261. *Derivatives of 3 : 5-Dioxopyrazolidine likely to possess Therapeutic Activity.*[1]

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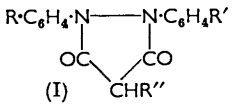
pp'-Dinitrohydrazobenzene condensed with *n*-propyl- and *n*-butylmalonyl dichlorides, giving high yields of 3 : 5-dioxopyrazolidine derivatives. Other hydrazo-compounds were similarly cyclised.

Although 4-*n*-butyl-1 : 2-diphenyl-3 : 5-dioxopyrazolidine (phenylbutazone: I; R = R' = H, R'' = Bu^n) is of value in the treatment of rheumatoid arthritis and allied conditions,[2] it has pronounced toxic side effects [3,4] and the need arose for a less toxic substitute. In the hope that introduction of appropriate substituents in the phenyl groups



(I)

(R and R' may be the same or different. R and R' = H, NHAc, OAc, OBz, CO_2H; R'' = Pr^n, Bu^n.)

of phenylbutazone would give a more suitable product, derivatives having the above general formula were synthesised, by cyclising substituted hydrazobenzenes with alkylmalonyl chlorides. The hydrazo-compounds were obtained by reducing the corresponding azo- or azoxy-derivatives. An attempt to prepare *pp'*-dinitroazobenzene by Green and Bearder's method [5] did not give satisfactory results. However, this azo-compound was obtained in 15% yield by oxidising *p*-nitroaniline with aqueous potassium permanganate; [6] but when the permanganate was replaced by ammonium persulphate and the oxidation was carried out in neutral medium *pp'*-dinitroazoxybenzene was afforded in 48% yield.[7] Oxidation in acid solution gave a 92% yield.

The alkylmalonyl chlorides were prepared by alkylation of ethyl malonate,[8] hydrolysis of the resulting esters to the acids,[9] and conversion of these into the corresponding acid chlorides by treatment with thionyl chloride.[10]

Condensation of *pp'*-dinitrohydrazobenzene with diethyl alkylmalonates in the presence of sodium ethoxide resulted in oxidation of the hydrazo-compound, probably owing to its tautomerisation to a readily oxidisable quinonoid form.[5] With alkylmalonyl chlorides in ether–pyridine (Geigy [11]) cyclisation did not occur. However, it was achieved in dry benzene at the reflux temperature. Reduction of the nitro-groups in the pyrazolidine derivative thus obtained (I; R = R' = NO_2, R'' = Pr^n or Bu^n) was accomplished with zinc dust and ammonium chloride.[12] The reduction product was always contaminated with zinc salts, which could be removed after acetylation. An attempt to convert the amino- into hydroxy-groups was unsuccessful. Nevertheless, derivatives of such hydroxy-compounds (I; R = R' = OAc or OBz) were obtained by condensing acyl derivatives of *p*-hydrazophenol with alkylmalonyl chlorides. This condensation was rendered difficult by the ease with which the hydrazo-compound was oxidised and its poor solubility in solvents recommended for such condensations. Use of an atmosphere of nitrogen did not avoid oxidation of the hydrazo-compound, especially when heat was applied. This

[1] Khalifa, Dissertation, London, 1955.
[2] Currie, *Lancet*, 1952, ii, 15.
[3] Kuzell, Schaffarzick, Brown, and Manble, *J. Amer. Med. Assoc.*, 1952, **149**, 729.
[4] Barter, Gee, and Hirson, *Brit. Med. J.*, 1952, ii, 1392.
[5] Green and Bearder, *J.*, 1911, **99**, 1967.
[6] Cf. Laar, *Ber.*, 1881, **14**, 1928.
[7] Bamberger and Hübner, *Ber.*, 1903, **36**, 3808.
[8] *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 250; Coll. Vol. II, p. 279
[9] Cf. *op. cit.*, Coll. Vol. II, p. 93.
[10] Cf. Staudinger and Bereza, *Ber.*, 1908, **41**, 4463.
[11] Geigy, Swiss P. 267,222 (1950).
[12] Cf. Morgan and Hickinbottom, *J.*, 1921, **119**, 1883.

difficulty, however, was overcome by addition of a trace of zinc dust to the reaction mixture. Acetic anhydride was the best solvent for the condensation because of the appreciable solubility of the hydrazo-compound in it and of the possibility that it might acetylate the hydrazo-compound, thus rendering it less susceptible to oxidation.

Experimental

(All m. p.s are uncorrected.)

pp'-*Dinitroazobenzene.*—*p*-Nitroaniline (20 g.) was almost dissolved in boiling water (2 l.) and powdered potassium permanganate (32 g.) was gradually added with brisk stirring. The reaction was continued for 5 hr. at 90—100°. Unreacted *p*-nitroaniline (7 g.) was recovered on concentration of the filtrate. The precipitated manganese dioxide was extracted with acetone, and the extract yielded pure *pp'*-dinitroazobenzene (3 g.), m. p. 216° (lit.,[13] 214—216°).

pp'-*Dinitroazoxybenzene.*—Finely powdered ammonium persulphate (24 g.) was stirred into ice-cold concentrated sulphuric acid (20 ml.), and when the mixture was homogeneous crushed ice (140 g.) was added, followed by *p*-nitroaniline (4·6 g.) added all at once with brisk stirring. The mixture was kept for 12 hr. at room temperature, then diluted with an equal volume of water. The crude product (4·5 g.) was steam distilled to remove *p*-dinitrobenzene (*ca.* 0·3 g.; m. p. 173—174°) and the residue, after one crystallisation from benzene, had m. p. 190—192° (lit.,[7] 190—192°).

pp'-Dihydroxyazobenzene and its diacetyl and dibenzoyl derivatives were prepared according to recorded methods.[14] Azobenzene-*p*-carboxylic acid was prepared by Anspon's method,[15] which is essentially that described by Angeli and Valori.[16] *pp'*-Dinitrohydrazobenzene was obtained by reducing the corresponding azo- or azoxy-derivative with alcoholic ammonium sulphide according to Werner and Stiasny's method.[17] Crystallisation from acetone gave yellow prisms, m. p. 248—250° (lit.,[19] 248—250°). Diacetyl- and dibenzoyl-*p*-hydrazophenol, prepared by reducing the azo-derivatives with zinc dust and acetic acid according to Khalifa and Linnell's modification [19] of Jacobsen and Steinbrenk's method,[20] melted at 138—140° and 188—190° respectively. Hydrazobenzene-*p*-carboxylic acid, prepared by the above modified procedure, had m. p. 194—195° (lit.,[20] 192—193°).

3 : 5-Dioxopyrazolidine derivative (I) R = R'	R''	Method of prepn.	M. p.	Yield (%)	Formula	Found (%) C	H	N	Required (%) C	H	N
p-NO_2	Pr^n	1	177—178°	85	$C_{18}H_{16}O_6N_4$	56·2	4·5	14·6	56·3	4·2	14·6
,,	Bu^n	1	157—158	85	$C_{19}H_{18}O_6N_4$	57·9	4·5	14·3	57·3	4·5	14·1
p-NHAc	Pr^n		234—236		$C_{22}H_{24}O_4N_4$	64·2	6·0	13·5	64·7	5·9	13·7
,,	Bu^n		216—218		$C_{23}H_{26}O_4N_4$	—	—	13·0	—	—	13·3 *
p-CO_2H ‡	Pr^n	1	218—219	80	$C_{19}H_{18}O_4N_2$	66·9	5·4	8·4	67·5	5·3	8·3
,,	Bu^n	1	250—251 †	80	$C_{20}H_{20}O_4N_2$	67·4	5·4	7·7	68·2	5·7	8·0
p-AcO	Pr^n	2	140—141	53	$C_{22}H_{22}O_6N_2$	63·9	5·4	6·9	64·4	5·4	6·8
,,	Bu^n	2	180—181	53	$C_{23}H_{24}O_6N_2$	64·6	5·6	6·6	65·1	5·7	6·6
p-BzO	Pr^n	2	187—188 †	69	$C_{32}H_{26}O_6N_2$	71·7	4·8	5·2	71·9	4·9	5·2
,,	Bu^n	2	179—180 †	69	$C_{33}H_{28}O_6N_2$	72·0	5·1	5·0	72·3	5·1	5·1

* Found: Ac, 20·9—21·3. Required: Ac, 20·4%.
† Crystallised from glacial acetic acid; other products from ethanol.
‡ R = *p*-CO_2H; R' = H.

n-*Butylmalonyl Chloride.*[10]—*n*-Butylmalonic acid (65 g.) was heated with thionyl chloride (100 ml.; purified according to Fieser, " Experiments on Organic Chemistry," Heath and Co., New York, 2nd edn., p. 381) for 48 hr. at 40—50° and then for 6 hr. at 60°. The product distilled over as colourless liquid, b. p. 88—92°/15 mm. (lit.,[21] 92—96°/22 mm.); yield 64 g. (75%).

n-Propylmalonyl chloride, similarly prepared, had b. p. 75—78°/15 mm.

[13] Cook and Jones, *J.*, 1939, 1310.
[14] Willstätter and Benz, *Ber.*, 1906, **39**, 3495; 1907, **40**, 1582.
[15] Anspon, *Org. Synth.*, 1945, **20**, 86.
[16] Angeli and Valori, *Atti R. Accad. Lincei*, 1913, **22**, 132.
[17] Werner and Stiasny, *Ber.*, 1899, **32**, 3272.
[18] Willgerodt, *J. prakt. Chem.*, 1890, **42**, 49.
[19] Khalifa and Linnell, *J. Org. Chem.*, in the press.
[20] Jacobson and Steinbrenk, *Annalen*, 1898, **303**, 384.
[21] Puterbaugh, Sivamer, and Hauser, *J. Amer. Chem. Soc.*, 1952, **74**, 3439.

3 : 5-*Dioxopyrazolidine Derivatives.*—(1) The hydrazo-compound, suspended in dry benzene, is heated with a slight excess of the acid chloride for 3 hr. at 70—80° with continuous stirring (mercury seal). Then the benzene and the excess of acid chloride are distilled off under vacuum, and the residue is extracted with sodium carbonate solution (charcoal). Acidification of the alkaline extract (Congo Red) with 5N-hydrochloric acid affords the pyrazolidine derivative.

(2) The hydrazo-compound, suspended in acetic anhydride (*ca.* 25 ml. per 1 g.), is heated with a slight excess of the acid chloride with continuous stirring (mercury seal) for 2 hr. at 50—60° under nitrogen and in the presence of a trace of zinc dust. The mixture is filtered from the zinc, most of the acetic anhydride and excess of acid chloride removed, and the residue refluxed with absolute alcohol for ½ hr. to esterify traces of the acid chloride and anhydride. (Extraction with aqueous sodium carbonate, as above, gave a product which could not be purified.) The alcoholic solution on concentration and cooling affords the pyrazolidine derivative. *Diacetamido pyrazolidine derivatives* (I; R = R′ = NHAc, R″ = Pr^n or Bu^n) were obtained by reducing the corresponding dinitro-derivatives with zinc dust and ammonium chloride [12] and acetylating the resulting diamino-derivatives.

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[*Received, October 8th,* 1958.]