Notes

[Chem. Pharm. Bull. 17(4) 810—814 (1969)] UDC 547.854.5.04 : 547.291.04 : 615.214.24.011.5

Formic Acid Reduction. VI.[1] Barbituric Acid Derivatives. Reduction of 5-Arylaminomethylene- and 5-Alkylaminomethylene-substituted Barbituric Acids converting to 5-Methylbarbituric Acids

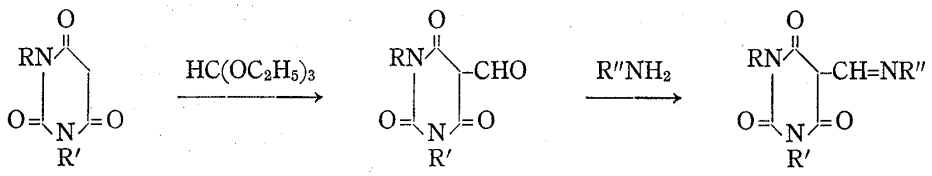
Minoru Sekiya and Chizuko Yanaihara[2]

Shizuoka College of Pharmacy[2]

(Received June 19, 1967)

Catalytic hydrogenation of 5-aminomethylene-, 5-Methylaminomethylene-, and 5-N-methylanilinomethylene-substituted 1,3-dimethylbarbituric acids over palladium-on-calcium carbonate has been reported by Clark-Lewis, *et al.*[3] to result in the formation of 1,3,5-trimethylbarbituric acid. Lately similar mode of the reaction was found to occur in formic acid reduction by means of using triethylammonium formate (TEAF), given by $5HCO_2H \cdot 2N(C_2H_5)_3$, as reducing agent and with a variety of other N-aryl- and N-alkylaminomethylene-barbituric acids this reaction mode was generalized.

Eight 5-arylaminomethylene- and 5-alkylaminomethylen-esubstituted barbituric acid derivatives were prepared as shown in Chart 1 in order to supply them as substrates to the TEAF reduction.



R	R′	R″	R	R′	R″
H	H	C_6H_5	H	H	$C_6H_5CH_2CH_2$
H	H	*p*-$O_2NC_6H_4$	H	H	C_6H_{11}
H	H	*p*-$CH_3OC_6H_4$	CH_3	H	C_6H_5
H	H	$C_6H_5CH_2$	CH_3	CH_3	C_6H_5

Chart 1

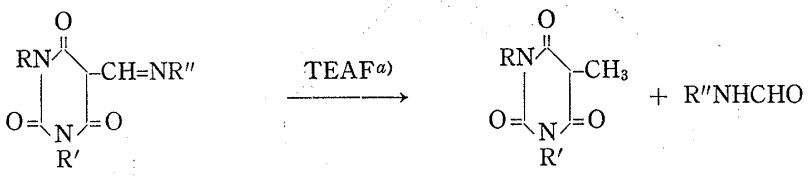
Preparation of the compounds analogous to these has previously reported by two means: a method[3,4] of fusing barbituric acid analog together with formanilide or its derivative and a method[5] through the reaction among barbituric acid analog, ethyl orthoformate and amine. However, we prepared them in better yields preferably according to the route shown in Chart 1, in which 5-formyl-, 1-methyl-5-formyl- and 1,3-dimethyl-5-formyl-barbituric acid were first prepared through the reactions between barbituric acid analogs and ethyl orthoformate on referring to the previously reported method,[3] and then the 5-formyl compounds obtained were reacted in aqueous triethylamine solution with the corresponding amines. Among the compounds shown in Chart 1, 5-(*p*-nitroanilino)methylene-, 5-benzylaminomethylene-, 5-

1) Part V: M. Sekiya, C. Yanaihara and J. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **17**, 752 (1969).
2) Location: *Oshika, Shizuoka.*
3) J.W. Clark-Lewis and M.J. Thompson, *J. Chem. Soc.*, **1959**, 2401.
4) H. Bredereck, R. Gompper, F. Effenberger, K.H. Popp and G. Simchen, *Chem. Ber.*, **94**, 1241 (1961).
5) H. Zenno, *Yakugaku Zasshi*, **73**, 1066 (1953).

NII-Electronic Library Service

phenethylaminomethylene-, 5-cyclohexylaminomethylene- and 1-methyl-5-anilinomethylenebarbituric acid has not been described previously.

The 5-aryl and 5-alkylaminomethylene barbituric acid derivatives thus prepared, and additional aminomethylenebarbituric acid prepared[6] from barbituric acid and formamide were subjected to TEAF reduction by means of heating each of them together with TEAF (12 mole equiv. as HCO_2H) at 140—150°. In every run of those, reaction took place with evolution of carbon dioxide to give 5-methylbarbituric acid derivative and N-aryl or N-alkylformamide generally in both reasonable yields. Results are summarized in Chart 2. As shown, with the exception of the runs with 5-aminomethylene- and 5-phenethylaminomethylenebarbituric acid, in which the reaction was much restrained, 60—75% of the conversion was observed throughout.



R	R′	R″	Reaction time, hr	Conversion[b)] %
H	H	H	20	20[c)]
H	H	C_6H_5	3	70—74
H	H	p-$O_2NC_6H_4$	2	66—70
H	H	p-$CH_3OC_6H_4$	7	72—75
H	H	$C_6H_5CH_2$	10	65—71
H	H	$C_6H_5CH_2CH_2$	20	26—29[c)]
H	H	C_6H_{11}	10	62—72
CH_3	H	C_6H_5	3	67—70
CH_3	CH_3	C_6H_5	2	61—67

a) General procedure are given in Experimental.
b) Percentage of conversion estimated from both yields of triethylammonium salts or free acid of 5-methylbarbituric acid analog and N-substituted formamide.
c) Most of the other portion resulted in recovery of the starting material.

Chart 2

Using 5-anilinomethylenebarbituric acid, attempts to carry out the reaction with formic acid were unsuccessful even on heating at its refluxing temperature for 20 hr, resulting recovery of the starting material. Therefore, TEAF is a distinguished reagent effective for the reaction, where the triethylamine component appears to act as a catalyst.

The TEAF reaction evidently involves reductive fission of the methylidyne-carbon-to-nitrogen bond induced by reducing action of formic acid. Course of the reaction probably is that first the carbon-nitrogen double bond is hydrogenated, as previously[7] known as the reduction of azomethine, then followed by reductive fission and N-formylation, as Chart 3 indicates.

In a previous papers in this series,[1,8] we reported the TEAF reaction of barbituric acid derivatives possessing methylidyne bond at 5-position, such as 5,5′-methylidynebis(barbituric acid) derivatives[8] and 5-(3-indolylmethylene)barbituric acid,[1] in which the formation of 5-methylbarbituric acids is given. When the said reaction is compared with this reaction, there would be said surprisingly to exist close resemblance between both of the fashions, leading to the same formation of 5-methylbarbituric acid analog, though distinguished only by the atom adjacent to the reacting methylidyne; $\rangle HC-CH=\underline{N}- \longleftrightarrow \rangle C=CH-\underline{N}H-$ in one and $\rangle CH-CH=\langle \longleftrightarrow C\rangle C=CH-CH\langle$ in the other. The hydrogenation of the double bond and the

6) P. Papini and R. Cimmarusti, *Gazz. Chim. Ital.*, **77**, 142 (1947); *C.A.*, **42**, 1286 (1948).
7) M. Sekiya, K. Ito, A. Hara, and J. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **15**, 802 (1967).
8) M. Sekiya and C. Yanaihara, *Chem. Pharm. Bull.* (Tokyo), **17** 738, 747 (1969)

NII-Electronic Library Service

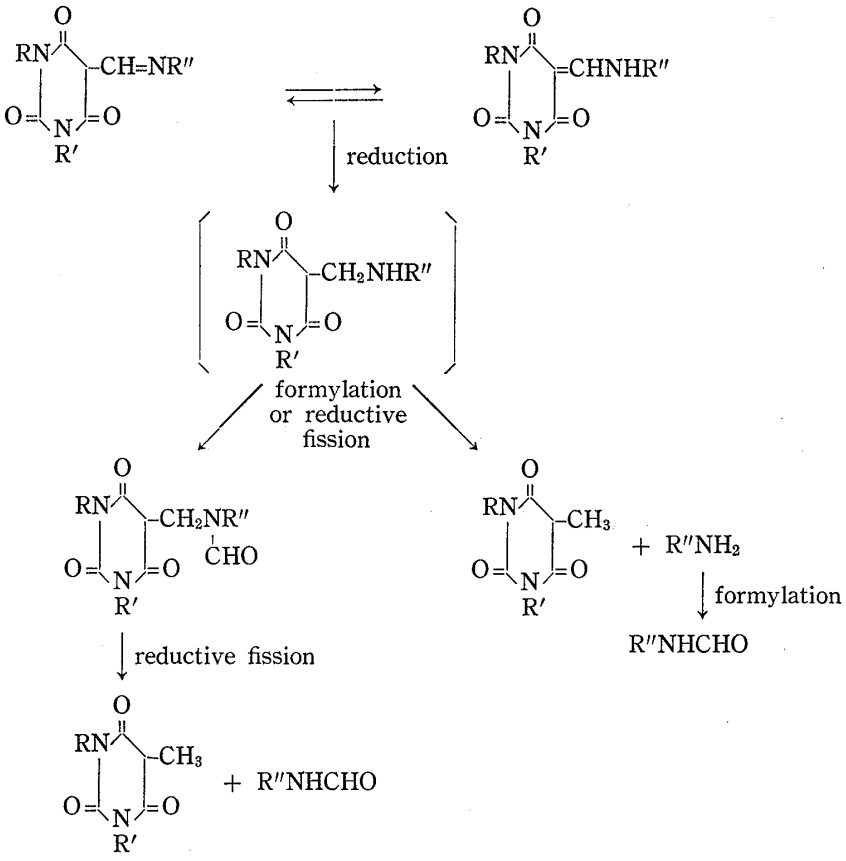


Chart 3

succeeding reductive fission, which were previously established[8] as the course of the latter reaction could also be stated to involve in the former reaction as described in the foregoing.

Experimental

Preparation of 5-Formylbarbituric Acids——On referring to the report[3] on the preparation of 1,3-dimethyl-5-formylbarbituric acid, a suspension of 0.05 mole each of barbituric acid analogs, barbituric acid and 1-methylbarbituric acid, in 60 ml of ethyl orthoformate was refluxed with stirring for 1.5 hr. On cool, the suspending crystals was collected by filtration and recrystallized to the following pure crystals.

5-Formylbarbituric Acid——Yield, 88%. Colorless fine needles (from AcOH), mp >300°. *Anal.* Calcd. for $C_5H_4O_4N_2$: C, 38.47; H, 2.58; N, 17.95. Found: C, 38.74; H, 2.87; N, 17.73.

5-Formyl-1-methylbarbituric Acid——Yield, 75%. Pale orange needles (from ethanol), mp 197—199° (decomp.). *Anal.* Calcd. for $C_6H_6O_4N_2$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.78; H, 3.73; N, 16.97.

Preparation of 5-Arylaminomethylene- and 5-Alkylaminomethylene-substituted Bartituric Acids——General Procedure: In 60 ml of aqueous solution containing 0.02 mole of triethylamine, 0.02 mole each of the materials, 5-formyl-, 1-methyl-5-formyl-, and 1,3-dimethyl-5-formyl-barbituric acid, was dissolved. On heating at 60—70° with well-stirring, a solution of 0.022 mole of the corresponding amine dissolved in 15 ml of ethanol was added dropwise, whereupon the product precipitated immediately. After the heating and the stirring were continued for 30 min, filtration, and washing with hot H_2O and then with methanol gave the product, which was shown to be nearly pure without recrystallization.

Only the preparation of 5-(*p*-nitroanilino)methylenebarbituric acid formed an exception to the above procedure, because of poor solubility of *p*-nitroaniline in ethanol. The preparation was successfully carried out by means of addition of a solution of *p*-nitroaniline in 20% hydrochloric acid to a heating and stirring solution of barbituric acid dissolved in an aqueous solution containing a sufficient excess of triethylamine.

The following are assignment and identification of the products obtained.

5-Anilinomethylenebarbituric Acid: Yield, 84%. Pale yellow fine needles, mp >320°, lit.,[9] mp about 330°. UV λ_{max}^{MeOH} mμ: 341, 223. *Anal.* Calcd. for $C_{11}H_9O_3N_3$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.16; H, 3.97; N, 18.38.

9) H. Zenno, *Yakugaku Zasshi*, **74**, 199 (1954).

NII-Electronic Library Service

5-(*p*-Nitroanilino)methylenebarbituric Acid: Yield, 82%. Pale rosy fine needles, mp >320°. UV λ_{max}^{MeOH} mμ: 365, 282, 221. *Anal.* Calcd. for $C_{11}H_8O_5N_4$: C, 47.83; H, 3.92; N, 20.29. Found: C, 47.79; H, 3.71; N, 20.07.

5-(*p*-Methoxyanilino)methylenebarbituric Acid: Yield, 82%. Pale yellow fine needles, mp >320°, lit.,[5] mp 334—336° (decomp.). UV λ_{max}^{MeOH} mμ: 353, 224, 304 (shoulder). *Anal.* Calcd. for $C_{12}H_{11}O_4N_3$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.20; H, 4.39; N, 15.82.

5-Benzylaminomethylenebarbituric Acid: Yield, 84%. Colorless fine needles, mp 273—275° (decomp.). UV λ_{max}^{MeOH} mμ: 303, 210, 235 (shoulder). *Anal.* Calcd. for $C_{12}H_{11}O_3N_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.67; H, 4.57; N, 17.25.

5-Phenethylaminomethylenebarbituric Acid: Yield, 92%. Colorless fine needles, mp 317—319° (decomp.). UV λ_{max}^{MeOH} mμ: 302, 210, 236 (shoulder). *Anal.* Calcd. for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.03; H, 5.14; N, 16.21.

5-Cyclohexylaminomethylenebarbituric Acid: Yield, 80%. Colorless fine needles, mp 271—274° (decomp.). UV λ_{max}^{MeOH} mμ: 303, 217, 235 (shoulder). *Anal.* Calcd. for $C_{11}H_{15}O_3N_3$: C, 55.68; H, 6.37; N, 17.71. Found: C, 55.27; H, 6.41; N, 17.43.

5-Anilinomethylene-1,3-dimethylbarbituric Acid: Yield, 81%. Colorless needles (from methanol), mp 198—200°, lit.,[4] mp 202—203°. UV λ_{max}^{MeOH} mμ: 342, 226, 282 (shoulder). *Anal.* Calcd. for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 59.97; H, 5.05; N, 15.97.

5-Anilinomethylene-1-methylbarbituric Acid: Yield, 87%. Colorless plates, mp 286—287°. UV λ_{max}^{MeOH} mμ: 342, 225, 282 (shoulder). *Anal.* Calcd. for $C_{12}H_{11}O_3N_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.44; H, 4.51; N, >17.10.

TEAF Reaction——General Procedure: A suspension of 0.025 mole each of various 5-aminomethylene-substituted barbituric acid analogs in 26.0 g (0.3 mole as HCO_2H) of TEAF (only 5-anilinomethylene-1, 3-dimethylbarbituric acid gave a solution nearly at the biginning) was heated at 140—150° with constant stirring, while a constant stream of air free from CO_2 was passed in order to check transfer of evolving CO_2 by $Ba(OH)_2$ solution. As the reaction proceeded, the suspension gradually turned into solution. After subsidence of the CO_2 evolution the reaction solution was concentrated under reduced pressure to remove triethylamine and excess of TEAF. Succeeding procedure is described for each run in the following. Triethylammonium 5-methylbarbiturate, a general product throughout all runs, was identified by noting exact correspondance of the IR spectrum with the spectrum of an authentic sample prepared previously.

Reaction with 5-Aminomethylenebarbituric Acid: Even after 20 hr of the reaction period, 61% of the 5-aminomethylene compound was recovered as a material remaining undissolved in the reaction mixture. The residue obtained by concentration of the filtrate was crystallized by addition of acetone. Filtration and washing with acetone gave triethylammonium 5-methylbarbiturate. Yield, 20%. A quick way of recrystallization from ethanol gave needles, mp 201—204° (decomp.), lit.,[8] mp 202—204° (decomp.). *Anal.* Calcd. for $C_{11}H_{21}O_3N_3$: C, 54.30; H, 8.70; N, 17.27. Found: C, 53.92; H, 8.51; N, 17.20.

Reaction with Anilinomethylenebarbituric Acid: To the distillation residue obtained from the general procedure (reaction period: 3 hr) acetone was added whereupon triethylammonium 5-methylbarbiturate was crystallized. After filtration and washing with acetone to yield the product (yield, 74%), the filtrate combined with washings was concentrated under reduced pressure and the residue was extracted with ether. From the residue obtained by concentration of the etheral extract, formanilide was crystallized and refined by distillation under reduced pressure. Yield, 70%. This material was identified by comparison of the IR spectrum with that of an authentic sample and by mixed melting point test.

Reaction with 5-(*p*-Nitroanilino)methylenebarbituric Acid: By addition of acetone to the residue obtained from the general procedure (reaction period: 2 hr) triethylammonium 5-methylbarbiturate was crystallized and collected by filtration. Yield, 70%. Then, water was added to the filtrate, whereupon *p*-nitroformanilide was precipitated. Filtration and recrystallization from H_2O gave brown-yellow crystals, mp 193—194°, lit.,[10] mp 194—195°. Yield, 66%. *Anal.* Calcd. for $C_7H_6O_3N_2$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.40; H, 3.85; N, 17.10.

Reaction with 5-(*p*-Methoxyanilino)methylenebarbituric Acid: The residue obtained from the general procedure (reaction period: 7 hr) was processed by the same procedures as in the reaction with 5-anilinomethylenebarbituric acid. Yield of triethylammonium 5-methylbarbiturate, 75%. Concentration of the etheral extract gave *p*-methoxyformanilide, which was refined by distillation under high reduced pressure. Yield, 72%. Colorless prisms, mp 80—81°, lit.,[11] 80—81°. *Anal.* Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.25; H, 6.15; N, 9.29.

Reaction with 5-Benzylaminomethylenebarbituric Acid: The residue obtained from the general procedure (reaction period: 10 hr) was processed by the same procedures as in the reaction with 5-anilinomethylenebarbituric acid. Yield of triethylammonium 5-methylbarbiturate, 65%. Concentration of the etheral extract gave N-benzylformamide which was refined by distillation under reduced pressure to crystals, mp

10) G.T. Morgan, F.M.G. Micklethweit, *J. Chem. Soc.*, **87**, 931 (1905).
11) S. Sugasawa, H. Shigehara, *Yakugaku Zasshi*, **62**, 531 (1942).

NII-Electronic Library Service

59—60° undepressed with an authentic sample. Yield, 71%. *Anal.* Calcd. for C_8H_9ON: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.60; H, 6.72; N, 10.47.

Reaction with 5-Phenethylaminomethylenebarbituric Acid: Even after 20 hr of reaction period, 47% of the starting aminomethylene compound was recovered as a material remaining undissolved in the reaction mixture. The residue obtained by concentration of the filtrate was processed by the same procedures as in the reaction with 5-anilinomethylenebarbituric acid. Yield of triethylammonium 5-methylbarbiturate, 26%. Concentration of the etheral extract followed by distillation under reduced pressure gave phenethylformamide, bp 127—128° (0.2 mmHg). Yield, 29%. *Anal.* Calcd. for $C_9H_{11}ON$: C, 72.45; H, 7.43; N, 9.39. Found: C, 71.94; H, 7.53; N, 9.24.

Reaction with 5-Cyclohexylaminomethylenebarbituric Acid: The residue obtained by the general procedure (reaction period: 10 hr) was processed by the same procedures as in the reaction with 5-anilinomethylenebarbituric acid. Yield of triethylammonium 5-methylbarbiturate, 62%. Concentration of the etheral extract followed by distillation under reduced pressure gave N-cyclohexylformamide, bp 135—140° (15 mmHg). mp 26—27°. Yield, 72%. *Anal.* Calcd. for $C_7H_{13}ON$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.31; H, 10.36; N, 11.17.

Reaction with 1-Methyl-5-anilinomethylenebarbituric Acid: The residue obtained by the general procedure (reaction period: 3 hr) was processed by the same procedures as in the reaction with 5-anilinomethylenebarbituric acid. 1,5-Dimethylbarbituric acid was obtained as free acid in 67% yield. Recrystallization from ethanol gave crystals of mp 169—170°, undepressed with an authentic sample prepared previously. *Anal.* Calcd. for $C_6H_8O_3N_2$: C, 46.16; H, 5.16; N, 17.94. Found: C, 46.10; H, 5.27; N, 17.82. Yield of formanilide, 70%, which was identified by mixed melting point test with an authentic sample.

Reaction with 1,3-Dimethyl-5-anilinomethylenebarbituric Acid: The residue obtained as indicated in the general procedure (reaction period: 2 hr) was extracted with ether. After removal of ether from the extract, the residue was distilled under reduced pressure to give formanilide, mp 46—47°, undepressed by admixture with an authentic sample. Yield, 67%. The foregoing unextracted residue was crystallized by addition of chloroform–ether. Filtration gave 1,3,5-trimethyldialuric acid. Yield, 61%. Recrystallization from benzene gave needles, mp 107°. *Anal.* Calcd. for $C_7H_{10}O_4N_2$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.21; H, 5.43; N, 15.24.

Acknowledgement The authors are indebted to the Members of the Central Analysis Room of this college for elementary analyses.

[Chem. Pharm. Bull. 17(4) 814—818 (1969)]

UDC 547.833.9.07 : 547.94.07

Dienone Synthesis by Phenolic Oxidation of Dihydroxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline and Sodium Borohydride Reduction[1)]

TETSUJI KAMETANI and FUMIO SATOH

Pharmaceutical Institute, Tohoku University School of Medicine[2)]

(Received February 27, 1968)

It has been reported that phenolic oxidation of 1-phenethylisoquinolines (II, III) gave dienones (Va, Vb, VI), whose dienone–phenol and dienol-benzene rearrangements afforded homoaporphines.[3–6)]

1) This forms Part CCCIX of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.
2) Location: *No. 85, Kita-4-bancho, Sendai.*
3) T. Kametani, K. Fukumoto, H. Yagi, and F. Satoh, *Chem. Comm.*, **1967**, 878.
4) A.R. Battersby, R.B. Bradbury, R.B. Herbert, M.H.G. Munro, and R. Ramage, *Chem. Comm.*, **1967**, 450.
5) A.R. Battersby, E. McDonald, M.H.G. Munro, and R. Ramage, *Chem. Commun.*, **1967**, 934.
6) T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *Chem. Commun.*, **1967**, 1103; *idem*, *J. Chem. Soc. (C)*, **1968**, 271; *idem*, *J. Org. Chem.*, 33, 690 (1968).

NII-Electronic Library Service