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Pyrimidine *N*-Oxides. IV*
The *N,N'*-Dihydroxy Derivatives of Phenobarbital and Veronal

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Abstract

5-Ethyl-1,3-dihydroxy-5-phenylbarbituric acid (*N,N'*-dihydroxyphenobarbital) and 5,5-diethyl-1,3-dihydroxybarbituric acid (*N,N'*-dihydroxyveronal) have been prepared by the condensation of 1,3-dibenzyloxyurea with ethylphenylmalonyl dichloride and diethylmalonyl dichloride respectively, followed by the removal of the benzyl protecting groups from the intermediate dibenzyloxy derivatives.

The synthesis of the *N,N'*-dihydroxy derivatives of some clinically important barbituric acid derivatives was part of a continuing interest in nuclear *N*-substituted pyrimidines[1–3] in general and barbituric acids[4,5] in particular. *N*-Hydroxybarbituric acid derivatives may yet be found among the human metabolites of the drugs in clinical use even though initial reports that *N*-hydroxyamobarbital[6] (1; $R^1 = H$, $R^2 = OH$, $R^3 = CH_2CH_2CHMe_2$) and *N*-hydroxyphenobarbital[7] (1; $R^1 = H$, $R^2 = OH$, $R^3 = Ph$) were metabolites of the drugs were later retracted.[8,9]

5,5-Disubstituted barbituric acids resist *N*-oxidation by typical oxidants such as hydrogen peroxide, peroxyacetic acid, trifluoroperoxyacetic acid and *m*-chloroperoxybenzoic acid. By contrast, 2,6-diamino-5,5-diethylpyrimidin-4(5*H*)-one (2) reacts with hydrogen peroxide to give a mono *N*-hydroxy product which on prolonged acid hydrolysis affords 5,5-diethyl-1-hydroxybarbituric acid (1; $R^1 = H$, $R^2 = OH$, $R^3 = Et$).[10] As direct oxidation was clearly an unsuitable route to the dihydroxybarbiturates, the compounds in question were synthesized by primary methods.

Initial attempts to condense diethyl ethylphenylmalonate (3; $R^1 = OEt$, $R^2 = Ph$) with *N,N'*-dibenzyloxyurea (4) were unsuccessful and this reflected the lower reactivity of the dialkyl malonate esters previously reported.[11] The reaction of ethylphenyl-

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[5] Jacobsen, N. W., McCarthy, B. L., and Smith, S., *Aust. J. Chem.*, 1979, **32**, 161.
[6] Tang, B. K., Inaba, T., and Kalow, W., *Drug Metab. Dispos.*, 1975, **3**(6), 479.
[7] Tang, B. K., Inaba, T., and Kalow, W., *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 1977, **36**, 966.
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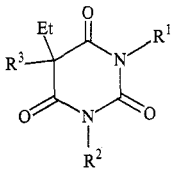
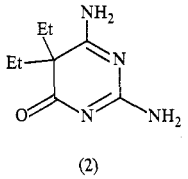
[9] Tang, B. K., Kalow, W., and Grey, A. A., *Drug Metab. Dispos.*, 1979, **7**, 315.
[10] Cowden, W., and Jacobsen, N. W., *Aust. J. Chem.*, 1978, **31**, 2517.
[11] Brown, D. J., 'The Chemistry of Heterocyclic Compounds' (The Pyrimidines) p. 53 (John Wiley: New York 1970).

malonyl dichloride (3; $R^1 = Cl$, $R^2 = Ph$) with (4), however, proceeded smoothly and gave 1,3-dibenzyloxy-5-ethyl-5-phenylbarbituric acid (1; $R^1 = R^2 = OCH_2Ph$, $R^3 = Ph$) in reasonable yield. Catalytic hydrogenolysis of the protecting benzyl groups did not proceed satisfactorily nor to completion. Cleavage of the benzyl groups was achieved with hydrogen bromide in acetic acid to give the required 5-ethyl-1,3-dihydroxy-5-phenylbarbituric acid (1; $R^1 = R^2 = OH$, $R^3 = Ph$).



(1)



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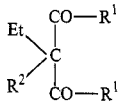

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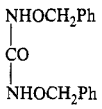

(4)

In like manner, diethylmalonyl dichloride (3; $R^1 = Cl$, $R^2 = Et$) condensed with the substituted urea (4) to give 1,3-dibenzyloxy-5,5-diethylbarbituric acid (1; $R^1 = R^2 = OCH_2Ph$, $R^3 = Et$). In this case, hydrogenolysis occurred smoothly in the presence of Adams catalyst (PtO_2) and afforded 5,5-diethyl-1,3-dihydroxybarbituric acid (1; $R^1 = R^2 = OH$, $R^3 = Et$).

Experimental

Melting points were determined in open capillary tubes in an electrically heated silicone oil bath and are uncorrected. ^1H n.m.r. spectra were obtained on a Varian EM360 spectrometer. Microanalyses were performed by Mr J. Kent and staff of the Microanalytical Service of the University of Queensland.

Ethylphenylmalonic Acid (Improved Method of Purification)

Diethyl ethylphenylmalonate (66 g, 0·25 mol) was refluxed in 2 M sodium hydroxide (500 ml) for 18 h. The cooled solution was acidified to pH 0–1 with 3 M sulfuric acid and extracted with ether (5 × 100 ml). The ether extracts were dried (Na_2SO_4) and evaporated to dryness; the residue was extracted twice with boiling chloroform (50 ml) as a greatly improved method to remove the considerable amount of the partial-decarboxylation product, 2-phenylbutanoic acid. The chloroform-insoluble residue was crystallized from water (150 ml) to yield ethylphenylmalonic acid (23 g, 44%), m.p. 158° (dec.) (lit.[12] 156–157°). ^1H n.m.r. δ [$CDCl_3/CD_3COCD_3$ (1:1), Me_4Si] 8·2, s, 2COOH; 7·2–7·6, m, Ph; 2·4, q, CH_2; 1·0, t, CH_3.

Ethylphenylmalonyl Dichloride

Phosphorus pentachloride (21·0 g, 0·10 mol) was added portionwise to ethylphenylmalonic acid (10·4 g, 0·05 mol) at 0° with thorough mixing after each addition. The reaction mixture was then refluxed for 1¼ h and finally distilled to yield ethylphenylmalonyl dichloride (6·3 g, 51%), b.p. 90–95°/1·0 mm (lit.[13] 176–185°/60 mm). ^1H n.m.r. δ ($CDCl_3$, Me_4Si) 7·5, s, Ph; 2·7, q, CH_2; 1·05, t, CH_3.

N,N′-*Dibenzyloxyurea*

Benzyloxyamine (4·92 g, 40 mmol) in tetrahydrofuran (25 ml) was added slowly (45 min) with stirring to a cold (−5° to 0°) solution of phosgene (9·8 g, 20 mmol) dissolved in a mixture of toluene

[12] Scheurer, P. J., and Cohen, S. G., *J. Am. Chem. Soc.*, 1958, **80**, 4933.
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(50 ml) and thf (25 ml). The mixture was stirred for 5 h and the temperature slowly raised to 20°. Triethylamine (4·0 g, 40 mmol) in tetrahydrofuran (20 ml) was then added slowly and the mixture allowed to stand overnight. Evaporation in a vacuum gave a solid residue which was triturated with a mixture of methanol and water (45 ml; 5:4). The insoluble product was collected, dried, and recrystallized from methylene chloride/pentane mixture to give N,N′-*dibenzyloxyurea* (3·53 g, 65%), m.p. 86° (Found: C, 66·0; H, 6·0; N, 10·65. $C_{15}H_{16}N_2O_3$ requires C, 66·2; H, 5·9; N, 10·3%). ^{1}H n.m.r. δ ($CDCl_3$, Me_4Si) 7·7, s, 2NH; 7·29, s, 2Ph; 4·75, s, $2CH_2$.

1,3-Dibenzyloxy-5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione

Ethylphenylmalonyl dichloride (21·4 g, 87 mmol) and dibenzyloxyurea (23·8 g, 87·5 mmol) were refluxed together in toluene (600 ml) for 22 h. The toluene was evaporated and the oily residue dissolved in ethanol (200 ml) and the solution set aside to crystallize. After several hours the solid was collected and recrystallized from ethanol (100 ml) to give *1,3-dibenzyloxy-5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione* (9·55 g, 25%), m.p. 115–116° (Found: C, 69·9; H, 5·4; N, 6·4. $C_{26}H_{24}N_2O_5$ requires C, 70·2; H, 5·4; N, 6·3%). ^{1}H n.m.r. δ ($CDCl_3$, Me_4Si) 7·1–7·7, m, 3Ph; 5·1, s, $2CH_2$; 2·5, q, CH_2; 0·9, t, CH_3.

5-Ethyl-1,3-dihydroxy-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione

1,3-Dibenzyloxy-5-ethyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (0·89 g, 2 mmol) was added to hydrogen bromide in acetic acid solution (30 ml; 27%) and the mixture refluxed for 6 h. A further quantity of hydrogen bromide in acetic acid solution (10 ml; 45%) was added and heating continued for a further 6 h. The mixture was evaporated to dryness in a vacuum and the residue extracted with boiling light petroleum (b.p. 40–60°; 3 × 20 ml). The insoluble residue was crystallized first from water and then from diisopropyl ether/cyclohexane to give *5-ethyl-1,3-dihydroxy-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione* (0·33 g, 62%), m.p. 159–161° (Found: C, 54·4; H, 4·5; N, 10·6. $C_{12}H_{12}N_2O_5$ requires C, 54·6; H, 4·6; N, 10·6%). ^{1}H n.m.r. δ [$CDCl_3/CD_3COCD_3$ (4:1), Me_4Si] 9·7, s(br), 2OH; 7·2, s, Ph; 2·44, q, CH_2; 0·93, t, CH_3.

1,3-Dibenzyloxy-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione

Diethylmalonyl dichloride[13] (1·96 g, 10 mmol) and dibenzyloxyurea (2·72 g, 10 mmol) were refluxed together in toluene (70 ml) for 24 h. Evaporation gave an oily residue which deposited crystals from ethanol. Further recrystallization from ethanol gave *1,3-dibenzyloxy-5,5-diethylpyrimidine-2,4,6(1H,3H,5H)-trione* (1·78 g, 45%), m.p. 131–132° (Found: C, 66·5; H, 6·2; N, 7·1. $C_{22}H_{24}N_2O_5$ requires C, 66·7; H, 6·1; N, 7·1%). ^{1}H n.m.r. δ ($CDCl_3$, Me_4Si) 7·2–7·7, m, 2Ph; 5·1, s, $2CH_2$; 1·96, q, $2CH_2$; 0·7, t, $2CH_3$.

5,5-Diethyl-1,3-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione

1,3-Dibenzyloxy-5,5-diethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (0·8 g, 2·0 mmol) in ethanol (40 ml) was hydrogenated over platinum oxide catalyst (0·1 g) at atmospheric temperature and pressure. When two-thirds of the calculated hydrogen uptake had taken place, the reaction mixture was warmed (60°) in a hot water bath and hydrogenation continued to completion. The spent catalyst was filtered off, the filtrate evaporated to dryness and the solid recrystallized from water to yield *5,5-diethyl-1,3-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione* (0·26 g, 59%), m.p. 194–196° (Found: C, 44·5; H, 5·7; N, 12·8. $C_8H_{12}N_2O_5$ requires C, 44·5; H, 5·6; N, 13·0%). ^{1}H n.m.r. δ [D_2O, $Me_3Si(CH_2)_3SO_3Na$] 2·06, q, $2CH_2$; 0·78, t, $2CH_3$.

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