1-*Phthalimidopentane*-2 : 4-*dione*.

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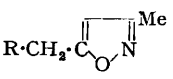
The above compound has been prepared and utilised for the synthesis of phthalimidomethyl-substituted heterocyclic compounds of types (III), (IV), and (V), from which the phthaloyl grouping has been removed with hydrazine.

Acid-catalysed acetolysis of α-acetyl-γ-phthalimidoacetoacetic ester (I) yielded 1-phthalimidopentane-2 : 4-dione (II), m. p. 129·5°, in almost quantitative yield. The latter has not, so far as we are aware, been described previously, although Scheiber (*Ber.*, 1909, **42**, 1442) reported that crystallisation of the ester (I) from acetic acid furnished a small quantity of a substance of unknown structure, m. p. 128°, which was probably (II).

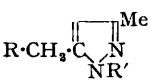
$$\underset{\text{(I)}}{o\text{-}C_6H_4(CO)_2N\cdot CH_2\cdot CO\cdot CHAc\cdot CO_2Et} \xrightarrow[-H^+]{AcOH} \underset{\text{(II)}}{o\text{-}C_6H_4(CO)_2N\cdot CH_2\cdot CO\cdot CH_2\cdot CO\cdot CH_3} + EtOAc + CO_2$$

The structure of the diketone was confirmed by methylation with methyl iodide in the presence of anhydrous potassium carbonate to give a *CC*-dimethyl derivative which unlike (II) did not give a ferric colour. In the Experimental section improved procedures for the preparation of (I) are detailed, including the use of calcioacetoacetic ester (Hackman, *J.*, 1951, 2505).

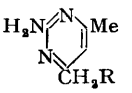
The diketone (II) with hydroxylamine furnished either a monoxime or 3(5)-methyl-5(3)-phthalimidomethyl*iso*oxazole (III; R = phthalimido; or its isomer), depending on the conditions of reaction. Fission of the latter with hydrazine hydrate gave the base (III; R = NH_2) which was converted into the sulphanilamide (III; R = *p*-$NH_2\cdot C_6H_4\cdot SO_2\cdot NH$) in the usual manner. With hydrazine the diketone gave the pyrazole (IV; R = phthalimido, R′ = H) and thence the free base and derived sulphanilamide; phenylhydrazine reacted analogously and furnished the *N*-phenyl derivative and thence the free base (IV; R = NH_2, R′ = Ph; or its isomer).



(III)



(IV)



(V)

Finally, reactions with urea, thiourea, and guanidine were investigated, but only in the last case was a product obtained and that, the pyrimidine (V; R = phthalimido), in small and variable yield. Treatment of this with hydrazine furnished 2-amino-4-aminomethylpyrimidine (V; R = NH_2) which was converted into the sulphanilamide as before. The ultra-violet absorption spectra of the basic pyrimidine (V; R = NH_2) in acid, alkaline, and neutral solutions were almost identical with those of 2-amino-4-methylpyrimidine (Marshall and Walker, *J.*, 1951, 1004) under corresponding conditions of pH, which is good evidence for the proposed structure.

Experimental

Ethyl α-Acetyl-γ-phthalimidoacetoacetate.—(*a*) A solution of phthalimidoacetyl chloride (85 g., 0·38 mol.) (Sheehan and Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1859) in dry benzene (200 ml.) was added slowly to a stirred slurry of sodioacetoacetic ester (0·83 mol.) in benzene (250 ml.). The resulting orange-red mixture was refluxed for 0·5 hr. and, after cooling to −5°, 5N-sulphuric acid (100 ml.) was added with cooling and stirring. The benzene extract was washed with water whereafter solvent and most of the acetoacetic ester were removed by distillation up to 100° (bath)/2 mm. The cooled residue was filtered off with suction and the slightly impure solid (57 g., 48%; m. p. 135°) crystallised from ethanol furnishing the pure product, m. p. 136°.

(*b*) A mixture of phthalimidoacetic acid (205 g.), thionyl chloride (130 g.), and benzene (1300 ml.) was refluxed until a clear solution was obtained. After removal of volatile material

(500 ml.) by distillation at 20 mm. fresh benzene (500 ml.) was added and a similar further amount distilled off. The resulting solution of acid chloride was treated as previously with calcioacetoacetic ester [from calcium oxide (101 g.) and ester (335 g.) in benzene (1 l.)] according to Hackman's instructions (*loc. cit.*). The reaction mixture was worked up as before except that sulphuric acid was replaced by hydrochloric acid. The total yield of crude product, m. p. 130°, was 120 g. (45%) and of recrystallised material, m. p. 136°, 100 g.

1-*Phthalimidopentane*-2 : 4-*dione*.—A solution of the foregoing keto-ester (100 g.) in acetic acid (400 ml.) containing sulphuric acid (20 drops) was boiled under reflux for 3 hr. The cooled solution was poured into water, and the solid *diketone* which separated was filtered off, washed with water (100 ml.), dried *in vacuo* at 40° (yield 73 g., 95%; m. p. 126—128°), and crystallised from benzene–light petroleum (b. p. 60—80°; 1 : 1), separating in plates, m. p. 129·5°, which gave a deep red ferric reaction; $\lambda_{max.}$ (in EtOH), 218 (ε 41,200) and 276 mμ (ε 11,900) with an inflexion at 240 mμ (ε 1100) (Found: C, 63·5; H, 4·5; N, 5·8. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5; N, 5·7%).

To a hot mixture of the diketone (2 g.), hydroxylamine hydrochloride (0·57 g.), and ethanol (20 ml. of 96%), a solution of sodium hydrogen carbonate (0·68 g.) in the minimum of water was slowly added. After 1 hour's refluxing, the *oxime* was isolated by dilution of the cooled reaction mixture with water and crystallised from ethanol forming prismatic needles, m. p. 187° (Found: C, 59·7; H, 4·4; N, 11·2. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·7; N, 10·8%).

3 : 3-*Dimethyl*-1-*phthalimidopentane*-2 : 4-*dione*.—The diketone (2·45 g.), methyl iodide (3·6 g.), anhydrous potassium carbonate (3·1 g.), and ethyl methyl ketone (15 ml.) were refluxed for 2 hr. After removal of solvent in steam, the *product*, which solidified on cooling, was filtered off and crystallised from ethanol, forming needles (2·0 g.), m. p. 108° (Found: C, 65·9; H, 5·5. $C_{15}H_{15}O_4N$ requires C, 65·9; H, 5·5%). It gave a negative ferric test and had $\lambda_{max.}$ (in EtOH) 220 (ε 37,900) and 295 mμ (ε 1180).

3(5)-*Methyl*-5(3)-*phthalimido*isoo*xazole*.—The reaction was carried out as for preparation of the oxime except that anhydrous potassium carbonate (11·4 g. per 20 g. of diketone) was used as condensing agent and refluxing was for 8 hr. The iso*oxazole* was obtained as needles (from ethanol), m. p. 133° (78%) (Found: N, 11·6. $C_{13}H_{10}O_3N_2$ requires N, 11·6%).

5(3)-*Aminomethyl*-3(5)-*methyl*isoo*xazole Hydrochloride*.—The foregoing crude product (13·2 g.) was refluxed with hydrazine hydrate (7 g. of 50%) in ethanol (50 ml.) for 3 hr. After removal of phthalhydrazide by filtration, the mother-liquor was evaporated to dryness *in vacuo*. The residue was then heated at 60°/2 mm. to remove excess of hydrazine and was extracted with 2N-hydrochloric acid (100 ml.) at 50° for 15 min. Evaporation of the aqueous extract to dryness on the steam-bath furnished the crude *hydrochloride* (5 g.), which crystallised from methanol as solvated plates, m. p. 201° (decomp.) (Found: C, 39·5; H, 6·8. $C_5H_9ON_2Cl,CH_3{\cdot}OH$ requires C, 39·8; H, 7·2%).

5(3)-p-*Aminobenzenesulphonamidomethyl*-3(5)-*methyl*isoo*xazole*.—The above crude hydrochloride (4 g.) was converted into the free base by refluxing with methanolic sodium methoxide (31 ml. from 0·62 g. of metal) for 30 min. The cooled solution was filtered and methanol removed *in vacuo*. To the residue, pyridine (10 ml.) and finely powdered *p*-acetamidobenzenesulphonyl chloride (6·3 g.) were slowly added. Heat was evolved during the addition and finally the mixture was heated to 100° for 5 min., poured into ice-water (900 ml.), and acidified to Congo-red with hydrochloric acid. After saturation with sodium chloride, the mixture was filtered and the residue boiled with 2N-sodium hydroxide (40 ml.) for 0·5 hr. Acidification of the cooled solution to pH 5 with acetic acid furnished the *product* as a solid, which was obtained as needles, m. p. 142°, from ethanol (Found: N, 15·7; S, 11·9. $C_{11}H_{13}O_3N_3S$ requires N, 15·7; S, 11·5%).

3-*Methyl*-5-*phthalimidomethylpyrazole*.—1-Phthalimidopentane-2 : 4-dione (24·5 g.) was caused to react with hydrazine hydrate (10 g. of 50%) in ethanol (100 ml.) under reflux for 1 hr. The resulting solution was diluted with water while still hot until opalescence occurred and allowed to cool; the product, m. p. 180—183°, crystallised A second crystallisation from aqueous ethanol furnished the pure *pyrazole* (17·3 g.) in needles, m. p. 185° (Found: C, 64·1; H, 4·6; N, 17·4. $C_{13}H_{11}O_2N_3$ requires C, 64·7; H, 4·6; N, 17·4%).

5-*Aminomethyl*-3-*methylpyrazole*.—The phthalimido-group was removed from the above compound (12 g.) as for the *iso*oxazole derivative, furnishing the *hydrochloride* (4·3 g.), plates (from ethanol), m. p. 266°, of the base (Found: N, 27·9; Cl, 24·0. $C_5H_{10}N_3Cl$ requires N, 28·5; Cl, 24·1%). The free base was liberated from its hydrochloride by treatment with the stoicheiometric amount of sodium methoxide in methanol and had b. p. 164°/3 mm., m. p. 60°. This product was extremely deliquescent and absorbed carbon dioxide from the atmosphere

with great rapidity making analysis difficult (Found : C, 53·0; H, 8·1. Calc. for $C_5H_9N_3$: C, 54·0; H, 8·1%). It formed a *dibenzoate* (Schotten–Baumann), plates (from ethanol), m. p. 138° (Found : C, 71·5; H, 5·3; N, 13·2. $C_{19}H_{17}O_2N_3$ requires C, 71·4; H, 5·4; N, 13·2%).

3-p-*Aminobenzenesulphonamidomethyl*-5-*methylpyrazole*, prepared as in the *iso*oxazole series, formed needles, m. p. 165—166°, from ethanol (Found : C, 49·6; H, 5·7; N, 21·0; S, 11·8. $C_{11}H_{14}O_2N_4S$ requires C, 49·6; H, 5·3; N, 21·0; S, 12·0%).

3(5)-*Methyl*-1-*phenyl*-5(3)-*phthalimidomethylpyrazole*.—1-Phthalimidopentane-2 : 4-dione (8·2 g.) was refluxed with phenylhydrazine (3·6 g.) in benzene (500 ml.) for 1·5 hr. The solvent was then removed under reduced pressure and the semi-solid residue left in a desiccator overnight, whereupon it solidified. Crystallisation from benzene–light petroleum (b. p. 60—80°) furnished the *pyrazole* (6·5 g., 61%) as needles, m. p. 118° (Found: C, 71·9; H, 4·7; N, 13·2. $C_{19}H_{13}O_2N_3$ requires C, 71·9; H, 4·8; N, 13·2%).

5(3)-*Aminomethyl*-3(5)-*methyl*-1-*phenylpyrazole*.—Removal of the phthalimido-grouping as before from the foregoing pyrazole yielded the *hydrochloride* as leaflets, m. p. 258° (Found : C, 58·6; H, 6·1; N, 18·3. $C_{11}H_{14}N_3Cl$ requires C, 59·1; H, 6·3; N, 18·8%), and thence the free *base*, a yellow oil, b. p. 138°/0·6 mm., n_D^{20} 1·5922 (Found : C, 70·1; H, 6·8. $C_{11}H_{13}N_3$ requires C, 70·6; H, 7·0%).

2-*Amino*-4-*methyl*-6-*phthalimidomethylpyrimidine*.—1-Phthalimidopentane-2 : 4-dione (24·6 g.) was added to a refluxing mixture of guanidine carbonate (9 g.) in ethanol (200 ml.). After a further 2 hours' refluxing the mixture was kept at room temperature for 24 hr., the almost pure *pyrimidine* separating (5 g.). This formed needles, m. p. 237°, from dioxan (Found : C, 62·6; H, 4·6. $C_{14}H_{12}O_2N_4$ requires C, 62·7; H, 4·5%). It had $\lambda_{max.}$ (in EtOH) 220 (ε 44,800) and 294 (ε 6600) with a slight inflexion at 240 mμ (ε 15,000).

2-*Amino*-6-*aminomethyl*-4-*methylpyrimidine*.—Fission of the preceding compound with hydrazine hydrate, as in the previous examples except that dioxan was used as solvent, gave the *hydrochloride* as needles, m. p. 265° (decomp.) (Found : C, 34·4; H, 6·0; N, 26·3. $C_6H_{12}N_4Cl_2$ requires C, 34·1; H, 5·7; N, 26·5%); $\lambda_{max.}$ (in 0·1N-HCl) 223 (ε 14,580) and 301 mμ (ε 6250); (in water at pH 7·0) 228 (ε 12,780) and 291 mμ (ε 4300); (in 0·1N-NaOH) 227 mμ (ε 12,000) and 289 mμ (ε 4900).

2-*Amino*-6-p-*aminobenzenesulphonamidomethyl*-4-*methylpyrimidine*, prepared as previously, formed prisms (from ethanol), m. p. 193° (Found : C, 49·4; H, 5·37; S, 10·3. $C_{12}H_{15}O_2N_5S$ requires C, 49·1; H, 5·16; S, 10·8%).

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