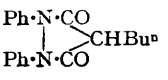
4-*Alkyl*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine Derivatives.*

By Richard Budziarek, D. J. Drain, (Miss) F. J. Macrae, John McLean, G. T. Newbold, D. E. Seymour, F. S. Spring, and Martin Stansfield.

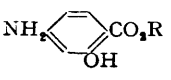
[Reprint Order No. 6341.]

Condensations of 4 : 4′-diethoxycarbonylhydrazobenzene with alkylmalonyl chlorides give 4-alkyl-3 : 5-dioxo-1 : 2-di-*p*-ethoxycarbonylphenylpyrazolidines which on hydrolysis yield the corresponding carboxylic acids. Oxidation of methyl 4-aminosalicylate by sodium perborate yields 3 : 3′-dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene reduction of which gives the hydrazobenzene. Acetylation of the latter, followed by condensation with alkylmalonyl chlorides and hydrolysis, gives the corresponding 4-alkyl-3 : 5-dioxo-1 : 2-di-(4-carboxy-3-hydroxyphenyl)pyrazolidines.

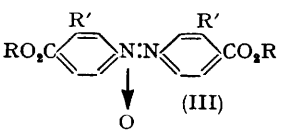
Although phenylbutazone (4-*n*-butyl-3 : 5-dioxo-1 : 2-diphenylpyrazolidine) (I) is of value in the treatment of rheumatoid arthritis and allied conditions, indications of toxic effects associated with its use have been reported (Leonard, *Brit. Med. J.*, 1953, I, 1311; Benstead, *ibid.*, p. 711; Johnson and Larkin, *ibid.*, 1954, II, 1088; Etess and Jacobson, *J. Amer. Med. Assoc.*, 1953, **151**, 639; Hinz, Lamont-Havers, Cominsky, and Gaines, *ibid.*, p. 38; Kiely and Stickney, *Proc. Mayo Clin.*, 1953, **28**, 341). Since it is possible that *in vivo*



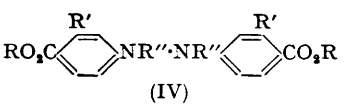
(I)



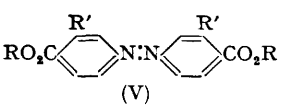
(II)



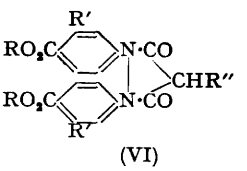
(III)



(IV)



(V)



(VI)

phenylbutazone may in part be degraded to hydrazobenzene, the toxic hazards associated with phenylbutazone may be attributable to hydrazobenzene. On this working hypothesis, the present investigation aimed at replacing the hydrazobenzene moiety in phenylbutazone by a related compound relatively free from toxic hazard. Although aniline, which we assume to be the parent of hydrazobenzene, is a systemic poison, the related *p*-aminobenzoic acid and 4-aminosalicylic acid (II; R = H) are relatively non-toxic. This paper describes the preparation of a series of 4-alkyl-3 : 5-dioxo-1 : 2-di-*p*-carboxyphenylpyrazolidines (VI; R = R′ = H, R″ = alkyl) and of a related series of hydroxy-derivatives (VI; R = H, R′ = OH, R″ = alkyl); the pharmacology of these compounds will be reported elsewhere.

Two practical methods for the preparation of 3 : 5-dioxopyrazolidines consist in (*a*) heating a malonic ester with hydrazobenzene and sodium alkoxide at 150—200° (Ruhkopf, *Ber.*, 1940, **73**, 820), and (*b*) reaction of a malonyl chloride with hydrazobenzene alone (Tsumaki, *Bull. Soc. Chem. Japan*, 1931, **6**, 1) or in the presence of pyridine at 0° (B.P.

646,597). Condensation of 4 : 4′-diethoxycarbonylhydrazobenzene with a number of malonic esters (method *a*) failed to give the desired product, extensive decomposition occurring. The use of alkylmalonyl chlorides in ether–pyridine gave the 3 : 5-dioxopyrazolidines in moderate yield. Use of chloroform–pyridine gave improved yields, probably owing to the greater solubility of the alkylmalonyl chloride–pyridine complex in chloroform. The yields also increased with the size of the alkyl group. Alkaline hydrolysis of the 3 : 5-dioxopyrazolidine esters (VI; R = Et, R′ = H, R″ = alkyl) gave the required acids, the properties of which are summarised in Table 1.

Oxidation of methyl 4-aminosalicylate (II; R = Me) by a modification of the sodium perborate method (Mehta and Vakilwala, *J. Amer. Chem. Soc.*, 1952, **74**, 563) gave 3 : 3′-dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene (III; R = Me, R′ = OH). In contrast, ethyl 4-aminobenzoate and the amines used by the Indian authors gave azo-derivatives under the same conditions. We find that oxidation of methyl and ethyl 4-aminosalicylates with hydrogen peroxide in acetic acid gives the azoxy-compounds (III; R = Me and Et respectively, R′ = OH). Reduction of 3 : 3′-dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene (III; R = Me, R′ = OH) with zinc dust and acetic acid gave the hydrazo-compound (IV; R = Me, R′ = OH, R″ = H) which was oxidised by sodium perborate to the azo-derivative (V; R = Me, R′ = OH); the latter is reconverted into the hydrazo-compound by zinc dust and acetic acid. These azoxy-, hydrazo-, and azo-esters have been characterised by diacetyl and dibenzoyl derivatives. Zinc and acetic acid reduced the dibenzoyloxyazoxy-compound (III; R = Me, R′ = OBz) or the dibenzoyloxyazo-analogue (V; R = Me, R′ = OBz) to the dibenzoyloxyhydrazo-compound (IV; R = Me, R′ = OBz, R″ = H) and, conversely, oxidation of the last product with sodium perborate gave the dibenzoyloxyazo-compound (V; R = Me, R′ = OBz). Hydrolysis of the azoxy-, hydrazo-, and azo-esters gave the corresponding acids. Vigorous benzoylation of the dihydroxyhydrazo-ester (IV; R = Me, R′ = OH, R″ = H) gave the tetrabenzoyl derivative (IV; R = Me, R′ = OBz, R″ = Bz).

Treatment of 3 : 3′-diacetoxy-4 : 4′-dimethoxycarbonylhydrazobenzene (IV; R = Me, R′ = OAc, R″ = H) with an alkylmalonyl chloride in pyridine–ether, followed by extraction of the product with aqueous potassium hydroxide, gave the 4-alkyl-1 : 2-di-(3-hydroxy-4-methoxycarbonylphenyl)-3 : 5-dioxopyrazolidine (VI; R = Me, R′ = OH, R″ = alkyl). When *n*-butylmalonyl chloride was used, however, the product was also isolated by extraction with aqueous sodium carbonate and 1 : 2-di-(3-acetoxy-4-methoxycarbonylphenyl)-4-*n*-butyl-3 : 5-dioxopyrazolidine (VI; R = Me, R′ = OAc, R″ = Bu^n) was obtained; it was identical with the acetylation product of the phenol (VI; R = Me, R′ = OH, R″ = Bu^n). Lower yields were obtained by reaction of the alkylmalonyl chloride with the hydrazo-compound in pyridine–chloroform, possibly because of emulsion formation during the alkali extraction and the consequent longer exposure of the products to alkali. Hydrolysis of the hydroxy-esters (VI; R = Me, R′ = OH, R″ = alkyl) gave the corresponding, desired acids (see Table 2).

Experimental

4 : 4′-*Diethoxycarbonylazoxybenzene* (III; R = Et, R′ = H).—4 : 4′-Dicarboxyazoxybenzene (103·5 g.) (Galbraith, Degering, and Hitch, *J. Amer. Chem. Soc.*, 1951, **73**, 1323) and thionyl chloride (250 c.c.) were refluxed for 6 hr. Excess of thionyl chloride was removed under reduced pressure, the crude acid chloride in dry benzene (200 c.c.) was treated with ethanol (80 c.c.), and the mixture refluxed for 30 min. The filtered solution was evaporated and the residue crystallised from ethanol (250 c.c.). The azoxy-ester (103 g., 82%) separated as salmon-pink plates, m. p. 110—112°. Meyer and Dahlem (*Annalen*, 1903, **326**, 334) describe this ester, which they obtained *via* the silver salt, as yellow needles (from ethanol), m. p. 114·5°.

4 : 4′-*Diethoxycarbonylhydrazobenzene* (IV; R = Et, R′ = R″ = H).—The azoxy-ester (III; R = Et, R′ = H) (114·5 g.) in hot glacial acetic acid (500 c.c.) was treated portionwise with zinc dust (100 g.) with stirring. The hot mixture was filtered and the filtrate diluted with water (500 c.c.). The hydrazo-compound (97·5 g., 89%) separated as needles, m. p. 117·5—119°. Meyer and Dahlem (*loc. cit.*) give m. p. 118°.

3 : 3′-*Dihydroxy*-4 : 4′-*dimethoxycarbonylazoxybenzene* (III; R = Me, R′ = OH).—(*a*) A solution of methyl 4-aminosalicylate (4·0 g.) in glacial acetic acid (100 c.c.) was treated with 54% sodium perborate (7·3 g.) at room temperature with shaking. Next morning the solid was collected, washed with water, and crystallised from ethyl acetate from which **3 : 3′-*dihydroxy*-4 : 4′-*dimethoxycarbonylazoxybenzene*** (1·3 g.) separated as red needles, m. p. 193—194° (Found : C, 55·8; H, 4·0. $C_{16}H_{14}O_7N_2$ requires C, 55·5; H, 4·1%).

(*b*) Methyl 4-aminosalicylate (80 g.) in warm acetic acid (650 c.c.) was treated with hydrogen peroxide (450 c.c.; 30%) and kept at room temperature for 72 hr. Crystallisation of the separated solid (41 g.) from glacial acetic acid gave the azoxy-compound as orange-red needles, m. p. and mixed m. p. 193—194° (Found : C, 55·8; H, 4·0; N, 8·15. $C_{16}H_{14}O_7N_2$ requires N, 8·1%).

The ***diacetyl*** derivative (III; R = Me, R′ = OAc), prepared by the action of acetic anhydride–pyridine at room temperature followed by isolation using ether, separated from methanol as orange needles, m. p. 123—124° (Found : C, 56·2; H, 4·2. $C_{20}H_{18}O_9N_2$ requires C, 55·8; H, 4·2%).

The ***dibenzoyl*** derivative (III; R = Me, R′ = OBz) was prepared by treating a solution of 3 : 3′-dihydroxy-compound (1·0 g.) in pyridine (40 c.c.), at 30°, with benzoyl chloride (5 c.c.). Next morning the product was precipitated by adding water and crystallised from glacial acetic acid, from which it forms yellow blades, m. p. 187—188° (Found : C, 65·2; H, 4·5. $C_{30}H_{22}O_9N_2$ requires C, 65·0; H, 4·0%).

By using the hydrogen peroxide–acetic acid method **4 : 4′-*diethoxycarbonyl*-3 : 3′-*dihydroxy*-*azoxybenzene*** (III; R = Et, R′ = OH) was prepared from ethyl 4-aminosalicylate. It formed orange needles or red prisms (from ethanol), m. p. 137° (Found : C, 57·9; H, 5·0; N, 7·7. $C_{18}H_{18}O_7N_2$ requires C, 57·75; H, 4·85; N, 7·5%).

4 : 4′-*Dicarboxy*-3 : 3′-*dihydroxyazoxybenzene* (III; R = H, R′ = OH).—3 : 3′-Dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene (0·5 g.) was refluxed with 10% aqueous potassium hydroxide (25 c.c.) for 1 hr. The cooled solution was acidified (Congo-red) with dilute hydrochloric acid, and the precipitate collected and washed with water : purification by extraction with hot acetone (100 c.c.), filtration, and concentration of the filtrate to *ca.* 10 c.c. gave the *acid* as a brown powder, decomp. above 300° (Found : C, 52·4; H, 3·4. $C_{14}H_{10}O_7N_2$ requires C, 52·8; H, 3·2%).

3 : 3′-*Dihydroxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene* (IV; R = Me, R′ = OH, R″ = H).—A solution of 3 : 3′-dihydroxy-4 : 4′-dimethoxycarbonylazoxybenzene (4·0 g.) in glacial acetic acid (50 c.c.) was heated on the steam-bath for 30 min. with zinc dust (8·0 g.). The filtered mixture was treated with water, and the solid collected and crystallised from glacial acetic acid from which **3 : 3′-*dihydroxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene*** (2·6 g.) forms needles, m. p. 198—199° (Found : C, 58·0; H, 4·75. $C_{16}H_{16}O_6N_2$ requires C, 57·8; H, 4·85%). This compound (m. p. and mixed m. p. 198—199°) is also obtained by zinc and acetic acid reduction of 3 : 3′-dihydroxy-4 : 4′ dimethoxycarbonylazobenzene.

Similar zinc and acetic acid reduction of 4 : 4′-diethoxycarbonyl-3 : 3′-dihydroxyazobenzene gave **4 : 4′-*diethoxycarbonyl*-3 : 3′-*dihydroxyhydrazobenzene*** (IV; R = Et, R′ = OH, R″ = H) which separates from aqueous ethanol as needles, m. p. 150—151° (Found : C, 59·8; H, 5·7; N, 7·5. $C_{18}H_{20}O_6N_2$ requires C, 60·0; H, 5·6; N, 7·8%).

3 : 3′-*Diacetoxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene* (IV; R = Me, R′ = OAc, R″ = H).—A solution of the hydrazo-compound (IV; R = Me, R′ = OH, R″ = H) (10 g.) in pyridine (60 c.c.) and acetic anhydride (60 c.c.) was kept overnight in nitrogen at room temperature. Isolation by means of ether gave **3 : 3′-*diacetoxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene*** (IV; R = Me, R′ = OAc, R″ = H) (12·3 g.) which separates from methanol as pink rosettes of small needles, m. p. 156—158° (Found : C, 57·8; H, 4·7. $C_{20}H_{20}O_8N_2$ requires C, 57·7; H, 4·8%).

3 : 3′-*Dibenzoyloxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene* (IV; R = Me, R′ = OBz, R″ = H).—(*a*) Treatment of the hydroxy-hydrazo-ester (IV; R = Me, R′ = OH, R″ = H) with 2 mols. of benzoyl chloride in pyridine at room temperature overnight was followed by isolation using ether. The dried ethereal solution was shaken with activated zinc and then evaporated, to give **3 : 3′-*dibenzoyloxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene*** (46%) as plates, m. p. 220—221°, from glacial acetic acid (Found : C, 66·6; H, 4·4. $C_{30}H_{24}O_8N_2$ requires C, 66·7; H, 4·5%).

(*b*) Reduction of either 3 : 3′-dibenzoyloxy-4 : 4′-dimethoxycarbonyl-azoxybenzene (III; R = Me, R′ = OBz), or -azobenzene (V; R = Me, R′ = OBz) with zinc dust and acetic acid at 90° gave, in good yield, 3 : 3′-dibenzoyloxy-4 : 4′-dimethoxycarbonylhydrazobenzene which separates from glacial acetic acid as plates, m. p. and mixed m. p. 219—220°.

NN'-*Dibenzoyl*-3 : 3'-*dibenzoyloxy*-4 : 4'-*dimethoxycarbonylhydrazobenzene* (IV; R = Me, R' = R'' = OBz).—The hydroxy-hydrazo-ester (IV; R = Me, R' = OH, R'' = H) (3·0 g.) in pyridine (30 c.c.) was heated with benzoyl chloride (10 c.c.) on the steam-bath for 2 hr. The mixture was worked up with ether. On standing, the ether solution deposited 3 : 3'-dibenzoyloxy-4 : 4'-dimethoxycarbonylazobenzene (0·3 g.), m. p. 201—203° undepressed on admixture with an authentic specimen (see below). Removal of the ether gave a red gum which crystallised from methanol. Recrystallisation from glacial acetic acid gave NN'-*dibenzoyl*-3 : 3'-*dibenzoyloxy*-4 : 4'-*dimethoxycarbonylhydrazobenzene* (1·2 g.) as plates, m. p. 180—181° (Found : C, 70·8; H, 4·4. $C_{44}H_{32}O_{10}N_2$ requires C, 70·6; H, 4·3%).

4 : 4'-*Dicarboxy*-3 : 3'-*dihydroxyhydrazobenzene* (IV; R = R'' = H, R' = OH).—(*a*) hydrolysis of the hydroxy-hydrazo-ester (IV; R = Me, R' = OH, R'' = H) with alkali, followed by purification of the product by dissolution in pyridine and precipitation with dilute hydrochloric acid, gave the *acid* as a cream-coloured amorphous solid, m. p. 206—207° (Found : C, 56·1; H, 3·8. $C_{14}H_{12}O_6N_2$ requires C, 55·3; H, 4·0%).

(*b*) 4-Nitrosalicylic acid (3·65 g.) in 5N-sodium hydroxide (20 c.c.) was treated on the steam-bath during 1½ hr. with zinc dust (8·0 g.). The filtered mixture was acidified (Congo-red) with dilute hydrochloric acid, and the precipitate digested with hot ethanol and further treated as above, to give the acid, m. p. and mixed m. p. 205° (Found : C, 55·2; H, 3·5%).

3 : 3'-*Dihydroxy*-4 : 4'-*dimethoxycarbonylazobenzene* (V; R = Me, R' = OH).—A hot solution of 3 : 3'-dihydroxy-4 : 4'-dimethoxycarbonylhydrazobenzene (0·5 g.) in glacial acetic acid (15 c.c.) was treated with 54% sodium perborate (0·25 g.). After cooling, the red solid was collected and crystallised from ethyl acetate from which 3 : 3'-*dihydroxy*-4 : 4'-*dimethoxycarbonylazobenzene* (400 mg.) separated as bright red needles, m. p. 214—216° (Found : C, 58·4; H, 4·2. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·3%).

3 : 3'-*Diacetoxy*-4 : 4'-*dimethoxycarbonylazobenzene* (V; R = Me, R' = OAc).—(*a*) 3 : 3'-Diacetoxy-4 : 4'-dimethoxycarbonylhydrazobenzene (0·5 g.) in warm glacial acetic acid (20 c.c.) was heated with 54% sodium perborate (0·2 g.) on the steam-bath for 15 min. The cooled mixture was filtered and the solid crystallised from chloroform–methanol, from which 3 : 3'-*diacetoxy*-4 : 4'-*dimethoxycarbonylazobenzene* (400 mg.) separated as red prismatic plates, m. p. 179—181° (Found : C, 58·4; H, 4·6. $C_{20}H_{18}O_8N_2$ requires C, 58·0; H, 4·4%).

(*b*) Acetylation of 3 : 3'-dihydroxy-4 : 4'-dimethoxycarbonylazobenzene (1·0 g.) with acetic anhydride (6 c.c.) and pyridine (6 c.c.) on the steam-bath for 1 hr., followed by isolation using ether, gave the diacetate (1·0 g.) as light red prisms, m. p. and mixed m. p. 178—180°, from ethyl acetate–light petroleum (b. p. 60—80°) (Found : C, 58·4; H, 4·3%).

3 : 3'-*Dibenzoyloxy*-4 : 4'-*dimethoxycarbonylazobenzene* (V; R = Me, R' = OBz).—(*a*) Oxidation of 3 : 3'-dibenzoyloxy-4 : 4'-dimethoxycarbonylhydrazobenzene with sodium perborate in glacial acetic acid gave 3 : 3'-*dibenzoyloxy*-4 : 4'-*dimethoxycarbonylazobenzene* which separates from ethyl acetate as orange needles, m. p. 208—209° (Found : C, 67·0; H, 3·8. $C_{30}H_{22}O_8N_2$ requires C, 66·9; H, 4·1%).

(*b*) Treatment of the hydroxy-azo-ester (V; R = Me, R' = OH) with benzoyl chloride and pyridine on the steam-bath for 30 min. gave the dibenzoate (V; R = Me, R' = OBz) as orange needles, m. p. and mixed m. p. 208—209°.

4 : 4'-*Dicarboxy*-3 : 3'-*dihydroxyazobenzene* (V; R = H, R' = OH).—3 : 3'-Dihydroxy-4 : 4'-dimethoxycarbonylazobenzene was hydrolysed by alkali. The amorphous red *acid* which decomposed at *ca.* 290° was purified by digestion with hot acetone (Found : C, 54·6; H, 3·4. $C_{14}H_{10}O_6N_2$ requires C, 55·6; H, 3·3%).

Condensations of 4 : 4'-*Diethoxycarbonylhydrazobenzene with Alkylmalonyl Chlorides*.—The alkylmalonyl chlorides were prepared by alkylation of ethyl malonate (*Org. Synth.*, Coll. Vol. I, 2nd. edn., p. 250; Coll. Vol. II, p. 279), and hydrolysis of the resulting esters to the malonic acids (cf. *Org. Synth.*, Coll. Vol. II, p. 93). These were refluxed for 2 hr. with thionyl chloride, the excess of reagent was removed, and the residue distilled under reduced pressure. n-*Hexylmalonyl chloride* has b. p. 124°/16 mm. (Found : Cl, 32·6. $C_9H_{14}O_2Cl_2$ requires Cl, 31·5%).

The acid chloride (0·17 mole) was added dropwise to a stirred solution of dry pyridine (85 c.c.) in dry chloroform (100 c.c.) at −10°. 4 : 4'-Diethoxycarbonylhydrazobenzene (50 g.) in chloroform (500 c.c.) was added with stirring at 0° and the mixture allowed to attain room temperature. After 12 hr., the mixture was washed with 2N-hydrochloric acid, water, and 2N-sodium carbonate. Acidification of the alkaline extracts and crystallisation of the product gave the 4-*alkyl*-3 : 5-*dioxo*-1 : 2-*di*-p-*ethoxycarbonylphenylpyrazolidine* (Table 1; yields, 40—80%).

Hydrolysis.—The diethyl esters (10 g.) were hydrolysed by refluxing N-sodium hydroxide

(100 c.c.) for 45 min. Acidification with dilute hydrochloric acid liberated the acids (see Table 1; yields, 70—80%).

Condensations of 3 : 3′-*Diacetoxy*-4 : 4′-*dimethoxycarbonylhydrazobenzene with Alkylmalonyl Chlorides*.—The acid chloride (0·018 mole) in dry ether (30 c.c.) was added dropwise to a stirred mixture of pyridine (20 c.c.) and dry ether (20 c.c.) at −15°. The suspension was then treated with a solution of 3 : 3′-diacetoxy-4 : 4′-dimethoxycarbonylhydrazobenzene (0·012 mole) in pyridine–ether (80 c.c.; 1 : 1) during 45 min. at −15°. Stirring was continued for 30 min. at −15°; the cooling-bath was then removed and stirring continued for 3 hr. The mixture was diluted with ether (100 c.c.) and washed with excess of 5% hydrochloric acid. The ether was extracted with 2% aqueous potassium hydroxide (3 × 50 c.c.), and the extracts were washed with ether and acidified (Congo-red) with 5% hydrochloric acid. The crude 4-alkyl-1 : 2-di-(3-hydroxy-4-methoxycarbonylphenyl)-3 : 5-dioxopyrazolidines were purified by crystallisation (Table 2; yields: 30—50%). The hydroxy-esters gave a purple colour with aqueous-ethanolic ferric chloride.

TABLE 1. 3 : 5-*Dioxopyrazolidines* (VI; R′ = H).

Substituent R	Substituent R″	M. p.	Solvent †	Form	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
Et	Et	200—201°	EtOH	Prisms	65·0	5·9	6·3	$C_{23}H_{24}O_6N_2$	65·1	5·7	6·6
H	Et	270—280 (decomp.)	Aq. MeOH	Micro-cryst.	62·0	4·5	7·9	$C_{19}H_{16}O_6N_2$	61·9	4·4	7·6
Et	Pr^n	198—200	EtOH	Prismatic needles	65·9	6·0	6·0	$C_{24}H_{26}O_6N_2$	65·7	6·0	6·4
H	Pr^n	228—229 (decomp.)	EtOAc	Prisms	62·5	5·0	7·4	$C_{20}H_{18}O_6N_2$	62·8	4·75	7·3
Et	Pr^i	180	EtOH	Needles	65·8	6·0	6·4	$C_{24}H_{26}O_6N_2$	65·7	6·0	6·4
H	Pr^i	275 (decomp.)	EtOAc–Pet	Rhombs	62·95	4·7	7·3	$C_{20}H_{18}O_6N_2$	62·8	4·75	7·3
Et	Bu^n	158—159	EtOH	Needles	65·9	6·2	—	$C_{25}H_{28}O_6N_2$	66·4	6·2	—
H *	Bu^n	222—224 (decomp.)	EtOAc–Pet	Needles	—	—	7·0	$C_{21}H_{20}O_6N_2$	—	—	7·1
Et	*n*-C_6H_{13}	132—133	EtOH	Needles	68·0	5·8	—	$C_{27}H_{32}O_6N_2$	67·5	6·7	—
H	*n*-C_6H_{13}	245 (decomp.)	EtOH	Needles	64·3	5·8	6·45	$C_{23}H_{24}O_6N_2$	65·1	5·7	6·6

* Crystallisation from 50% aqueous ethanol yielded the *hemihydrate* as needles, m. p. 209—210° (Found: C, 62·0; H, 5·3; N, 6·75. $C_{21}H_{20}O_6N_2,\frac{1}{2}H_2O$ requires C, 62·2; H, 5·2; N, 6·9%).
† Pet = light petroleum (b. p. 60—80°).

TABLE 2. 3 : 5-*Dioxopyrazolidines* (VI; R′ = OH).

Substituent R	Substituent R″	M. p.	Solvent *	Form	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Me	Me	283—284°	AcOH	Prismatic needles	57·8	4·5	$C_{20}H_{18}O_8N_2$	58·0	4·4
H	Me	272—273 †	MeOH–H_2O	Micro-cryst.	56·0	3·6	$C_{18}H_{14}O_8N_2$	56·0	3·7
Me	Et	244—246	$CHCl_3$–MeOH	Prisms	58·7	4·6	$C_{21}H_{20}O_8N_2$	58·9	4·7
H	Et	280—282 †	Et_2O–Pet	Square plates	57·4	4·1	$C_{19}H_{16}O_8N_2$	57·0	4·0
Me	Pr^n	164	$CHCl_3$–MeOH	Prismatic needles	59·7	4·7	$C_{22}H_{22}O_8N_2$	59·7	5·0
H	Pr^n	256 †	AcOH	Prisms	58·3	4·8	$C_{20}H_{18}O_8N_2$	58·0	4·4
Me	Pr^i	186—187	$CHCl_3$–MeOH	Prismatic needles	60·0	5·0	$C_{22}H_{22}O_8N_2$	59·7	5·0
H	Pr^i	270 †	EtOH	Microcryst.	58·3	4·4	$C_{20}H_{18}O_8N_2$	58·0	4·4
Me	Bu^n	154	$CHCl_3$–MeOH	Prismatic needles	60·4	5·1	$C_{23}H_{24}O_8N_2$	60·5	5·3
H	Bu^n	220 †	Et_2O–Pet	Plates	59·2	4·7	$C_{21}H_{20}O_8N_2$	58·9	4·7
Me	*iso*-C_5H_{11}	180—181	$CHCl_3$–EtOH	Needles	61·2	5·3	$C_{24}H_{26}O_8N_2$	61·3	5·6
H	*iso*-C_5H_{11}	255 †	Et_2O–Pet	Needles	59·7	4·8	$C_{22}H_{22}O_8N_2$	59·7	5·0
Me	*n*-C_6H_{13}	123—124	MeOH	Prismatic needles	61·75	5·7	$C_{25}H_{28}O_8N_2$	62·0	5·8
H	*n*-C_6H_{13}	225—227 †	Et_2O–Pet	Prismatic needles	60·7	5·0	$C_{23}H_{24}O_8N_2$	60·5	5·3

* Pet = light petroleum (b. p. 60—80°). † With decomp.

1 : 2-*Di*-(3-*acetoxy*-4-*methoxycarbonylphenyl*)-4-n-*butyl*-3 : 5-*dioxopyrazolidine* (VI; R = Me, R′ = OAc, R″ = Bu^n).—Condensation of *n*-butylmalonyl chloride was carried out as described above, with the difference that the ethereal solution of the product was extracted with 5%

aqueous sodium carbonate instead of 2% potassium hydroxide. The extract was acidified (Congo-red) with hydrochloric acid and the product isolated by means of ether. Crystallisation from ether–light petroleum (b. p. 100—120°) and then from light petroleum (b. p. 100—120°) gave **1 : 2-*di*-(3-*acetoxy*-4-*methoxycarbonylphenyl*)-4-n-*butyl*-3 : 5-*dioxopyrazolidine*** as felted needles, m. p. **143—144°** (Found : C, 60·3; H, 5·1. $C_{27}H_{28}O_{10}N_2$ requires C, 60·0; H, 5·2%). This compound (m. p. and mixed m. p. 142—143°) was also obtained by treatment of **4-*n*-butyl-1 : 2-di-(3-hydroxy-4-methoxycarbonylphenyl)-3 : 5-dioxopyrazolidine** with pyridine and acetic anhydride at room temperature overnight.

4-*Alkyl*-1 : 2-*di*-(4-*carboxy*-3-*hydroxyphenyl*)-3 : 5-*dioxopyrazolidines*.—A solution of the **1 : 2-di-(4-alkoxycarbonyl-3-hydroxyphenyl)-4-alkyl-3 : 5-dioxopyrazolidine** (0·5 g.) in 5% potassium hydroxide (20 c.c.) was heated on the steam-bath for 30 min. The cooled solution was acidified (Congo-red) with hydrochloric acid, the solid collected, and crystallised. The acids (Table 2; yields, 50—70%) give a purple colour with aqueous ethanolic ferric chloride and dissolve with effervescence in aqueous sodium hydrogen carbonate.

THE ROYAL TECHNICAL COLLEGE, GLASGOW.
SMITH AND NEPHEW RESEARCH LTD.,
HUNSDON LABORATORIES, WARE.

[*Received, April 19th*, 1955.]