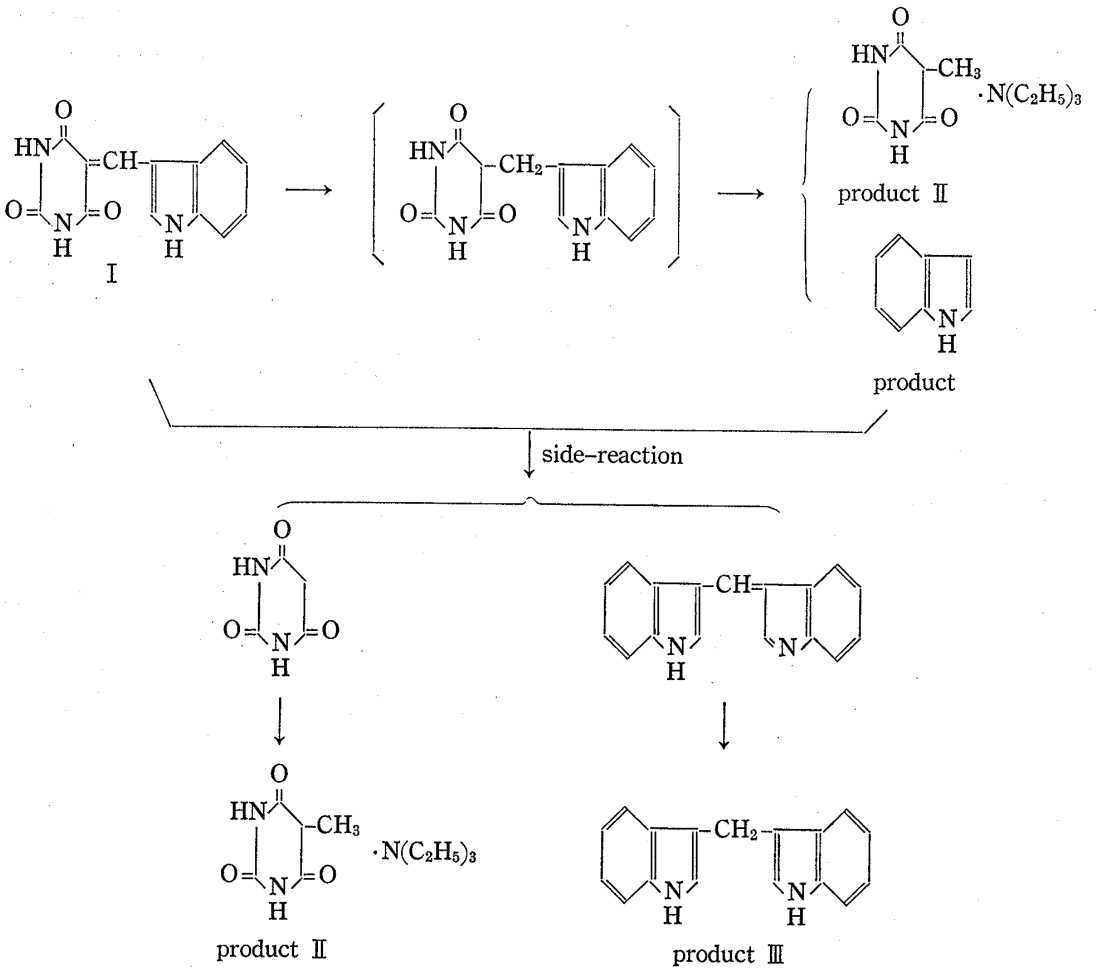

Chart 3. Courses of the TEAF Reaction of 5-(3-Indolylmethylene)barbituric Acid

Experimental

TEAF Reaction of 5-(3-Indolylmethylene)barbituric Acid (I)——A mixture of 31.1 g (0.36 mole as HCO_2H) of TEAF and 7.6 g (0.03 mole) of I was heated with constant stirring. Evolution of CO_2 set in at about 80°. The temperature was raised at 135—140° and maintained at this temperature for about 2 hr. From

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7) J. Harley-Mason and J.D. Búlock, *Biochem. J.*, **51**, 430 (1952).

the reaction solution TEAF was removed off by evaporation under reduced pressure. The resulting residue was thoroughly washed with ether. By concentration of the etheral solution indole, mp 51—52°, was obtained, which weighed 1.3 g (37%). This material was identified by mixed melting point test with an authentic sample and comparison of their infrared (IR) spectra.

To the foregoing residue insoluble in ether an appropriate amount of methanol was added and after standing over night, insoluble part was crystallized. Filtration and washing with methanol gave II, weighing 5.25 g (72%), which was identified by comparison of the IR spectrum with that of an authentic sample. The methanolic filtrate combined with the washings was concentrated and the residue was crystallized by washing with H_2O. The crude crystals were recrystallized from methanol-H_2O to give plates, mp 164—165°, lit.,[8] mp 164—165°, weighing 1.5 g (41%), which was identified as 3,3′-methylenebisindole. UV $\lambda_{\text{max}}^{\text{MeOH}}$ mμ: 225, 283, 291, lit.,[8] UV $\lambda_{\text{max}}^{\text{MeOH}}$ mμ: 224, 283. *Anal.* Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.70; H, 5.50; N, 11.52.

TEAF Reaction of 3,3′-Methylidynebisindole (IV)——A mixture of 20.7 g (0.24 mole as HCO_2H) of TEAF and 2.8 g (0.01 mole) of 3,3′-methylidynebisindole hydrochloride was heated with constant stirring. The mixture first turned a red homogenous liquid and considerable evolution of CO_2 was observed at about 100—110°. The temperature was raised at 135—140° and maintained for 2 hr, while the color gradually disappeared. The reaction solution was concentrated under reduced pressure to remove TEAF. The residue was crystallized from H_2O–methanol. Recrystallization from the same solvent gave coloreless plates, mp 164—165°, weighing 2.2 g (91%), which were identified as 3,3′-methylenebisindole by mixed melting point test with that obtained by the TEAF reaction of I and by comparison of the infrared spectra with the same.

Reaction between 5-(3-Indolylmethylene)barbituric Acid (I) and Indole——A suspension of 5.2 g (0.02 mole) of I in a solution of 9.4 g (0.08 mole) of indole dissolved in 26 g of a constant boiling mixture of acetic acid and triethylamine, bp 74° (16 mmHg) (content of CH_3CO_2H: 69%) was heated with stirring at 100—103°. After 3 hr by filtration on cool 3.4 g of the starting I was recovered. The filtrate was concentrated under reduced pressure and the residue was steam-distilled to remove excess of indole. The steam-distillation residue insoluble in H_2O was collected by filtration and recrystallized from ethanol to give prisms, mp 243—245°, lit.,[7] mp 244—246°, weighing 2.3 g (91% based on the reacting I), which was identified as tri-3-indolylmethane. *Anal.* Calcd. for $C_{25}H_{19}N_3$: C, 83.08; H, 5.25; N, 11.53. Found: C, 83.28; H, 5.42; N, 11.30. The aqueous filtrate was concentrated to dryness and redissolved in H_2O, whereupon a little amount of insoluble material was removed. By acidification with HCl crystals, mp 244—247° (decomp.), weighing 0.68 g (76% based on the reacting I) were obtained. This material was identified as barbituric acid by comparison of the IR spectrum with that of authentic sample and by mixed melting point test with the same.

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[8] E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).