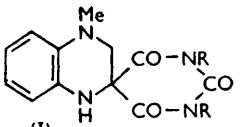
481. 5-*Aminomethylene*-1 : 3-*dimethylbarbituric Acids.*

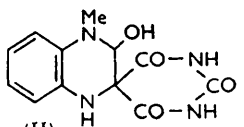
By J. W. Clark-Lewis and M. J. Thompson.

N-Alkyl and *N*-aryl derivatives of 5-aminomethylene-1 : 3-dimethylbarbituric acid are described; they are readily hydrogenolysed to 1 : 3 : 5-trimethylbarbituric acid over a palladium catalyst. Methylamine 1 : 3 : 5-trimethylbarbiturate suffers autoxidation and ring contraction to 5-methylcarbamoyl-3 : 5-dimethyloxazolid-2 : 4-dione when its ethanolic solution is boiled in air.

Interaction of *o*-aminodimethylaniline and alloxan gives the *spiro*barbituric acid (I; R = H) through participation of an *N*-methyl group in an unusual cyclisation leading to incorporation of the methyl-carbon atom into the quinoxaline ring.[1] Confirmation of this structure by synthesis appeared desirable, particularly because the more problematical carbinolamine formulation for the aerial oxidation product (II) rests largely on its derivation



(I)



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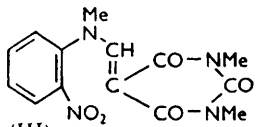
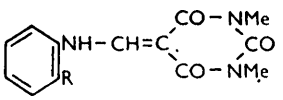


(III)

from that of the spiran (I; R = H).[2] Aminomethylenebarbituric acids (*e.g.*, III) might be useful in synthesis of the dimethylspiran (I; R = Me), and preparation and properties of these intermediates have therefore been investigated. The *o*-nitroanilino-compound (IV; R = NO_2) was readily obtained, but the *N*-methyl derivative (III) could not be prepared; a further disadvantage is that the aminomethylenebarbituric acids are susceptible to hydrogenolysis.



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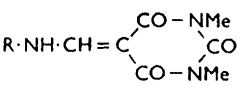


(V)

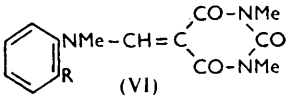
Diethyl ethoxymethylenemalonate reacts readily with primary aromatic amines [3,4] and, although an *o*-nitro-group retards the reaction, diethyl *o*-nitroanilinomethylenemalonate [4] was obtained quantitatively in an improved preparation under more vigorous conditions than were required for aniline. *N*-Methylaniline also reacts less readily [5] than aniline, and the combined effects of the methyl and the nitro-group in *N*-methyl-*o*-nitroaniline inhibited reaction completely. Ethoxymethylenemalonic ester was then replaced by 1 : 3-dimethylbarbituric acid to avoid having to close the pyrimidine ring at a later stage, and several of the methods used have been applied also to preparation of aminomethylene derivatives from barbituric acid.[6] 1 : 3-Dimethylbarbituric acid was first converted by reaction with ethyl orthoformate and aniline, with formanilide, with *NN'*-diphenylformamidine,[7] or with methyl *N*-phenylformimidate into 5-anilinomethylene-1 : 3-dimethylbarbituric acid (IV; R = H), which was also readily formed from aniline and

[1] King and Clark-Lewis, *J.*, 1951, 3080.
[2] *Idem*, *J.*, 1953, 172.
[3] Claisen, *Annalen*, 1897, **297**, 77; Gould and Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890; Price and Roberts, *ibid.*, 1946, **68**, 1204; Snyder, Freier, Kovacic, and van Heyningen, *ibid.*, 1947, **69**, 371; Price, Snyder, Bullitt, and Kovacic, *ibid.*, p. 374; Duffin and Kendall, *J.*, 1948, 893.
[4] Riegel, Lappin, Adelson, Jackson, Albisetti, Dodson, and Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 1264.
[5] (*a*) Baker and Schlesinger, *ibid.*, p. 2009; (*b*) Hickinbottom, "Reactions of Organic Compounds," Longmans, London, 1957, pp. 20, 73.
[6] Ridi and Papini, *Gazzetta*, 1946, **76**, 376; Papini and Cimmarusti, *ibid.*, 1947, **77**, 142; Ridi, *ibid.*, 1949, **79**, 175; 1952, **82**, 756; Ridi and Testa, *ibid.*, 1950, **80**, 542; Zenno, *J. Pharm. Soc. Japan*, 1953, **73**, 1063; *Chem. Abs.*, 1954, **48**, 8545.
[7] Nightingale and Alexander, *J. Amer. Chem. Soc.*, 1936, **58**, 794.

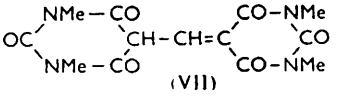
5-amino- or 5-hydroxy-methylene-1 : 3-dimethylbarbituric acid. *o*-Nitroaniline, though less reactive than aniline, gave under more vigorous conditions an excellent yield of 1 : 3-dimethyl-5-*o*-nitroanilinomethylenebarbituric acid (IV; R = NO_2) by the ethyl orthoformate method. 2 : 2′-Dinitro-*NN*′-diphenylformamidine similarly gave a high yield of this product (IV; R = NO_2) in a rapid reaction with 1 : 3-dimethylbarbituric acid. The orthoformate method, however, is more convenient as it obviates preparation of 2 : 2′-dinitrodiphenylformamidine, which was obtained from *o*-nitroaniline and ethyl orthoformate in variable yield, and with m. p. 161—163° differing considerably from the value recorded by Walther (m. p. 124—125°).[8]

Many standard syntheses of aminomethylene derivatives from compounds containing a reactive methylene group appear to give inferior results or to fail completely when applied to secondary amines. Thus formamide, *N*-methylformamide, and formanilide yield the aminomethylene compounds (V; R = H, Me, and Ph) when heated with 1 : 3-dimethylbarbituric acid, but no reaction occurred with *NN*-dimethylformamide or with *N*-methylformanilide, probably because they are unable to enolise. Conditions used for the analogous preparation of 4-*N*-methylanilinomethylene-2-phenyloxazolone [9] have not been tested in the present case. Aniline and *o*-nitroaniline readily undergo amine-exchange with 5-aminomethylene-1 : 3-dimethylbarbituric acid (V; R = H) to yield the compounds (IV; R = H and NO_2), but no exchange occurred with methylaniline or with *N*-methyl-*o*-nitroaniline. Attempts to methylate 1 : 3-dimethyl-5-*o*-nitroanilinomethylenebarbituric acid (IV; R = NO_2) were unsuccessful.

The nitro-group of 1 : 3-dimethyl-5-*o*-nitroanilinomethylenebarbituric acid (IV; R = NO_2) was reduced catalytically without affecting the double bond, and the *o*-aminoanilinomethylene compound (IV; R = NH_2) thus formed was also prepared from *o*-phenylenediamine by the orthoformate method. *o*-Phenylenedi-(5-aminomethylene-1 : 3-dimethylbarbituric acid) was obtained as a by-product through reaction of both amino-groups of *o*-phenylenediamine, and formed the sole product when the reactants were used in the requisite molecular proportions; 5-*o*-aminoanilinomethylene-1 : 3-dimethylbarbituric acid (IV; R = NH_2) gave the same bis-product when heated with ethyl orthoformate and 1 : 3-dimethylbarbituric acid. *o*-Aminoacetanilide was similarly converted into 5-*o*-acetamidoanilinomethylene-1 : 3-dimethylbarbituric acid (IV; R = NHAc), but *o*-acetamido-*N*-methylaniline apparently cyclises to 1 : 2-dimethylbenziminazole too readily [10] for it to be useful in preparation of 5-*o*-acetamido-*N*-methylanilinomethylene-1 : 3-dimethylbarbituric acid (VI; R = NHAc).



(VI)



(VII)

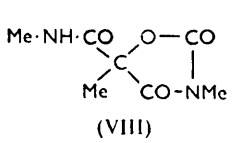
Reaction of ethyl orthoformate with 1 : 3-dimethylbarbituric acid gave 5-ethoxymethylene-1 : 3-dimethylbarbituric acid which was readily hydrolysed to the 5-hydroxymethylene compound even by moist solvents. However, the latter proved to be reactive and gave aminomethylene derivatives readily even with methylaniline and *o*-nitroaniline, and with 1 : 3-dimethylbarbituric acid it yielded the methine (VII) identical with a by-product from the preparation of the ethoxymethylenebarbituric acid. The yellow, sparingly soluble methine (VII) is also formed when *N*-methyl-*o*-nitroaniline, ethyl orthoformate, and 1 : 3-dimethylbarbituric acid are heated together; even pure hydroxymethylene-1 : 3-dimethylbarbituric failed to yield the *N*-methyl-*o*-nitroanilinomethylene compound (III) when heated with *N*-methyl-*o*-nitroaniline.

Hydrogenation of aminomethylene-1 : 3-dimethylbarbituric acids gave amines and

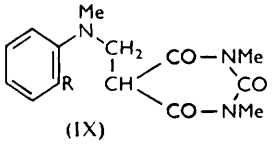
[8] Walther, *J. prak. Chem.*, 1895, **52**, 430.
[9] Boon, Carrington, and Jones, " The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 816.
[10] Roeder and Day, *J. Org. Chem.*, 1941, **6**, 25.

1 : 3 : 5-trimethylbarbituric acid through hydrogenolyses similar to those observed [5a] with aminomethylenemalonic esters. 5-Amino- and 5-methylamino-methylene-1 : 3-dimethylbarbituric acid (V; R = H and Me) gave ammonium and methylamine 1 : 3 : 5-trimethylbarbiturate respectively, from which the barbituric acid was isolated after acidification. 1 : 3-Dimethyl-5-*N*-methylanilinomethylenebarbituric acid (VI; R = H) similarly gave 1 : 3 : 5-trimethylbarbituric acid and methylaniline when hydrogenated at room pressure, but at a higher pressure gave *N*-methyl*cyclo*hexylamine and *N*-methylaniline in 5 : 1 ratio, while the 5-anilinomethylene compound gave approximately equal quantities of aniline, *cyclo*hexylamine, and di*cyclo*hexylamine. These ring hydrogenations of aromatic amines under moderate conditions with a palladium catalyst are noteworthy.[5b] 1 : 3 : 5-Trimethylbarbituric acid formed in the hydrogenolysis of 5-anilinomethylene-1 : 3-dimethylbarbituric acid was usually contaminated with traces of 1 : 3 : 5-trimethyldialuric acid although, for reasons which are not clear, only the dialuric acid was obtained on two occasions.

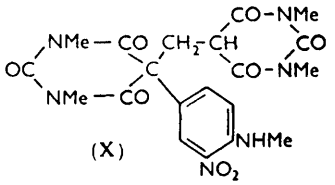
Determination of the course of these hydrogenations was complicated by the slow transformation of methylamine 1 : 3 : 5-trimethylbarbiturate into a compound, $C_7H_{10}O_4N_2$, with loss of methylamine, when boiled with ethanol. The product showed infrared absorption bands corresponding to free and hydrogen-bonded amide N–H, and carbonyl bands, including one at 1831 cm.$^{-1}$ typical of five-membered lactones, *e.g.*, oxazolones [11] and oxazolid-2 : 4-diones,[12] and we infer that the product $C_7H_{10}O_4N_2$ is 3 : 5-dimethyl-5-methylcarbamoyloxazolid-2 : 4-dione (VIII). Oxygen is necessary for formation of the oxazolid-2 : 4-dione (VIII) from methylamine 1 : 3 : 5-trimethylbarbiturate, and we presume that the barbituric acid becomes oxidised to the corresponding dialuric acid. Oxazolid-2 : 4-diones are readily formed from dialuric acids,[13] and some *NN'*-dialkyldialuric acids undergo ring-contraction when merely boiled with water, as in the formation of 5-benzyl-5-methylcarbamoyl-3-phenyloxazolid-2 : 4-dione, an analogue of (VIII) described by Aspelund.[14]



(VIII)



(IX)



(X)

The more direct approach to aminomethyl compounds by the Mannich reaction with diethoxymethane failed to yield the desired 1 : 3-dimethyl-*N*-methyl-5-*o*-nitroanilinomethylbarbituric acid (IX; R = NO_2). Aniline, diethoxymethane, and 1 : 3-dimethylbarbituric did not react, and aniline hydrochloride merely catalysed formation of the dibarbiturylmethane identical with the product obtained by hydrogenating the methine (VII). *N*-Methyl-*o*-nitroaniline hydrochloride, diethoxymethane, and 1 : 3-dimethylbarbituric acid gave a product, possibly (X), and some 4 : 4'-di(methylamino)-3 : 3'-dinitrophenylmethane, which was also obtained in the absence of 1 : 3-dimethylbarbituric acid.

Experimental

1% Palladised calcium carbonate was used as hydrogenation catalyst. Compounds were dissolved in 95% alcohol for determination of ultraviolet light absorption curves with a Uvispek spectrophotometer.

[11] Cornforth, " The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 730; Thompson, Brattain, Mandall, and Rasmussen, *ibid.*, p. 387.
[12] Clark-Lewis, *Chem. Rev.*, 1958, **58**, 91.
[13] *Idem*, *ibid.*, p. 68.
[14] Aspelund, *Acta Acad. Aboensis, Math. Phys.*, 1942, **13**, No. 1, p. 22; *Chem. Abs.*, 1945, **39**, 2053.

Diethyl o-Nitroanilinomethylenemalonate.—Ethyl ethoxymethylenemalonate [15] (2·16 g.) and *o*-nitroaniline (1·38 g.) were heated at 120° for 4 hr. and, after cooling, the solidified melt was washed with hexane to give diethyl *o*-nitroanilinomethylenemalonate (3·18 g., 100%), m. p. 100—107° raised by crystallisation from ethanol to m. p. 107—108° (lit.,[4] m. p. 101—102°) (Found: C, 54·6; H, 5·1; N, 8·9. Calc. for $C_{14}H_{16}O_6N_4$: C, 54·5; H, 5·2; N, 9·1%).

2 : 2′-*Dinitrodiphenylformamidine.*—*o*-Nitroaniline (2 mol.) was heated with ethyl orthoformate (1 mol.) at 160—180° for 1 hr. and the ethanol formed was allowed to escape through a short air-condenser; the residue was digested with ethanol and filtered hot from 2 : 2′-dinitrodiphenylformamidine, m. p. 161—163° (lit.,[6] m. p. 124—125°) (Found: C, 54·6; H, 3·4; N, 20·1. Calc. for $C_{13}H_{10}O_4N_4$: C, 54·6; H, 3·5; N, 19·6%). An attempt to prepare *o*-nitromethyl*iso*formanilide by the procedure used for the *meta*-compound [16] and for methyl*iso*formanilide [17] also gave the formamidine: a suspension of the silver salt (40 g.) of *o*-nitroformanilide in anhydrous ether (200 c.c.) was shaken with methyl iodide (15 c.c.) in the dark for 40 hr. and then filtered. The solid was washed with ether and, after the removal of ether from the combined filtrate and washings, distillation gave a few drops of methyl orthoformate, b. p. 40°/19 mm., a fraction (8·9 g.), b. p. 100—120°/0·1 mm., consisting mainly of *o*-nitroaniline, and a residue of 2 : 2′-dinitrodiphenylformamidine (12·1 g.), m. p. 158—161°.

1 : 3-*Dimethylbarbituric Acid.*—This acid, m. p. 122—123°, was prepared by a slight modification [18] of Biltz and Wittek's method.[19]

5-*Hydroxymethylene*-1 : 3-*dimethylbarbituric Acid and* (1 : 3-*Dimethylbarbitur*-5-*yl*)*methylene*-1 : 3-*dimethylbarbituric Acid* (VII).—1 : 3-Dimethylbarbituric acid (6·0 g.) was heated with ethyl orthoformate (25 c.c.) in an open flask at 120° for 30 min. before removal of the excess of ester under reduced pressure. The residue was extracted in a Soxhlet apparatus with hexane, and recrystallisation (Soxhlet) of the soluble material from hexane gave 5-*hydroxymethylene*-1 : 3-*dimethylbarbituric acid* (5·0 g., 71%) in flat, orange-yellow needles, m. p. 124° (Found: C, 45·9; H, 4·4; N, 15·2. $C_7H_8O_4N_2$ requires C, 45·7; H, 4·4; N, 15·2%). The hexane-insoluble residue (1·2 g.), m. p. 273°, which remained in the thimble, crystallised from benzene (Soxhlet) in yellow needles (0·95 g.), m. p. 276—277°, consisting of the methine [20] (VII) [Found: C, 48·7; H, 4·5; N, 17·5%; *M* (Rast), 270. Calc. for $C_{13}H_{14}O_6N_4$: C, 48·5; H, 4·4; N, 17·4%; *M*, 322]. The methine was indistinguishable from a sample prepared from 1 : 3-dimethylbarbituric acid and formic acid,[20] and it was readily obtained by heating equimolecular quantities of 1 : 3-dimethylbarbituric acid and its 5-hydroxymethylene derivative at 120° for a few minutes.

5-*Aminomethylene*-1 : 3-*dimethylbarbituric Acid* (V; R = H).—1 : 3-Dimethylbarbituric acid (6 g.) and formamide (20 c.c.) were heated at 120° for 3 hr. and the product was collected and washed with ethanol. 5-*Aminomethylene*-1 : 3-*dimethylbarbituric acid* (4·9 g., 69%) crystallised from water in needles, m. p. 228—229° (Found: C, 46·2; H, 5·2; N, 22·9. $C_7H_9O_3N_3$ requires C, 45·9; H, 5·0; N, 22·9%).

1 : 3-*Dimethyl*-5-*methylaminomethylenebarbituric Acid* (V; R = Me).—1 : 3-Dimethylbarbituric acid (5 g.) and *N*-methylformamide [21] (10 c.c.) were heated at 150° for 1½ hr. The product crystallised from the hot solution, and was collected and washed with ethanol. 1 : 3-*Dimethyl*-5-*methylaminomethylenebarbituric acid* crystallised from water in needles (5·0 g., 79%), m. p. 230—231° (Found: C, 48·8; H, 5·4; N, 21·3. $C_8H_{11}O_3N_3$ requires C, 48·7; H, 5·6; N, 21·3%). It was moderately soluble in chloroform and only slightly soluble in ethanol, benzene, ethyl acetate, and water.

5-*Anilinomethylene*-1 : 3-*dimethylbarbituric Acid* (IV; R = H).—(*a*) A solution of 1 : 3-dimethylbarbituric acid (0·78 g.) in boiling ethanol (20 c.c.) was added to aniline (0·46 g.) and ethyl orthoformate (1 c.c.) in boiling ethanol (10 c.c.). Crystals appeared within 2 min. but boiling was maintained for 5 min. and the *product* (1·2 g., 94%), m. p. 198—199°, was collected from the cold solution. It crystallised from ethanol in needles, m. p. 199—200° (Found: N, 15·8. $C_{13}H_{13}O_3N_3$ requires N, 16·2%), sparingly soluble in ethanol, but dissolving readily in chloroform and in ethyl acetate, and under ultraviolet light showing blue fluorescence. It had

[15] *Org. Synth.*, 1948, **28**, 60; Duffin and Kendall, *J.*, 1948, 893.
[16] Comstock and Wheeler, *Amer. Chem. J.*, 1891, **13**, 518; *J.*, 1892, **62**, Ai, 705.
[17] Farrow and Ingold, *J.*, 1924, **125**, 2546.
[18] Clark-Lewis and Thompson, *J.*, 1959, 1628.
[19] Biltz and Wittek, *Ber.*, 1921, **54**, 1037.
[20] Gysling and Schwarzenbach, *Helv. Chim. Acta*, 1949, **32**, 1484.
[21] Mitchell and Reid, *J. Amer. Chem. Soc.*, 1931, **53**, 1879; D'Alelio and Reid, *ibid.*, 1937, **59**, 109.

$\lambda_{max.}$ 223—225 (ε 20,400) and 342 (ε 30,600), $\lambda_{min.}$ 266—267 mμ (ε 1100). Anilinomethylene-dimethylbarbituric acid was also obtained readily from *NN'*-diphenylformamidine and dimethylbarbituric acid in boiling ethanol, and from 5-hydroxymethylene-1 : 3-dimethylbarbituric acid and aniline in cold ethanol, and by mixing cold ethanolic solutions of methyl *N*-phenylformimidate [17] and 1 : 3-dimethylbarbituric acid.

(*b*) 5-Aminomethylene-1 : 3-dimethylbarbituric acid (0·5 g.) was heated with aniline (2 g.) at 170° for 30 min.; ammonia was evolved and crystals separated. 5-Anilinomethylene-1 : 3-dimethylbarbituric acid (0·65 g., 92%), needles, m. p. 198—199°, was collected and washed with ethanol.

(*c*) 5-Anilinomethylene-1 : 3-dimethylbarbituric acid (0·74 g., 89%), m. p. 196—198°, was obtained by heating formanilide (2 g.) and 1 : 3-dimethylbarbituric acid (0·5 g.) at 180° for 1½ hr. and then washing the solid product with ethanol.

1 : 3-*Dimethyl*-5-N-*methylanilinomethylenebarbituric Acid* (VI; R = H).—*N*-Methylaniline (0·6 g.), ethyl orthoformate (1·0 c.c.), and 1 : 3-dimethylbarbituric acid (0·78 g.) were warmed gently until a homogeneous melt was obtained, and then at 100° for several minutes. A vigorous reaction ensued and the solid *product* (0·85 g., 56%) was collected and washed with ethanol. It was obtained as needles, m. p. 198—199° (from ethanol; yellow solution) (Found: C, 61·2; H, 5·5; N, 15·1. $C_{14}H_{15}O_3N_3$ requires C, 61·5; H, 5·5; N, 15·4%). The acid was also readily obtained from 5-hydroxymethylene-1 : 3-dimethylbarbituric acid and methylaniline in cold ethanol, but methylaniline did not exchange with aminomethylenedimethylbarbituric acid. Heating 1 : 3-dimethylbarbituric acid with *N*-methylformanilide under the conditions described above for formanilide did not yield the *N*-methylanilino-derivative.

1 : 3-*Dimethyl*-5-o-*nitroanilinomethylenebarbituric Acid* (IV; R = NO_2).—(*a*) An immediate reaction occurred when 1 : 3-dimethylbarbituric acid (1·6 g.) was added to a suspension of 2 : 2'-dinitrodiphenylformamidine (3·0 g.) in boiling ethanol (250 c.c.), and the product crystallised; boiling was continued for 30 min. and filtration of the cold suspension then gave 1 : 3-*dimethyl*-5-o-*nitroanilinomethylenebarbituric acid*, needles (2·8 g., 90%), m. p. 262—263° (from chloroform–ethanol) (Found: C, 51·4; H, 3·9; N, 18·0. $C_{13}H_{12}O_5N_4$ requires C, 51·3; H, 4·0; N, 18·4%), $\lambda_{max.}$ 275 (ε 10,100), 321—323 (ε 13,800), and 374 mμ (ε 15,800), $\lambda_{min.}$ 252 (ε 8100), 295 (ε 6700), and 341 mμ (ε 10,200), with inflexions at 308—312 (ε 10,300—10,600) and 326—330 mμ (ε 13,700—13,600). The compound is insoluble in water, slightly soluble in ethanol, more soluble in ethyl acetate and readily so in chloroform. 1 : 3-Dimethyl-*o*-nitroanilinomethylenebarbituric acid (1·0 g., 100%) was recovered after it had been heated with methyl iodide (10 c.c.) and dimethylformamide (20 c.c.) in a sealed tube at 100° for 30 hr. It was recovered (0·8 g., 100%) with m. p. 263—265° after being heated with methyl toluene-*p*-sulphonate (5 c.c.) at 170° for 3 hr.

(*b*) *o*-Nitroaniline (0·7 g.), ethyl orthoformate (1·5 c.c.), and 1 : 3-dimethylbarbituric acid (0·8 g.) were heated carefully until a homogeneous melt was obtained, and thereafter at 120° for 2 min. The product (1·34 g., 93%), m. p. 261—263°, was collected with the aid of ethanol.

(*c*) 5-Aminomethylene-1 : 3-dimethylbarbituric acid (0·5 g.) was heated for 1 hr. at 180° with *o*-nitroaniline (2 g.), and the product, after being washed with ethanol, consisted of 1 : 3-dimethyl-5-*o*-nitroanilinomethylenebarbituric acid (0·14 g., 24%), yellow needles, m. p. 257—258°.

(*d*) A mixture of 1 : 3-dimethylbarbituric acid (0·5 g.) and *o*-nitroformanilide (2·5 g.) was heated at 175° for 95 min. and then treated with boiling ethanol (100 c.c.), which left a residue of sparingly soluble 1 : 3-dimethyl-5-*o*-nitroanilinomethylenebarbituric acid (0·76 g., 78%), m. p. 259—262°.

5-o-*Aminoanilinomethylene*-1 : 3-*dimethylbarbituric Acid* (IV; R = NH_2) *and* o-*Phenylene-di*-(5-*aminomethylene*-1 : 3-*dimethylbarbituric Acid*).—(*a*) 1 : 3-Dimethyl-5-*o*-nitroanilinomethylenebarbituric acid in dimethylformamide was reduced with hydrogen at room temperature and pressure over 1% palladised calcium carbonate. The catalyst was removed, then the solvent was distilled under reduced pressure. The residue was extracted with boiling benzene and gave 5-o-*aminoanilinomethylene*-1 : 3-*dimethylbarbituric acid*, yellow needles, m. p. 200—201° (from benzene) (Found: C, 57·1; H, 5·1; N, 20·7. $C_{13}H_{14}O_3N_4$ requires C, 56·9; H, 5·1; N, 20·4%), $\lambda_{max.}$ 310 (ε 10,800) and 364 (ε 16,500); $\lambda_{min.}$ 272—278 (ε 4500) and 320 mμ (ε 10,200); inflexions at 224—232 (ε 17,700—17,400) and 354—358 mμ (ε 16,200—16,300).

(*b*) A mixture of *o*-phenylenediamine (0·5 g.), ethyl orthoformate (1 c.c.), 1 : 3-dimethylbarbituric acid (0·8 g.), and ethanol (20 c.c.) was boiled for 5 min. and the product was collected

by filtration of the cold solution. Extraction of the product (0·5 g.) with hot ethanol left an insoluble residue (0·25 g.), and the cold solution deposited 5-*o*-aminoanilinomethylene-1 : 3-dimethylbarbituric acid (0·18 g.) in yellow needles, m. p. and mixed m. p. 200°. The ethanol-insoluble material (0·25 g.) consisted of o-*phenylenedi*-(5-*aminomethylene*-1 : 3-*dimethylbarbituric acid*) which crystallised from chloroform in faintly yellow needles, m. p. 340° (Found: C, 54·2; H, 4·3; N, 18·5. $C_{20}H_{20}O_6N_6$ requires C, 54·5; H, 4·6; N, 19·1%). This compound was obtained in better yield when ethyl orthoformate (2 mol.), 1 : 3-dimethylbarbituric acid (2 mol.), and *o*-phenylenediamine (1 mol.) were heated, and was also prepared from 5-*o*-aminoanilinomethylene-1 : 3-dimethylbarbituric acid, ethyl orthoformate, and 1 : 3-dimethylbarbituric acid. The *o*-phenylenediamine bis-product is very sparingly soluble in organic solvents; a chloroform solution showed a blue fluorescence and the solid possessed a strong yellow fluorescence under ultraviolet light. Light absorption maxima in chloroform were at 314 (ε 24,100) and 362 mμ (ε 19,700), and minima at 271 (ε 2700) and 335—339 mμ (ε 16,600).

o-*Acetamidoanilinomethylene*-1 : 3-*dimethylbarbituric Acid* (IV; R = NHAc).—Ethyl orthoformate (0·8 c.c.) in boiling ethanol (20 c.c.) was added to a boiling solution of *o*-aminoacetanilide [22] (0·6 g.) and 1 : 3-dimethylbarbituric acid (0·6 g.). Heating was continued for 5 min. and the solution was filtered when cold from the crystalline product; the filtrate was boiled again after addition of further orthoformate (0·8 c.c.). Crystallisation of the combined product (0·56 g., 46%) from water gave 5-o-*acetamidoanilinomethylene*-1 : 3-*dimethylbarbituric acid* as needles, m. p. 251° (decomp.) when heated slowly and m. p. 257° (decomp.) when heated more rapidly (Found: C, 57·1; H, 5·0; N, 17·4. $C_{15}H_{16}O_4N_4$ requires C, 57·0; H, 5·1; N, 17·7%), $\lambda_{max.}$ 222 (ε 23,100) and 343—344 mμ (ε 26,800); $\lambda_{min.}$ 271 mμ (ε 1250). The solid exhibited a blue fluorescence under ultraviolet light.

1 : 3 : 5-*Trimethylbarbituric Acid*.—This was prepared from diethyl methylmalonate [23] and *NN'*-dimethylurea by condensation with sodium ethoxide.[24] It crystallised from benzene in solvated crystals which effloresced in air, and it was readily purified to m. p. 89·5—90° by sublimation (lit.,[24] m. p. 89·5—90°). 1 : 3 : 5-Trimethylbarbituric acid (25%) was also obtained from methylmalonic acid by condensation with *NN'*-dimethylurea and acetic anhydride essentially as described for 1 : 3-dimethylbarbituric acid.[18]

Hydrogenation of 5-*Aminomethylene*-1 : 3-*dimethylbarbituric Acid*.—5-Aminomethylene-1 : 3-dimethylbarbituric acid (2 g.) in 70% aqueous ethanol (100 c.c.) was hydrogenated at 70°/35 atm. for 20 hr. The filtrate from the catalyst was treated with a few drops of dilute hydrochloric acid and the ethanol removed by distillation. The acidified aqueous solution was extracted with chloroform, and evaporation of the dried ($MgSO_4$) extract left 1 : 3 : 5-trimethylbarbituric acid (1·7 g., 91%) which crystallised from benzene–hexane in needles (1·4 g., 77%), m. p. and mixed m. p. 88—89°. The solution after hydrogenation contained ammonium 1 : 3 : 5-trimethylbarbiturate, which was identified by comparison with an authentic specimen of the salt which crystallised in needles, m. p. 240°, when methanolic solutions of ammonia and the acid were mixed.

Hydrogenation of 1 : 3-*Dimethyl*-5-*methylaminomethylenebarbituric Acid*.—The methylamino-compound (2·0 g.) in ethanol (100 c.c.) was hydrogenated at 70—90°/35 atm. for 15 hr. The hot solution was filtered and the ethanol was distilled; evaporation of the distillate after addition of a few drops of hydrochloric acid left a residue of methylamine hydrochloride, m. p. and mixed m. p. 220—225°. The distillation residue was boiled with benzene and the solution was filtered from the insoluble *methylamine* 1 : 3 : 5-*trimethylbarbiturate* (1·5 g.), m. p. 255° (short sealed capillary) or 224° (decomp.; open capillary) (Found, after sublimation at 180°/20 mm.: C, 48·2; H, 7·5; N, 20·2. $C_8H_{15}O_3N_3$ requires C, 47·8; H, 7·5; N, 20·9%). The salt (1·5 g.) was dissolved in water (70 c.c.) containing a few drops of hydrochloric acid, and the solution was extracted with ether. The ether residue (1·0 g.) consisted of 1 : 3 : 5-trimethylbarbituric acid which crystallised from benzene–hexane in large needles (0·84 g.), m. p. and mixed m. p. 88—89° after loss of solvate benzene. The methylamine salt was regenerated by evaporating to dryness a solution of the barbituric acid in methanolic methylamine; it was identical (m. p. and infrared absorption) with the salt isolated from the hydrogenation; its isolation from the hydrogenation products was complicated initially by its slow conversion into the oxazolid-2 : 4-dione described below.

[22] Leuchs, *Ber.*, 1907, **40**, 1084.
[23] *Org. Synth.*, Coll. Vol. II, p. 279.
[24] Cope, Heyl, Peck, Eide, and Arroyo, *J. Amer. Chem. Soc.*, 1941, **63**, 356.

3 : 5-*Dimethyl*-5-*methylcarbamoyloxazolid*-2 : 4-*dione* (VIII).—A slow stream of nitrogen was passed through a boiling solution of methylamine 1 : 3 : 5-trimethylbarbiturate (0·5 g.) in ethanol (20 c.c.) and then into aqueous boric acid containing Methyl Red; the indicator did not change during 1½ hr. Oxygen was then passed through the boiling solution, and an alkaline reaction of the indicator was observed after 10 min., and in 7 hr. evolution of methylamine (titration equivalent 17·5 c.c. of 0·1N-HCl) had reached 70% of the calculated figure. Evaporation of the ethanol and extraction of the residue with carbon tetrachloride left recovered methylamine salt (0·15 g., 30%), and from the concentrated carbon tetrachloride solution (10 c.c.) 3 : 5-*dimethyl*-5-*methylcarbamoyloxazolid*-2 : 4-*dione* (0·1 g., 31%) crystallised in needles, m. p. 115—116° raised to m. p. 117° by recrystallisation [Found: C, 45·2; H, 5·8; N, 14·6%; *M* (Rast), 189. $C_7H_{10}O_4N_2$ requires C, 45·2; H, 5·4; N, 15·1%; *M*, 186·2], $\nu_{max.}$ (in CCl_4; CaF_2 prism) were observed for free and hydrogen bonded amide N–H at 3450 and 3400 cm.$^{-1}$ and for carbonyl (±1 cm.$^{-1}$) at 1831, 1762, 1740, and 1705 cm.$^{-1}$.

Hydrogenation of 1 : 3-*Dimethyl*-5-N-*methylanilinomethylenebarbituric Acid*.—(*a*) Methylaniline (0·17 g., 44%) was isolated after hydrogenation of the *N*-methylanilino-compound (1 g.) in ethanol at 60°/1 atm. Hydrogen (2 mol.) was absorbed rapidly at constant rate.

(*b*) 1 : 3-Dimethyl-5-*N*-methylanilinomethylenebarbituric acid (2 g.) in ethanol (100 c.c.) was hydrogenated at 70°/35 atm. for 15 hr. and the cooled suspension was filtered from the catalyst. Ethanol was distilled from the filtrate after addition of a few drops of hydrochloric acid, and an aqueous solution of the residue was extracted with ether, to give 1 : 3 : 5-trimethylbarbituric acid (0·96 g., 77%) which crystallised from benzene–hexane in needles (0·6 g., 48%), m. p. 86—89°. The bases (0·3 g.) were extracted with ether, dried ($MgSO_4$), and distilled, and analysis by gas chromatography on a silicone column showed *N*-methyl*cyclo*hexylamine and *N*-methylaniline in ratio 5 : 1 (from the area under the curve). Addition of a benzene solution of picric acid to a solution of the bases in benzene gave methyl*cyclo*hexylamine picrate, needles (0·5 g.), m. p. 168—170° (lit.,[25] 170°).

Hydrogenation of 5-*Anilinomethylene*-1 : 3-*dimethylbarbituric Acid*.—The acid (2 g.) in ethanol (100 c.c.) was hydrogenated for 15 hr. at 70—80°/35 atm. The catalyst was removed and the ethanolic filtrate was evaporated after addition of a few drops of hydrochloric acid. An aqueous solution of the residue was extracted with ether to remove acidic products (A) (see below), and the aqueous layer was then basified with sodium hydroxide and again extracted with ether. Evaporation of the dried ($MgSO_4$) extract left a mixture of bases (0·5 g.) with wide b. p. range found by gas chromatography on a silicone column to contain *cyclo*hexylamine, aniline, and di*cyclo*hexylamine in approximately equal quantities. The bases were identified by retention times, and the identity of aniline was confirmed by diazotisation and coupling with 2-naphthol, and of di*cyclo*hexylamine by the isolation of its hydrochloride, m. p. 338° [lit.,[26] m. p. 344° (corr.)].

Evaporation of the ethereal solution of the acidic products (A) left a residue of 1 : 3 : 5-trimethylbarbituric acid (0·5—0·7 g.), m. p. 81—84°, usually contaminated with a few crystals of 1 : 3 : 5-trimethyldialuric acid. These data are representative for four experiments, but in two others similarly conducted the entire acidic product extracted by ether proved to be 1 : 3 : 5-*trimethyldialuric acid*, which crystallised from benzene in needles or prisms without solvent of crystallisation, which distinguishes the dialuric acid from the barbituric acid. When heated *in vacuo* at 65° for several hours, the needle-shaped crystals changed into prisms, m. p. 107° (Found: C, 45·6; H, 5·65; N, 15·1. $C_7H_{10}O_4N_2$ requires C, 45·2; H, 5·4; N, 15·1%). In Nujol mull the dialuric acid had a band at 2·87 μ while 1 : 3-dimethyldialuric acid and 5-chloromethyl-1 : 3-dimethyldialuric acid [27] had bands at 2·82 and 2·84 μ. An alcoholic solution of the 1 : 3 : 5-trimethyldialuric acid did not take up bromine at room temperature; when boiled with methanolic methylamine the dialuric acid gave 3 : 5-dimethyl-5-methylcarbamoyloxazolid-2 : 4-dione (38%), m. p. 116·5—117° (from carbon tetrachloride).

Di-(1 : 3-*dimethylbarbitur*-5-*yl*)*methane*.—(*a*) Aniline hydrochloride (3·25 g.) and 1 : 3-dimethylbarbituric acid (3·9 g.) were melted together and then heated at 140° during the dropwise addition of diethoxymethane (3·2 c.c.). A white solid separated immediately and after a further 5 minutes' heating the residue was cooled and triturated with warm water. The water-insoluble material (3 g.), which crystallised from benzene in prisms, and from ethanol in needles,

[25] Skita and Rolfes, *Ber.*, 1920, **53**, 1250.
[26] Beilstein's " Handbuch der Organischen Chemie," Vol. XII, E II, p. 7.
[27] Biltz and Paetzold, *Annalen*, 1923, **433**, 74; Arndt, Eistert, and Ender, *Ber.*, 1929, **62**, 44.

consisted of *di*-(1 : 3-*dimethylbarbitur*-5-*yl*)*methane*, m. p. 167—168° (Found: C, 48·6; H, 5·1; N, 17·0; O, 29·3. $C_{13}H_{16}O_6N_4$ requires C, 48·2; H, 5·0; N, 17·3; O, 29·6%).

(*b*) The methine (VII) (0·5 g.) in ethanol (100 c.c.) containing 1 drop of concentrated hydrochloric acid was hydrogenated over Adams catalyst at 50°/1 atm. until the solution was colourless (5—6 hr.). The catalyst was removed and after concentration of the filtrate to 40 c.c. the dibarbiturylmethane crystallised in needles (0·27 g., 54%), m. p. 163—168° raised to m. p. and mixed m. p. 167—168° by recrystallisation from benzene.

4 : 4′-*Di*(*methylamino*)-3 : 3′-*dinitrodiphenylmethane*.—*N*-Methyl-*o*-nitroaniline in anhydrous ether was converted by dry hydrogen chloride into the sparingly soluble colourless hydrochloride, m. p. 125—126° (decomp., with loss of HCl), which was dried *in vacuo* over sulphuric acid. The hydrochloride (3 g.) and diethoxymethane (7 c.c.) were heated in an oil-bath at 115°, and further diethoxymethane (2 c.c.) was added after 5 hr. The mixture was heated for 8½ hr. (total), and ethanol and the excess of diethoxymethane were then removed under reduced pressure. A benzene solution of the crystalline residue was washed with dilute aqueous sodium hydroxide and then chromatographed on alumina: *N*-methyl-*o*-nitroaniline (0·94 g.) was not retained, and 4 : 4′-*di*(*methylamino*)-3 : 3′-*dinitrodiphenylmethane* (0·8 g.) was eluted with benzene more slowly. Crystallisation from benzene (crystals retain benzene) and then ethanol gave dark red needles, m. p. 191—192° [Found: C, 56·9; H, 5·3; N, 17·3%; *M* (Rast), 342. $C_{15}H_{16}O_4N_4$ requires C, 57·0; H, 5·1; N, 17·7%; *M*, 316·4].

Interaction of Diethoxymethane, N-*Methyl*-o-*nitroaniline*, *and* 1 : 3-*Dimethylbarbituric Acid*.—*N*-Methyl-*o*-nitroaniline hydrochloride (4·5 g.), 1 : 3-dimethylbarbituric acid (3·9 g., 1·05 equiv.), and diethoxymethane (5 c.c.) were heated at 110° (bath) under reflux for 1½ hr. The excess of liquids was removed by distillation, and the residue warmed and stirred with dilute aqueous ammonia (500 c.c.). Insoluble material (2 g.) was collected and crystallisation from benzene gave 4 : 4′-di(methylamino)-3 : 3′-dinitrodiphenylmethane (0·84 g.), m. p. and mixed m. p. 186—189°. The dark red ammoniacal filtrate was extracted with chloroform, and the extract dried ($MgSO_4$) and evaporated; chromatographing the residue on alumina then gave recovered *N*-methyl-*o*-nitroaniline (0·5 g.). The ammoniacal solution was then acidified and again extracted with chloroform, and evaporation of the dried ($MgSO_4$) extract left a residue which was digested with boiling ethanol. The sparingly soluble product was collected as orange prisms (3·24 g.), m. p. 203—210° raised to m. p. 209—210° by several crystallisations from aqueous dimethylformamide (Found: C, 51·6, 51·4; H, 5·1, 5·0; N, 16·9, 17·0. $C_{21}H_{24}O_8N_6$ requires C, 51·6; H, 5·0; N, 17·2%). The *product* (X?) apparently contains two 1 : 3-dimethylbarbituric acid moieties to each *N*-methyl-*o*-nitroaniline, as indicated by elementary analysis and confirmed by comparison of the extinction coefficients of the product and *N*-methyl-*o*-nitroaniline in the long-wave band at 425—435 mμ (Found: *M*, 474. $C_{21}H_{24}O_8N_6$ requires *M*, 488·4). A Nujol mull of the product showed an absorption band at the same position (2·94 μ) as *N*-methyl-*o*-nitroaniline.

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