Some Derivatives of Tetra- and Hexa-hydro-4 : 6-dioxopyrimidine.

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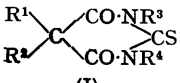
Hydrogenolysis of 5 : 5-di-, and 1 : 3 : 5- and 1 : 5 : 5-tri-, and 1 : 3 : 5 : 5-tetra-substituted 2-thiobarbituric acids in alcohol gives, according to the conditions, hexahydro-4 : 6-dioxopyrimidines or the corresponding 2-alkoxy-derivatives. The transformations of these substances and further methods for their synthesis are described.

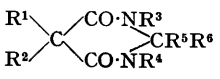
Carrington, Vasey, and Waring (*J.*, 1953, 3105) prepared a number of di- and tetra-hydro-oxoglyoxalines by hydrogenolysis of the corresponding monothiohydantoin derivatives with Raney nickel. A related pyrimidine derivative, 5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine ("Mysoline," primidone) (II; R^1 = Ph, R^2 = Et, R^3 = R^4 = R^5 = R^6 = H) is an effective anticonvulsant, both in the control of experimentally induced convulsions in laboratory animals (Bogue and Carrington, *Brit. J. Pharmacol.*, 1953, **8**, 230) and in the treatment of epilepsy (Handley and Stewart, *Lancet*, 1952, **242**, 742). The present paper describes methods for the preparation of pyrimidine derivatives of this type, and considers some of their reactions. Only those compounds are recorded here which are important in illustrating the chemistry of this group of substances. Others are described in B.P. 666,027 and in pending Applications.

The synthetical methods fall into two classes. In the first class, reduction of barbituric acids or their 2-thio-derivatives leads to the hexahydrodioxopyrimidines themselves, or, in some cases where alcohols are used as solvents, to 2-alkoxy-derivatives which are converted on further reduction into the hexahydrodioxopyrimidines. In the second class are methods in which malonic acid derivatives react with carboxylic acids or their derivatives; a special case is the reaction of *C*-disubstituted malonodiamides with formic acid or formamide, leading directly to the hexahydrodioxopyrimidines; the other methods of this class, in which various malonic acid derivatives (chlorides, esters, amides, etc.) react with amidines, esters, acid chlorides, etc., vary widely in their usefulness, but they all lead first to the tetrahydrodioxopyrimidines, or to the related 2-alkoxy-compounds, from which the hexahydro-compounds are obtained by reduction; and, in some cases, they are adaptable to the synthesis of 2-alkyl derivatives.

Only one other member of this series (II; R^1 = R^2 = Et, R^3 = R^4 = R^5 = R^6 = H) has been described previously. It was obtained by Tafel and Thompson (*Ber.*, 1907, **40**, 4491) by electrolytic reduction of barbitone and by Einhorn and Diesbach (*ibid.*, p. 4902; *Annalen*, 1908, **359**, 171) by reduction of 5 : 5-diethyl-2-thiobarbituric acid with sodium amalgam. Primidone was first prepared by hydrogenolysis of 5-ethyl-5-phenyl-2-thiobarbituric acid with the W5 Raney nickel of Adkins and Billica (*J. Amer. Chem. Soc.*, 1948, **70**, 695). Sodium amalgam, or zinc and formic acid, could also be used, and electrolytic reduction of phenobarbitone itself gave the same product. Hydrogenolysis of a 5 : 5-disubstituted 2-thiobarbituric acid is a satisfactory general method for the preparation of hexahydro-4 : 6-dioxopyrimidines (II; R^5 = R^6 = H), including those in which R^3 and/or R^4 are alkyl. In contrast, hydrogenolysis of 5-phenyl-2-thiobarbituric acid (I; R^1 = Ph, R^2 = R^3 = R^4 = H) gave only 4 : 6-dihydroxy-5-phenylpyrimidine (Hull, *J.*, 1951, 2214), while that of the 1 : 3-dimethyl-5-phenyl analogue (I; R^1 = Ph, R^3 = R^4 = Me, R^2 = H) proceeded normally to give the hexahydropyrimidine (II; R^1 = Ph, R^3 = R^4 = Me, R^2 = R^5 = R^6 = H), presumably because in the former case the intermediate tetrahydro-compound is a tautomer of the aromatic dihydroxy-compound, which resists further reduction, while in the latter an aromatic structure is impossible. The only other restrictions on the use of the hydrogenolysis procedure appear to be that the substituents in the thiobarbituric acid must not be sensitive to reduction by Raney nickel; *e.g.*, hydrogenolysis of the *cyclo*hex-1-enyl compound (I; R^1 = C_6H_9, R^2 = Et, R^3 = R^4 = H) gave, as main product, the *cyclo*hexyl compound (II; R^1 = C_6H_{11}, R^2 = Et, R^3 = R^4 = R^5 = R^6 = H); and under similar conditions primidone was obtained from the *o*-, *m*-, or *p*-chlorophenyl compound (I; R^1 = C_6H_4Cl, R^2 = Et, R^3 = R^4 = H).

When the hydrogenolysis was effected in methanol or ethanol solution with W1 Raney nickel (Adkins and Pavlic, *ibid.*, 1947, **69**, 3039), which contains less adsorbed hydrogen than the W5 type, or with Raney cobalt, prepared as W5 nickel, the products were 2-alkoxyhexahydro-4 : 6-dioxopyrimidines, *e.g.*, (I; R^1 = Ph, R^2 = Et, $R^3 = R^4$ = H) gave (II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = R^5$ = H, R^6 = OMe or OEt); in *n*- or *iso*-propanol the hexahydropyrimidines (II; $R^5 = R^6$ = H) were obtained. Similarly 5-ethyl-1 : 3-dimethyl-5-phenyl-2-thiobarbituric acid (I; R^1 = Ph, R^2 = Et, $R^3 = R^4$ = Me) gave the 2-methoxy-compound (II) on hydrogenolysis in methanol. By contrast, hydrogenolysis of 5-ethyltetrahydro-2-methoxy(or methylthio)-4 : 6-dioxo-5-phenylpyrimidine (IV; X = O or S) with W1 Raney nickel or Raney cobalt gave primidone. The assignment of the alkoxyhexahydropyrimidine structure to substances such as (II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = R^5$ = H) is based, first, on their reaction with formaldehyde to give bishydroxymethyl derivatives (*e.g.*: II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = CH_2{\cdot}OH$, R^5 = H, R^6 = OMe) and, secondly, on the existence of similar alkoxy-compounds when $R^3 = R^4$ = alkyl, the alternative alcoholate structure being then impossible.


(I)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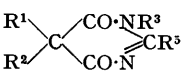
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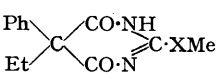
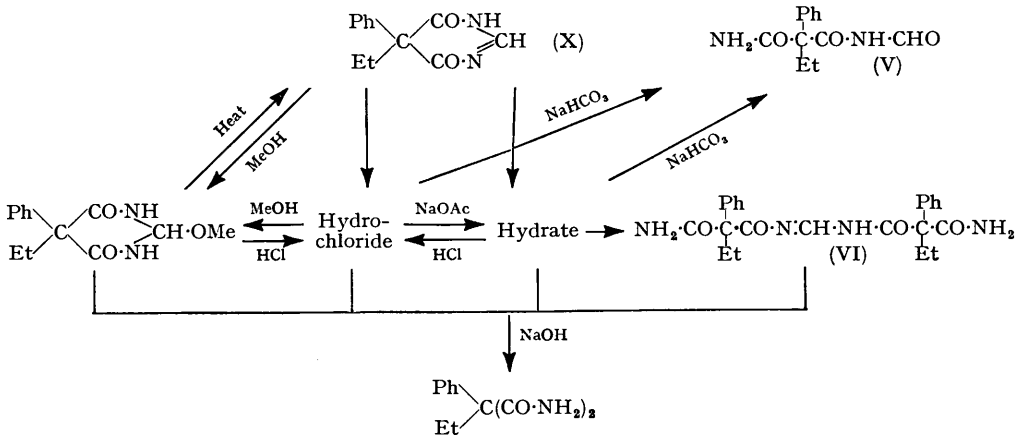

(IV)

The main transformations of the 2-alkoxyhexahydro-4 : 6-dioxopyrimidines are well exemplified by the behaviour of (II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = R^5$ = H, R^6 = OMe). It was unchanged on crystallisation from any alcoholic solvent examined but lost methanol at 180° in a high vacuum to give the tetrahydropyrimidine (III; R^1 = Ph, R^2 = Et, $R^3 = R^5$ = H) which, although it could not be purified satisfactorily, regenerated the starting material on crystallisation from methanol and, with other alcohols gave the corresponding 2-alkoxy-derivatives. When heated above 200° the 2-alkoxy-derivatives gave insoluble, infusible polymers. With ethereal hydrogen chloride the 2-alkoxy-derivatives gave the hydrochloride of the tetrahydro-compound, which was converted into the hydrate of the latter in sodium acetate solution, but into *C*-ethyl-*N*-formyl-*C*-phenylmalonodiamide (V) in sodium hydrogen carbonate solution. With alcohols both the hydrate and the hydrochloride gave the 2-alkoxy-derivatives. The hydrate with boiling water gave *NN'*-di-(α-carbamoyl-α-phenylbutyryl)formamidine (VI), converted by further heating into *C*-ethyl-*C*-phenylmalonodiamide.

Compounds of type (II) in which R^5 = alkyl, and R^6 = OAlkyl, are somewhat less stable than when R^5 = H; it was also not possible to obtain derivatives in which R^6 was other than OMe, or occasionally OEt. 5-Ethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine (II; R^1 = Ph, R^2 = Et, $R^3 = R^4 = R^5$ = H, R^6 = OMe), and the corresponding tetrahydro-compound (III; R^1 = Ph, R^2 = Et, $R^3 = R^5$ = H) and its hydrochloride and hydrate, as well as *C*-ethyl-*N*-formyl-*C*-phenylmalonodiamide (V) and the corresponding bis-compound (VI), gave *C*-ethyl-*C*-phenylmalondiamide with cold dilute sodium hydroxide solution.

For the second class of syntheses, the most promising method would formally be the condensation of a derivative of malonodiamide with formaldehyde or of a malonyl chloride or malonic ester with methylenediamine. Einhorn (*Annalen*, 1905, **343**, 207) reported a number of unsuccessful attempts to prepare the hexahydro-compound (II; $R^1 = R^2$ = Et, $R^3 = R^4 = R^5 = R^6$ = H) by reaction of diethylmalonyl chloride with methylenediamine and of *CC*-diethylmalonodiamide with formaldehyde. Many attempts to synthesise primidone on these lines were unsuccessful. *C*-Ethyl-*C*-phenylmalondiamide and formaldehyde gave smoothly a bishydroxymethyl compound but attempts to convert this into a mono(hydroxymethyl) derivative directly, or to effect cyclisation, were fruitless. However *C*-ethyl-*C*-phenylmalondiamide with boiling formamide or with formic acid at a high temperature gave primidone smoothly; and this reaction was generally applicable to *CC*-disubstituted malonodiamides and their *N*-monosubstituted derivatives. From *C*-ethyl-*C*-phenyl-*N*-*iso*propylmalonodiamide and formamide the only product was primidone. A similar, though usually incomplete, amide interchange was always observed

with derivatives of *C*-methyl-*C*-phenylmalonodiamide. Heating *CC*-diphenylmalonodiamide with formamide caused gross decomposition if the reaction period were prolonged; the monosubstituted malonodiamide (IX; R^1 = Ph, R^2 = H) was converted into phenylacetamide. There is little doubt that the cyclisation reaction proceeds *via* the *N*-formylmalonodiamide which then cyclises, with loss of water, to the tetrahydropyrimidine, which is, in turn, reduced by the excess of formic acid or formamide. The intermediate compounds have never been isolated from the reaction mixture, apparently because the last



stage occurs at a lower temperature than the earlier ones. Thus, 5-ethyltetrahydro-4 : 6-dioxo-5-phenylpyrimidine is rapidly reduced by boiling formic acid, which hydrolyses *C*-ethyl-*N*-formyl-*C*-phenylmalonodiamide to the parent diamide. The requisite malonodiamides were prepared by treating the malonyl chlorides with ammonia, or more conveniently by hydrolysis of the corresponding cyanoacetamides with concentrated sulphuric acid. The latter method was less satisfactory with α-cyano-α-phenyl-*N*-*iso*propylbutyramide (VII; R^1 = Ph, R^2 = Et, R^3 = Pr^i), from which *C*-ethyl-*C*-phenylmalonodiamide and *C*-ethyl-*C*-phenyl-*NN'*-di*iso*propylmalonodiamide were obtained in addition to a small amount of the expected product; a possible explanation is that propylene is eliminated and then, in the form of *iso*propyl hydrogen sulphate, reacts with the nitrile (cf. Benson and Ritter, *J. Amer. Chem. Soc.*, 1949, **71**, 4128) The method failed with (VII; R^1 = Ph, R^2 = Et, R^3 = CH_2Ph, or CH_2·CH·CH_2), only sulphonated water-soluble products being obtained.

$R^1R^2C(CN)\cdot CO\cdot NHR^3$ (VII) Me·NH·CO·CPhEt·CO·N:CH·NH·CO·CPhEt·CO·NHMe (VIII) $R^1R^2C(CO\cdot NH_2)_2$ (IX)

All the other methods of synthesis of hexahydro-4 : 6-dioxopyrimidines which have been employed involve the intermediate isolation of a tetrahydro-4 : 6-dioxopyrimidine, or the corresponding 2-alkoxyhexahydro-4 : 6-dioxopyrimidine. These methods can be used for the preparation of 2-alkyl-derivatives. Freund and Fleischer (*Annalen*, 1910, **379**, 30) prepared the 2-methyl derivative (III; R^1 = R^2 = Et, R^3 = R^4 = R^6 = H, R^5 = Me) from diethylmalonyl chloride and an excess of acetamide. The same product is obtained (B.P. Appln. 17,043/1947) by the condensation of ethyl diethylmalonate with acetamidine. Freund and Fleischer's method failed when applied to ethylphenylmalonyl chloride. Condensation of ethyl ethylphenylmalonate with propionamidine in presence of sodium methoxide occurred readily at 105—110°, to give the hexahydro-2-methoxy-derivative (II; R^1 = Ph, R^2 = R^5 = Et, R^3 = R^4 = H, R^6 = OMe); with acetamidine under similar conditions the yield was very much poorer, while with formamidine the product (II; R^1 = Ph, R^2 = Et, R^3 = R^4 = R^5 = H, R^6 = OMe) was obtained only by prolonged reaction at 0—10°.

Condensation of *C*-ethyl-*C*-phenylmalondiamide with ethyl formate in presence of

sodium methoxide gave (II; R^1 = Ph, R^2 = Et, R^3 = R^4 = R^5 = H), also obtained by reaction of (V) with sodium methoxide. Condensation of a *C*-disubstituted malonodiamide (IX) with ethyl formate appeared to be a general reaction, but substitution on the amide-nitrogen atom prevented ring closure. Thus *C*-ethyl-*N*-methyl-*C*-phenylmalonodiamide gave as the only identifiable product *NN'*-di-(α-methylcarbamoyl-α-phenylbutyryl)-formamidine (VIII).

Although *C*-ethyl-*C*-phenylmalonodiamide condensed smoothly with ethyl acetate in presence of sodium methoxide to give the 2-methoxy-compound (II; R^1 = Ph, R^2 = Et, R^3 = R^4 = H, R^5 = Me, R^6 = OMe), no product was isolated from the reaction of *C*-methyl(or *C*-*n*-propyl)-*C*-phenylmalonodiamide under similar conditions.

Reaction of the malonodiamides with acetyl chloride was the most satisfactory method for the preparation of 1-alkyltetrahydro-2-methyl-4 : 6-dioxopyrimidines, as their hydrochlorides; with diprimary malonodiamides the *NN'*-diacetylamide was also obtained. When *C*-ethyl-*C*-phenylmalonodiamide reacted with keten the products were ethylphenylmalononitrile and *N*-acetyl-α-cyano-α-phenylbutyramide (VII; R^1 = Ph, R^2 = Et, R^3 = Ac).

Reduction of the tetrahydro-4 : 6-dioxopyrimidines either as their hydrochlorides or as the corresponding 2-alkoxy-derivatives was readily effected by a number of methods, *e.g.*, catalytically, by boiling with W5 Raney nickel, or when R^5 = H by heating under reflux with formamide or formic acid.

2 : 5-Diethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (II; R^1 = Ph, R^2 = R^5 = Et, R^3 = R^4 = R^6 = H) exists in two geometrical isomers which were separated from the reduction product of 2 : 5-diethylhexahydro-2-methoxy-4 : 6-dioxopyrimidine.

In view of its formal structure as a diacylmethylenediamine derivative, the stability of primidone is noteworthy. It was unchanged on boiling with 5% hydrochloric acid or 2N-sodium hydroxide. Boiling 60% w/w sulphuric acid liberated formaldehyde. Oxidation with alkaline permanganate gave *C*-ethyl-*C*-phenylmalonodiamide. Primidone could not be methylated by means of methyl sulphate in alkali; on the other hand, 1 : 3-dimethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (II; R^1 = Ph, R^2 = R^5 = R^6 = H, R^3 = R^4 = Me) was readily methylated by this reagent at position 5.

Primidone is readily nitrated to the 3'-nitro-derivative, whose constitution was determined by conversion into the 3'-chloro-derivative, identical with that synthesised from *m*-chlorotoluene. During the reduction of the nitro-compound some azoxy-derivative was obtained, as well as the amine. In addition to undergoing the Sandmeyer reaction, this amine was readily methylated to the dimethylamino-derivative and the trimethylammonium iodide, and was converted into the hydroxy-compound and thence by methyl sulphate and alkali into the methoxy-derivative.

The fact that primidone gave the 3'-nitro-derivative appeared, at first sight, surprising, since Bourquet and Adams (*J. Amer. Chem. Soc.*, 1930, **52**, 224) suggested that nitration of phenobarbitone gave the 4'-nitro-compound which was converted into the corresponding chloro-compound. Repetition of this work, however, showed that the product was 5-*m*-chlorophenyl-5-ethylbarbituric acid identical with the product obtained from *C*-*m*-chlorophenyl-*C*-ethylmalonodiamide and diethyl carbonate. Bourquet and Adams based their assignment of the structure on the fact that nitration of diethyl ethylphenylmalonate gives predominantly, the *p*-nitro-compound.

Since this work was completed our attention has been drawn to the paper by Staněk and Sidle (*Československá farmacie*, 1953, **2**, 117), describing the desulphurisation of a number of cyclic thioamides by Raney nickel.

Experimental

Ethyl m-*Chlorophenylacetate*.—3-Chlorobenzyl cyanide (76 g.) in absolute ethanol (210 c.c.) was saturated with dry hydrogen chloride at 0°. After 15 hr., the excess of solvent was removed under reduced pressure, the residual syrup was dissolved in ethanol (200 c.c.), and water (200 c.c.) was added. After 1 hr., the oil which separated was extracted with ether, dried ($MgSO_4$), and distilled, to give *ethyl* m-*chlorophenylacetate* (80 g.), b. p. 143°/6 mm. (Found: C, 60·4; H, 5·3. $C_{10}H_{11}O_2Cl$ requires C, 60·5; H, 5·55%).

Ethyl phenylpropylmalonate, b. p. 174°/20 mm. (Found : C, 69·4; H, 7·7. $C_{16}H_{22}O_4$ requires C, 69·0; H, 7·9%), was made in 93% yield by catalytic reduction of ethyl allylphenylmalonate over Adams platinum.

Ethyl m-*chlorophenylethylmalonate*, b. p. 184°/17 mm. (Found : C, 59·9; H, 6·3; Cl, 12·4. $C_{15}H_{19}O_4Cl$ requires C, 60·2; H, 6·4; Cl, 11·9%), and *ethyl* p-*chlorophenylethylmalonate*, b. p. 190—196°/18 mm. (Found : C, 60·7; H, 6·3; Cl, 12·4%), were prepared by substantially the method of Wallingford, Homeyer, and Jones (*J. Amer. Chem. Soc.*, 1941, **63**, 2056; cf. Wallingford, Thorpe, and Homeyer, *ibid.*, 1942, **64**, 580). By using an equivalent quantity of the appropriate benzyl cyanide (Wallingford, Jones, and Homeyer, *ibid.*, p. 576) were prepared *ethyl* α-m-, b. p. 177°/21 mm. (Found : C, 62·5; H, 5·8; N, 5·2; Cl, 14·8. $C_{13}H_{14}O_2NCl$ requires C, 62·0; H, 5·6; N, 5·6; Cl, 14·2%), and *ethyl* α-p-*chlorophenyl*-α-*cyanobutyrate*, b. p. 175°/20 mm. (Found : C, 62·3; H, 5·4; N, 5·2; Cl, 14·6%).

α-Cyano-α-phenylbutyramide, m. p. 117° (Found : N, 14·7. Calc. for $C_{11}H_{12}ON_2$: 14·9%), was obtained by reaction of ethyl α-cyano-α-phenylbutyrate with ammonia, substantially as described in G.P. 309,508 (Friedländer, **13**, 801). Other substituted *cyanoacetamides* prepared similarly are shown in Table 1. When a primary amine was used instead of ammonia it was frequently necessary to heat the mixture at 80—100° for a prolonged period.

TABLE 1. *Cyanoacetamides*, $R^1R^2C(CN)\cdot CO\cdot NHR^3$.

R^1	R^2	R^3	M. p.	Formula	Found : N, %	Reqd. : N, %
Ph	Me	H	107°	$C_{10}H_{10}ON_2$	16·3	16·1
Ph	Et	Me	73	$C_{12}H_{14}ON_2$	13·8	13·9
Ph	Et	Et	51	$C_{13}H_{16}ON_2$	12·9	13·0
Ph	Et	Pr^i	62	$C_{14}H_{18}ON_2$	12·2	12·2
Ph	Et	Allyl	*	$C_{14}H_{16}ON_2$	12·1	12·3
Ph	Et	CH_2Ph	81	$C_{18}H_{18}ON_2$	10·0	10·1
m-C_6H_4Cl	Et	H	108	$C_{11}H_{11}ON_2Cl$	12·9	12·6
p-C_6H_4Cl	Et	H	105	$C_{11}H_{11}ON_2Cl$	12·3	12·6

* B. p. 118°/0·4 mm.

CC-*Disubstituted Malonodiamides*.—These were made essentially by the method given in G.P. 310,426 (Friedländer, **13**, 802) for the preparation of ethylphenylmalonodiamide; in general, however, the reaction was effected at room temperature. Details of the various products are given in Table 2. Hydrolysis of α-cyano-α-phenyl-*N*-*iso*propylbutyramide gave, in addition to ethylphenyl-*N*-*iso*propylmalonodiamide, ethylphenylmalonodiamide and *ethylphenyl*-NN′-*di*iso*propylmalonodiamide*, m. p. 105° (from methanol) (Found : C, 70·4; H, 9·0; N, 9·6. $C_{17}H_{26}O_2N_2$ requires C, 70·3; H, 9·0; N, 9·7%), identical with material obtained from ethylphenylmalonyl chloride and *iso*propylamine. *Phenyl*-n-*propylmalonodiamide*, as well as some of the symmetrical diamides reported in Table 2, were made by treating the appropriate malonyl chloride with ice-cold aqueous ammonia. The malonyl chlorides were prepared by reaction of the acids with 2 mols. of phosphorus pentachloride, the acid being obtained in the usual way by hydrolysis of the diethyl ester. Neither the acids nor the chlorides were purified for analysis.

TABLE 2. *Malonodiamides*, $R^1R^2C(CO\cdot NH_2)\cdot CO\cdot NHR^3$.

R^1	R^2	R^3	M. p.	Formula	Found : N, %	Reqd. : N, %
Ph	Me	H	151°	$C_{10}H_{12}O_2N_2$	14·2	14·6
Ph	Et	Me	144	$C_{12}H_{16}O_2N_2$	12·5	12·7
Ph	Et	Et	127	$C_{13}H_{18}O_2N_2$	11·8	12·0
Ph	Et	Pr^n	173	$C_{12}H_{16}O_2N_2$	12·3	12·7
Ph	Et	Pr^i	111	$C_{14}H_{20}O_2N_2$	11·4	11·3
m-C_6H_4Cl	Et	H	137	$C_{11}H_{13}O_2N_2Cl$	11·6	11·7
p-C_6H_4Cl	Et	H	138	$C_{11}H_{13}O_2N_2Cl$	11·3	11·7

C-*Ethyl*-NN′-*bishydroxymethyl*-C-*phenylmalonodiamide*.—*C*-Ethyl-*C*-phenylmalonodiamide (21 g.), 37% formaldehyde (28 c.c.), water (75 c.c.), and potassium carbonate (1 g.) were heated at 70° for 30 min. The solid which separated was extracted with boiling methanol, to give the *hydroxymethyl* derivative (10 g.), m. p. 188—189° (Found : C, 59·4; H, 6·7; N, 10·5. $C_{13}H_{18}O_4N_2$ requires C, 58·7; H, 6·8; N, 10·5%).

C-*Ethyl*-N-*formyl*-C-*phenylmalonodiamide*.—The above bishydroxymethyl derivative (10 g.) was added with shaking to potassium dichromate (30 g.) and sulphuric acid (25 g.) in water (150 c.c.) at 35—37°. After 3 hours' stirring at this temperature the white solid was filtered off and extracted with boiling acetone. Addition of water to the extract precipitated the *amide*,

m. p. 170° (from aqueous acetone) (Found: C, 61·1; H, 5·6; N, 12·1. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%).

Thiobarbituric Acids.—Two methods of preparation were employed: (a) *Condensation of an ethyl malonate with thiourea.* To a solution of sodium (46 g., 2 mol.) in methanol (700 c.c.), thiourea (74 g. 1 mol.) and the substituted ethyl malonate (1 mol.) were added. After 6 hours' heating under reflux the bulk of the solvent was removed under reduced pressure and the residual syrup was dissolved in ice-water. After removal of unchanged ester by extraction with ether, the thiobarbituric acid was precipitated by the addition of hydrochloric acid and crystallised from methanol. Details of the *products* are given in Table 3.

TABLE 3. *2-Thiobarbituric acids* (I).

R^1	R^2	R^3	R^4	M. p.	Formula	Found: N, %	Reqd.: N, %
Ph	H	H	H	264—267° *	$C_{10}H_8O_2N_2S$	12·0	12·7
Ph	H	Me	Me	220	$C_{12}H_{12}O_2N_2S$	11·2	11·3
Ph	Et	Me	H	125	$C_{13}H_{14}O_2N_2S$	10·5	10·7
Ph	Et	Me	Me	112	$C_{14}H_{16}O_2N_2S$	10·0	10·0
m-C_6H_4Cl	Et	H	H	167	$C_{12}H_{11}O_2N_2SCl$	9·9	9·9
p-C_6H_4Cl	Et	H	H	193	$C_{12}H_{11}O_2N_2SCl$	9·3	9·9
·CH_2·CH_2·CH_2·		H	H	365 *	$C_7H_8O_2N_2S$	15·1	15·2

* With decomp.

(b) *Reaction of a malonyl chloride with thiourea.* This method was preferred for the preparation of *N*-substituted thiobarbituric acids. The malonyl chloride (0·25 mol.) and the thiourea (0·42 mol.) were heated on the steam-bath for 9 hr., and the resulting mass was then crystallised from methanol. Ethylphenylmalonyl chloride and *N-iso*propylthiourea reacted abnormally, to give on crystallisation from methanol N-(α-*methoxycarbonyl*-α-*phenylbutyryl*)-N'-iso*propylthiourea*, m. p. 107° (Found: C, 59·5; H, 6·7; N, 8·9. $C_{16}H_{22}O_3N_2S$ requires C, 59·6; H, 6·8; N, 8·7%).

5-Ethyltetrahydro-2-methylthio-4 : 6-dioxo-5-phenylpyrimidine.—5-Ethyl-5-phenyl-2-thiobarbituric acid (12·4 g.), methyl iodide (10 g.), methanol (150 c.c.), water (2 c.c.), and sodium hydroxide (2·2 g.) were mixed. After 15 hr. some solvent was removed under reduced pressure, the oily layer was taken up in ether and dried ($MgSO_4$), and the ether was removed. Trituration of the residue with ethyl acetate gave unchanged starting material which was removed by filtration; concentration of the mother-liquor gave crystals which, recrystallised from ethyl acetate, had m. p. 159—161° (1 g.) (Found: C, 59·4; H, 5·1; N, 10·7. $C_{13}H_{14}O_2N_2S$ requires C, 59·5; H, 5·3; N, 10·7%).

Reduction of Substituted Barbituric and 2-Thiobarbituric Acids.—(i) *Reduction of 2-thiobarbituric acids with* W5 *Raney nickel.* 5-Ethyl-5-phenyl-2-thiobarbituric acid (10 g.), ethanol (250 c.c.), and freshly prepared W5 Raney nickel (Adkins and Billica, *loc. cit.*) (*ca.* 16 c.c. of alcohol-wet paste) were heated under reflux for 4 hr., then filtered through kieselguhr, and the residue was washed with hot ethanol. The solid, which separated on cooling, was crystallised from ethanol, to give *5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine* (primidone) (4·1 g.) m. p. 281°. The same compound was obtained when either of the three isomeric 5-chlorophenyl-5-ethyl-2-thiobarbituric acids was submitted to the same procedure.

Other hexahydro-4 : 6-dioxopyrimidines prepared by this method and by those illustrated below are shown in Table 4. When 5-phenyl-2-thiobarbituric acid was submitted to this procedure the product was 4 : 6-dihydroxy-5-phenylpyrimidine.

(ii) *Reduction of a 2-thiobarbituric acid with sodium amalgam.* 5-Ethyl-5-phenyl-2-thiobarbituric acid (10 g.), water (1·5 l.), and 3% sodium amalgam (160 g.) were stirred at room temperature for 6 hr., sufficient dilute hydrochloric acid being added, from time to time, to maintain neutrality. Next morning the procedure was repeated with more sodium amalgam (60 g.). Acidification of the supernatant liquor precipitated unchanged starting material; after removal of this, concentration of the mother-liquor yielded primidone (1 g.).

(iii) *Reduction of a 2-thiobarbituric acid with zinc and formic acid.* 5-Ethyl-5-phenyl-2-thiobarbituric acid (2 g.) in formic acid (15 c.c.) was heated on the steam-bath and zinc dust (6 g.) was added during 1 hr. and, after a further 2 hr., water (50 c.c.). The solid was collected and extracted, first with dilute aqueous sodium hydroxide to remove unchanged thiobarbituric acid, and then with hot ethanol to obtain primidone.

(iv) *Electrolytic reduction of a barbituric acid.* Phenobarbitone (5 g.), suspended in 80% w/w sulphuric acid (100 c.c.) in a porous-earthenware pot containing a U-shaped lead tube as cathode,

TABLE 4. *Hexahydro-4 : 6-dioxopyrimidines* (II).

No.	R^1	R^2	R^3	R^4	R^5	R^6	M. p.	Method of preparation	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
1	Ph	H	Me	Me	H	H	131°	(a) (i)	$C_{12}H_{14}O_2N_2$	66·2	6·4	13·0	66·1	6·4	12·9
2	Ph	Me	Me	Me	H	H	145	From No. 1	$C_{13}H_{16}O_2N_2$	67·4	6·6	11·9	67·3	6·9	12·1
3	Ph	Me	H	H	Et	H	249	(c)	$C_{13}H_{16}O_2N_2$	67·2	6·9	12·4	67·3	6·9	12·1
4	Ph	Me	H	H	Et	OMe	151 *	(e)	$C_{14}H_{18}O_3N_2$	63·8	6·6	11·2	64·1	6·9	10·7
5	Ph	Et	H	H	H	H	281	(a) (i, ii, iii, iv); (c); (d) (i)	$C_{12}H_{14}O_2N_2$	66·1	6·5	12·8	66·1	6·4	12·9
6	Ph	Et	Me	H	H	H	186	(a) (i); (d) (i)	$C_{13}H_{16}O_2N_2$	67·2	6·5	12·2	67·3	6·9	12·1
7	Ph	Et	Me	Me	H	H	106	(a) (i)	$C_{14}H_{18}O_2N_2$	68·3	7·2	11·6	68·4	7·3	11·4
8	Ph	Et	H	Et	H	H	139	(d) (i)	$C_{14}H_{18}O_2N_2$	68·3	7·5	11·7	68·4	7·3	11·4
9	Ph	Et	H	H	H	OMe	186 *	(a) (v); (d) (ii); (e)	$C_{13}H_{16}O_3N_2$	62·8	6·2	11·2	62·8	6·4	11·3
10	Ph	Et	H	H	H	OPr^i	155 *	Pr^{i}OH on tetrahydro-derivative	$C_{15}H_{20}O_3N_2$	64·9	7·0	10·1	65·2	7·3	10·2
11	Ph	Et	Me	H	H	OMe	157 *	(a) (v)	$C_{14}H_{18}O_3N_2$	64·6	6·7	10·8	64·2	6·9	10·7
12	Ph	Et	Me	Me	H	OMe	119	(a) (v)	$C_{16}H_{22}O_3N_2$	65·8	7·5	9·8	66·2	7·6	9·7
13	Ph	Et	H	H	Et	H	281 †	(c)	$C_{14}H_{18}O_2N_2$	68·3	7·3	11·9	68·4	7·3	11·4
14	Ph	Et	H	H	Et	H	265 ‡	(c)	,,	68·5	7·5	11·3	,,	,,	,,
15	Ph	Et	H	H	Me	OMe	160 *	(d) (ii); (e)	$C_{14}H_{18}O_3N_2$	64·3	6·8	11·0	64·1	6·9	10·7
16	Ph	Et	H	H	Et	OMe	196	(e)	$C_{15}H_{22}O_3N_2$	64·7	7·2	10·3	65·0	7·2	10·2
17	*p*-C_6H_4Cl	Et	H	H	H	H	303	(d) (i)	$C_{12}H_{13}O_2N_2Cl$	56·5	5·3	10·9	56·9	5·2	11·1
18	*m*-$NO_2{\cdot}C_6H_4$	Et	H	H	H	H	249	From No. 5	$C_{12}H_{13}O_4N_3$	55·0	5·5	15·0	54·8	5·0	15·9
19	*m*-$NH_2{\cdot}C_6H_4$	Et	H	H	H	H	300 *	From No. 18	$C_{12}H_{15}O_2N_3$	62·1	6·6	17·3	61·7	6·4	18·0
20	*m*-C_6H_4Cl	Et	H	H	H	H	280	From No. 19	$C_{12}H_{13}O_2N_2Cl$	57·3	4·8	11·3	56·9	5·2	11·1
21	*m*-$HO{\cdot}C_6H_4$	Et	H	H	H	H	295	From No. 19	$C_{12}H_{14}O_3N_2$	61·0	5·6	12·1	61·5	6·0	12·0
22	*m*-$MeO{\cdot}C_6H_4$	Et	H	H	H	H	234	From No. 21	$C_{13}H_{16}O_3N_2$	62·6	6·2	11·0	62·8	6·5	11·3
23	*m*-$NMe_2{\cdot}C_6H_4$	Et	H	H	H	H	273	From No. 19	$C_{14}H_{19}O_2N_3$	63·9	6·9	16·0	64·4	7·3	16·1
24	*m*-$NMe_3{\cdot}C_6H_4$}I	Et	H	H	H	H	160 *	From No. 23	$C_{15}H_{22}O_2N_3I$	44·6	5·5	10·4	45·1	6·1	10·2
25	*cyclo*Hexyl	Et	H	H	H	H	301	(a) (i) §	$C_{12}H_{20}O_2N_2$	64·3	4·1	12·4	64·3	4·2	12·5
26	*cyclo*Hex-1-enyl	Ph	H	H	H	H	338	(d) (i)	$C_{16}H_{14}O_2N_2$	71·7	5·3	10·5	71·7	5·3	10·5
27	Ph	Et	Ph	H	H	H	190	(a) (i)	$C_{18}H_{18}O_2N_2$	72·9	6·2	9·6	73·4	6·1	9·6

* With decomp. † α-Isomer. ‡ β-Isomer. § From 5-ethyl-5-*cyclo*hexenyl-2-thiobarbituric acid.

was electrolysed at 12 v for 2½ hr. with an initial current of 20 amp. falling to 3 amp.; the cathode compartment was contained in a beaker of 60% w/w sulphuric acid and surrounded by a cylindrical anode made of sheet-lead; water was circulated through the cathode to keep the catholyte temperature below 50°. After removal of unchanged phenobarbitone the catholyte was poured on ice, and the separated solid collected and crystallised from ethanol, to give primidone (0·1 g.).

(v) *Reduction of a 2-thiobarbituric acid with* W1 *Raney nickel or Raney cobalt.* 5-Ethyl-5-phenyl-2-thiobarbituric acid (10 g.), methanol (250 c.c.), and W1 Raney nickel (Adkins and Pavlic, *loc. cit.*) or (Raney cobalt prepared as W5 Raney nickel) (20 c.c.) were heated under reflux for 4 hr. Filtration through kieselguhr and concentration of the filtrate gave *5-ethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine*, m. p. 186° (decomp.) (from methanol). When ethanol was used as the solvent the corresponding 2-ethoxy-derivative was obtained; for details of this and other preparations see Table 4. When *n*- or *iso*-propanol was used as solvents the products were identical with those obtained by using W5 Raney nickel.

Reduction of 2-Alkoxy(or Alkylthio)tetrahydro-4 : 6-dioxopyrimidines.—5-Ethyltetrahydro-2-methoxy- (G.P. 249,722, Friedländer, **11**, 928) and -2-methylthio-4 : 6-dioxo-5-phenylpyrimidine were reduced to 5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine when heated under reflux with either W1 or W5 Raney nickel.

Reduction of 2-Alkoxyhexahydro-4 : 6-dioxopyrimidines.—(i) 2 : 5-Diethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine. 2 : 5-Diethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine (13·8 g.) in glacial acetic acid (250 c.c.) was reduced by hydrogen at room temperature and pressure over Adams platinum oxide. After removal of the catalyst, the solution was evaporated to dryness and the residue fractionally crystallised from methanol, to yield the *α-form* of 2 : 5-diethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (3·3 g.), m. p. 281°. Removal of solvent from the mother-liquor and fractional crystallisation from acetone yielded the *β-form* (2·2 g.), m. p. 265—266°, mixed m. p. with α-form 235—240°

(ii) 5-(*p*-Chlorophenyl)-5-ethylhexahydro-4 : 6-dioxopyrimidine. This preparation exemplifies a method applicable to substances containing substituents sensitive to catalytic reduction. 5-(*p*-Chlorophenyl)-5-ethylhexahydro-2-methoxy-4 : 6-dioxopyrimidine (2 g.) and formamide (50 g.) were heated under reflux for 1 hr. The solid which separated on the addition of water was crystallised from ethanol, to give 5-p-*chlorophenyl-5-ethylhexahydro-4 : 6-dioxopyrimidine*, m. p. 303°.

Reaction of Substituted Malonodiamides with Derivatives of Formic or Acetic Acid.—(i) *With formic acid or formamide to produce hexahydro-4 : 6-dioxopyrimidine derivatives.* *C*-Ethyl-*C*-phenylmalonodiamide monohydrate (22·4 g.) and 98% formic acid (6 c.c.) were heated to 190° (internal temp.) for 1 hr.; formic acid (8 × 4 c.c.) was then added during 2 hr. and heating was continued for a further 2 hr. After cooling, the mixture was triturated with methanol, and the solid collected and washed with methanol, to give 5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (9 g.). The same product was obtained when *N*-formyl- or *NN'*-bishydroxymethylmalonodiamide was heated with formic acid in boiling dimethylformamide.

The following method is to be preferred with *N*-monoalkylmalonodiamides: *CN*-diethyl-*C*-phenylmalonodiamide (10 g.) and formamide (80 c.c.) were heated under vigorous reflux for 3 hr. The solid which separated on cooling and dilution with water crystallised from aqueous ethanol, to give 1 : 5-*diethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine*, m. p. 138—139°.

(ii) *With ethyl formate or ethyl acetate to produce 2-alkoxyhexahydro-4 : 6-dioxopyrimidine.* *C*-Ethyl-*C*-phenylmalonodiamide hydrate (112 g.) was dried by distillation with toluene and filtered. The toluene-wet filter-cake was then added, together with ethyl acetate (50 g.), to a solution of sodium (11·5 g.) in methanol (200 c.c.). After 4 hours' heating under reflux the mixture was cooled, neutralised with methanolic hydrogen chloride, and filtered. The residue, after being washed with water, crystallised from methanol, to give *5-ethylhexahydro-2-methoxy-2-methyl-4 : 6-dioxo-5-phenylpyrimidine* (35 g.), m. p. 160° (decomp.).

A similar procedure may be employed with ethyl formate, to give 2-alkoxyhexahydro-4 : 6-dioxopyrimidines without further 2-substituents. *C*-Ethyl-*N*-methyl-*C*-phenylmalonodiamide with ethyl formate gave a small amount of *di-(α-methylcarbamoyl-α-phenylbutyryl)formamidine*, m. p. 193—194° (from aqueous methanol) (Found: C, 66·8; H, 6·5; N, 12·8. $C_{25}H_{30}O_4N_4$ requires C, 66·7; H, 6·7; N, 12·4%), together with much unchanged starting material.

Reaction of *C*-ethyl-*N*-formyl-*C*-phenylmalondiamide with sodium methoxide under similar conditions yielded 5-ethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine.

Reaction of Substituted Diethyl Malonates with Amidines.—To a solution of sodium (9·2 g.) in methanol (200 c.c.), propionamidine hydrochloride (21·7 g.) and ethyl methylphenyl-

malonate (50 g.) were added. After being heated at 105—110° for 20 hr., the mixture was cooled and neutralised with methanolic hydrogen chloride. After filtration, the solid was washed first with methanol, then with water, and crystallised from methanol, to give *2-ethylhexahydro-2-methoxy-5-methyl-4 : 6-dioxo-5-phenylpyrimidine* (24·0 g.), m. p. 151—152°, when acetamidine or formamidine was employed the yields were much reduced. In addition, in the case of formamidine, it was necessary to continue the reaction for 5 days and at a low temperature, 0° initially.

5-Ethylhexahydro-5-m-nitrophenyl-4 : 6-dioxopyrimidine.—To 5-ethylhexahydro-4 : 6-dioxo-5-phenylpyrimidine (50 g.) in 98% sulphuric acid (200 c.c.), a mixture of nitric acid (*d* 1·5; 11 c.c.) and 98% sulphuric acid (50 c.c.) was added, with stirring, at <3°. Then the mixture was poured on ice (600 g.), and the solid which separated was washed with cold water and crystallised from 80% aqueous ethanol, to give the *nitro*-compound (36 g.), m. p. 248—249°. This substance (22 g.) in acetic acid (44 c.c.) was reduced with hydrogen over Adams platinum catalyst at 48 atm. and room temperature during 30 min. After removal of the catalyst the solution was evaporated to dryness, and the residue was stirred with excess of cold 2N-hydrochloric acid and filtered. The solid *azoxy*-compound, m. p. >350°, was digested with boiling ethanol for analysis (Found : C, 60·9; H, 5·7; N, 16·8. $C_{24}H_{26}O_5N_6$ requires C, 60·2; H, 5·4; N, 17·6%). Basification of the filtrate gave the *amino*-compound, m. p. 299—300° (decomp.) (from aqueous ethanol). This was converted by standard procedures into the corresponding m-*chloro*- (identical with material synthesised from *m*-chlorotoluene), m-*hydroxy*-, m-*dimethylamino*-derivative, and the m-*trimethylammonium iodide* (see Table 4). The *m*-hydroxy-compound was converted into the m-*methoxy*-derivative by methyl sulphate in aqueous sodium hydroxide.

Hexahydro-1 : 3 : 5-trimethyl-4 : 6-dioxo-5-phenylpyrimidine.—To a solution of hexahydro-1 : 3-dimethyl-4 : 6-dioxo-5-phenylpyrimidine (2·18 g.) and sodium hydroxide (0·6 g.) in water (10 c.c.), methyl sulphate (1·6 c.c.) was added with vigorous stirring. When the solution became acid further portions of sodium hydroxide (0·3 g.) and methyl sulphate (0·8 c.c.) were added. The product which separated after the addition of excess of alkali was filtered off and crystallised from water, to give *hexahydro-1 : 3 : 5-trimethyl-4 : 6-dioxo-5-phenylpyrimidine*, m. p. 144—145°.

1 : 5-Diethyltetrahydro-2-methyl-4 : 6-dioxo-5-phenylpyrimidine.—*CN*-Diethyl-*C*-phenylmalonodiamide (4·7 g.), acetyl chloride (9·6 g.), and glacial acetic acid (1·2 c.c.) were heated at 100° in a sealed vessel for 1 hr. After cooling, the *hydrochloride* was collected, washed with acetyl chloride, then with ether, and crystallised from glacial acetic acid; it had m. p. 211° (decomp.) (Found : C, 61·3; H, 6·2; N, 9·7; Cl, 12·3. $C_{15}H_{19}O_2N_2Cl$ requires C, 61·0; H, 6·1; N, 9·5; Cl, 12·1%).

In addition to *tetrahydro-2-methyl-4 : 6-dioxo-5-phenyl-5-n-propylpyrimidine hydrochloride*, m. p. 215° (decomp.) (Found : C, 59·5; H, 6·1; N, 10·2; Cl, 12·5. $C_{14}H_{16}O_2N_2$,HCl requires C, 59·7; H, 6·1; N, 10·0; Cl, 12·6%), *C*-phenyl-*C*-*n*-propylmalonodiamide with acetyl chloride under similar conditions yielded *NN'-diacetyl-C-phenyl-C-n-propylmalonodiamide*, m. p. 155—156° (from aqueous methanol) (Found : C, 62·8; H, 6·5; N, 8·8. $C_{16}H_{20}O_4N_2$ requires C, 63·0; H, 6·6; N, 9·2%). Reaction of *C*-ethyl-*C*-phenylmalonodiamide with keten in xylene solution at 100—120° gave, on removal of the solvent, a gum which, on trituration with light petroleum and crystallisation from aqueous methanol, gave *N-acetyl-α-cyano-α-phenylbutyramide*, m. p. 101° (Found : C, 67·7; H, 6·0; N, 12·5. $C_{13}H_{14}O_2N_2$ requires C, 67·9; H, 6·1; N, 12·2%), together with ethylphenylmalononitrile.

5-m-Chlorophenyl-5-ethylbarbituric Acid.—To *C-m*-chlorophenyl-*C*-ethylmalonodiamide (12 g.), dissolved in a solution of sodium (7 g.) in methanol (150 c.c.), diethyl carbonate (5·2 g.) was added and the whole was heated under reflux for 1·5 hr. At the end of this time and again after a similar period, two further lots of diethyl carbonate (5·2 g.) were added. After a final period of 1·5 hr., the mixture was cooled, diluted with water (200 c.c.), and filtered (charcoal). The solid which separated on acidification of the filtrate with dilute hydrochloric acid was collected and crystallised from methanol, to give *5-m-chlorophenyl-5-ethylbarbituric acid* (7 g.), m. p. 244°, undepressed on admixture with the acid prepared by Bourquet and Adams's method (*loc. cit.*) (Found : C, 53·7; H, 4·1; N, 9·5. $C_{12}H_{11}O_3N_2Cl$ requires C, 54·0; H, 4·1; N, 10·0%).

5-Ethyltetrahydro-4 : 6-dioxo-5-phenylpyrimidine.—5-Ethyl-2-methoxy-4 : 6-dioxo-5-phenylhexahydropyrimidine (10 g.) in ether (100 c.c.) was saturated with hydrogen chloride, with ice-cooling. After 2 hr. the *hydrochloride* was collected and, crystallised from glacial acetic acid, had m. p. 370° (Found : C, 55·6; H, 5·1; N, 11·2; Cl, 13·6. $C_{12}H_{12}O_2N_2$,HCl requires C, 55·4;

H, 5·1; N, 11·1; C, 14·0%). A solution of the hydrochloride (8 g.) in water (20 c.c.) was adjusted to pH 6—7 by the addition of saturated potassium acetate solution; after 3 hr. the crystalline *hydrate* was collected; recrystallised from water (below 60°), it had m. p. 122—123° (decomp.) (Found : C, 61·4; H, 6·0; N, 11·9. $C_{12}H_{12}O_2N_2,H_2O$ requires C, 61·5; H, 6·0; N, 12·0%). Boiling the hydrate with water for 5 min. gave NN-*di*-(α-*carbamoyl*-α-*phenylbutyryl*)-*formamidine*, m. p. 205° (decomp.) (from methanol) (Found : C, 64·5; H, 5·8; N, 13·1. $C_{23}H_{26}O_4N_4$ requires C, 65·4; H, 6·2; N, 13·3%); longer boiling gave *C*-ethyl-*C*-phenylmalonodiamide. Heating the hydrate at 120°/0·01 mm. or 2-alkoxy-5-ethylhexahydro-5-phenylpyrimidine-4 : 6-dione at 180—185°/0·01 mm. for 2 hr. gave crude 5-ethyltetrahydro-4 : 6-dioxo-5-phenylpyrimidine, m. p. 116° (decomp.) (Found : C, 62·8; H, 6·0; N, 12·5. Calc. for $C_{12}H_{12}O_2N_2$: C, 66·7; H, 5·6; N, 12·9%), which could not be purified. Further heating at 200° yielded an amorphous polymer insoluble in all solvents. The base, hydrate, and hydrochloride reacted with a wide range of alcohols to give the corresponding 2-alkoxy-derivative, *e.g.*, with *iso*propyl alcohol to give 5-*ethylhexahydro*-4 : 6-*dioxo*-5-*phenyl*-2-iso*propoxypyrimidine*, m. p. 155—156° (decomp.).

5-Ethylhexahydro-2-methoxy-4 : 6-dioxo-5-phenylpyrimidine (2·5 g.), 37% formaldehyde (8 c.c.), potassium carbonate (0·1 g.), and water (20 c.c.) were warmed to 40° to complete dissolution; on cooling, 5-*ethylhexahydro*-1 : 3-*bishydroxymethyl*-2-*methoxy*-4 : 6-*dioxo*-5-*phenylpyrimidine* separated, having m. p. 127—128° (decomp. at 132°) (Found : C, 57·8; H, 6·3; N, 9·1. $C_{15}H_{20}O_5N_2$ requires C, 58·4; H, 6·5; N, 9·1%). This substance could not be crystallised without decomposition.

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