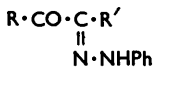
304. *The Reduction of Some α-Phenylhydrazono-ketones with Alkali Borohydrides.*

By R. E. Bowman and C. S. Franklin.

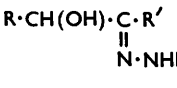
Several α-phenylhydrazono-ketones (I) have been reduced by alkali borohydrides to the corresponding alcohols (II) although in a few cases these proved too unstable for isolation. Some reactions of the alcohols have been examined, including hydrogenolysis as exemplified by the reduction of ethyl β-hydroxy-α-phenylhydrazonobutyrate (II; R = Me, R′ = CO_2Et) to an equimolar mixture of racemic and *allo*-threonine.

There appears to be no report of the reduction of phenylhydrazono-ketones of type (I) by alkali borohydrides and indeed, except for the sugar osazones, α-phenylhydrazono-alcohols (II) have received little study. This investigation had as object to obtain some members of this group and to develop a new route to α-amino-alcohols by their hydrogenolysis.

We began with two simple members, pyruvaldehyde and phenylglyoxylaldehyde monophenylhydrazones (I; R = Me and Ph respectively, R′ = H): with potassium or sodium borohydride in aqueous ethanol, at room temperature or slightly above, excellent yields of the alcohols (II; R = Me and Ph, R′ = H) were obtained. Analogous reductions took place with the monophenylhydrazones of ethyl αβ-dioxo-butyrate (I; R = Me, R′ = CO_2Et) and -succinate (R = R′ = CO_2Et) but in the latter case cyclisation of the product yielded the pyrazolone ester (III; R = CO_2Et).



(I)



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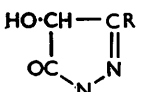
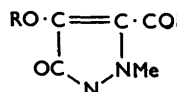


(III)



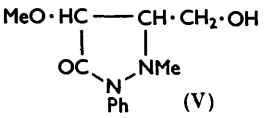
(IV)

Similar reductive cyclisations occurred with other compounds of type (I) when R = CO_2Et; thus the esters (I; R = CO_2Et, R′ = CN or Ac) furnished the 4-hydroxypyrazol-5-ones (III; R = CN or CHMe·OH respectively), in the latter case further reduction of the 3-substituent yielding the corresponding secondary alcohol. The ester (III; R = CO_2Et) with methyl iodide in methanol at 110° furnished the 2-methyl derivative (IV; R = H, R′ = OEt) and we prepared a considerable number of such derivatives for biological evaluation. Although the anilide (IV; R = H, R′ = NHPh) could be prepared by interaction of the ester with anilinomagnesium iodide, the amide and hydrazide could not be obtained directly. However, the 4-hydroxyl group in these substances is phenolic (pK_a' 6·4) and the 4-methyl and 4-benzyl ether were readily obtained. These ethers, in contrast to the corresponding alcohols, reacted normally with ammonia and hydrazine, to give the corresponding amide and hydrazide; in the *O*-benzyl series, the benzyl group was removed by catalytic hydrogenolysis, yielding the hydroxy-amide and -hydrazide (R = H, R′ = NH_2, and NH·NH_2 respectively).

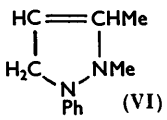
Esters (IV; R′ = OEt, R = H, Me, and CH_2Ph) were readily hydrolysed by alkali to the acids and, as with simple pyrazol-5-one-3-carboxylic acids, these lost carbon dioxide at 180° to give the pyrazol-5-ones. We also examined the further reduction of the ester (IV; R = Me, R′ = OEt) where the 4-hydroxyl grouping is protected by methylation; with lithium borohydride good yields of the corresponding 3-hydroxymethyl-4-methoxy-compound were obtained, but with lithium aluminium hydride the sole product was the saturated pyrazolidone (V). The latter reduction contrasts with that of antipyrine itself which under apparently identical conditions gives the pyrazoline (VI) and a smaller quantity of dihydroantipyrine (VII).

Among further reductions, the monophenylhydrazone of αβ-dioxo-β-phenylpropionitrile (I; R = Ph, R′ = CN) appeared to react normally with potassium borohydride

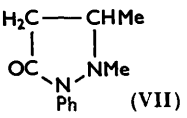
but the only crystalline product isolated (in low yield) was the unsaturated nitrile (VIII), which presumably arose by elimination of water from the expected reduction product reacting in its tautomeric phenylazo- (IX) rather than in the alternative phenylhydrazone structure (II; R = Ph, R′ = CN); as would be expected, the unsaturated nitrile, unlike the other compounds described so far, was highly coloured. Reduction of the analogous



(V)



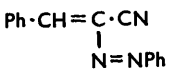
(VI)



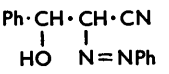
(VII)

nitro-compound (I; R = Ph, R′ = NO_2) was expected to take a similar course in view of the ready elimination of water from β-hydroxy-β-phenyl-α-nitroalkanes,[1] but a high yield of the nitro-alcohol (II; R = Ph, R′ = NO_2) was obtained. Catalytic reduction of the latter furnished a crystalline base which was shown by analysis and comparison with an authentic specimen obtained by interaction of ethyl mandelimidate[2] and phenylhydrazine to be the amidine (X).

Reduction of 2-oxo-2-phenyl-1-phenylhydrazonoethanesulphonic acid (I; R = Ph, R′ = SO_3H) was expected to be normal in view of the reported stability of 2-hydroxyalkane-1-sulphonic acids of which 2-hydroxy-2-phenylethanesulphonic acid is the nearest analogy.



(VIII)



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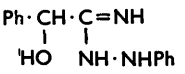
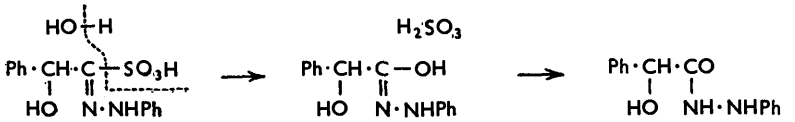


(X)

However, on acidification of the reduction mixture sulphur dioxide was evolved and chloroform extracted mandelic phenylhydrazide (XII), presumably formed from (XI) by hydrolysis and rearrangement.

Reaction of a phenylhydrazono-ketone containing two carbonyl functions, *viz.*, 3-phenylhydrazonopentane-2 : 4-dione (I; R = Me, R′ = Ac), with potassium borohydride was confined to one carbonyl group, yielding the 1 : 3-hydroxy-ketone (II; R = Me, R′ = Ac), under all conditions tried.

The ultraviolet absorption spectra of most of these compounds (see Table) fall into two groups: those possessing two strong bands at *ca.* 240 and 360—390 mμ where R or R′ are



(XI) (XII)

strong electron-attracting groups, and those with only one band at *ca.* 280 mμ which is usually associated with aliphatic non-conjugated phenylhydrazones and where R or R′ has weak or negligible activating effects. This difference could be useful in the diagnosis of phenylhydrazones possessing vicinal carbonyl groups.

Finally we examined the hydrogenolysis of a phenylhydrazono-alcohol in the presence of Raney nickel. Ethyl β-hydroxy-α-phenylhydrazonobutyrate (II; R = Me, R′ = CO_2Et) at atmospheric pressure slowly gave an oil, hydrolysis of which furnished DL-threonine and DL-*allo*threonine which were shown microbiologically to be present in equimolar proportion. However, the overall yield was low and the method does not compare favourably with the standard method in which the phenylhydrazone group is reduced before the carbonyl substituent.[3,4]

[1] Rosenmund, *Ber.*, 1913, **46**, 1037.
[2] Mackenzie, *J.*, 1918, 1.
[3] Pfister, Robinson, Shabica, and Tishler, *J. Amer. Chem. Soc.*, 1948, **70**, 2297.
[4] Bolhofer, *ibid.*, 1953, **75**, 4469.

Absorption spectra of some phenylhydrazones, RR'C:N·NHPh.

R	R'	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
Ac	Ac	243	13,230	360	24,900
,,	CO_2Et	240	11,830	351	19,300
,,	$CO·CO_2Et$	248	13,400	376	26,700
$CO·CO_2Et$	CO_2Et	243	12,380	363	20,820
$CO·CO_2Et$	CN	244	8,100	354	21,850
Bz	NO_2	246	13,900	393	14,600
,,	CN	245	11,800	379	21,800
Ac	H	237	10,090	350	22,460
,,	CHMe·OH	236	11,100	341	21,350
Me	CO_2Et	223	10,070	324	21,140
CHMe·OH	CO_2Et	231	9,830	329	20,900
Bz	H	247	14,150	380	19,810
CHPh·OH	NO_2	238	15,400	400	13,400
CHMe·OH	H	—	—	277	18,200
$Ph·CH_2$	H	—	—	281	18,470
CHPh·OH	H	—	—	280	19,020
,,	NH_2	—	—	267	12,000
Ph·CH:C(CN)·N:NPh		236	7,500	348	40,000

Experimental

Ultraviolet absorption spectra were determined for EtOH solution, the Unicam S.P. 500 Spectrophotometer being used. Light petroleum was the fraction of b. p. 60—80°.

Reduction of α-Phenylhydrazono-ketones.—Method A. A 1% solution of sodium or potassium borohydride (0·5 mol.) in aqueous ethanol (H_2O : EtOH, 3 : 1) was added dropwise with stirring to a solution of the phenylhydrazono-ketone (1 mol.) in ethanol and after 1—2 hr. at 20—40° the mixture was concentrated *in vacuo*. The phenylhydrazono-alcohol was isolated by extraction with ethyl acetate and crystallised from benzene–light petroleum, except where otherwise stated.

Method B. The procedure was the same but the reaction temperature was kept below 25° and the solution acidified with 2N-sulphuric acid at the end of the reduction; after removal of the inorganic salts by filtration, the product was isolated as before.

Method C. The reduction was carried out as for method *B* but in an atmosphere of nitrogen and with an equimolar quantity of potassium borohydride (10% solution in water). On concentration of the filtered solution the product solidified and was purified by crystallisation. The following were thus obtained (method indicated in parentheses) :

Lactaldehyde phenylhydrazone [5] [from pyruvaldehyde phenylhydrazone [6] (*A*)], prisms (53%), m. p. 90·5—91·5° (Wöhl gives m. p. 93°) (Found : C, 66·4; H, 7·6; N, 16·7. Calc. for $C_9H_{12}ON_2$: C, 65·8; H, 7·4; N, 17·1%).

Mandelaldehyde phenylhydrazone [from phenylglyoxylaldehyde phenylhydrazone [7] (*A*)], needles, m. p. 103° (Found : C, 74·3; H, 6·2; N, 12·0. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%).

4-Oxo-3-phenylhydrazonopentan-2-ol [from 3-phenylhydrazonopentane-2 : 4-dione [8] (*A*)], yellow needles (40%), m. p. 138—138·5° (Found : C, 64·2; H, 6·7; N, 13·6. $C_{11}H_{14}O_2N_2$ requires C, 64·1; H, 6·8; N, 13·6%).

Ethyl β-hydroxy-α-phenylhydrazonobutyrate [from ethyl β-oxo-α-phenylhydrazonobutyrate [9] (*B*)], prisms (55%), m. p. 93—94° (Found : C, 61·1; H, 6·8; N, 11·5. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8; N, 11·9%).

β-Phenyl-α-phenylazoacrylonitrile [from β-oxo-β-phenyl-α-phenylhydrazonopropionitrile [10] (*B*)], orange needles (11%), m. p. 119—120° (Found : C, 77·1; H, 4·7; N, 18·1. $C_{15}H_{11}N_3$ requires C, 77·2; H, 4·8; N, 18·0%).

2-Nitro-1-phenyl-2-phenylhydrazonoethanol [from the corresponding nitro-ketone [11] (*B*)],

[5] Wöhl, *Ber.*, 1908, **41**, 3611.
[6] Japp and Klingemann, *J.*, 1888, **53**, 519.
[7] Muller and von Pechmann, *Ber.*, 1889, **22**, 2557.
[8] Bulow, *Ber.*, 1902, **35**, 2188.
[9] *Idem*, *Ber.*, 1912, **45**, 3736.
[10] Haller, *Compt. rend.*, 1889, **108**, 1116.
[11] Parkes, *J.*, 1934, 67.

deep orange needles (67%) (from xylene), m. p. 121—122° (Found: C, 62·3; H, 5·0; N, 15·1. $C_{14}H_{13}O_3N_3$ requires C, 62·0; H, 4·8; N, 15·5%).

Mandelic acid phenylhydrazide [12] [from 2-oxo-2-phenyl-1-phenylhydrazonoethanesulphonic acid [13] (*B*)], needles (13%) (from alcohol), m. p. and mixed m. p. 181—183° (Found: C, 69·6; H, 5·7. Calc. for $C_{14}H_{14}O_2N_2$: C, 69·4; H, 5·8%).

3-*Ethoxycarbonyl*-4-*hydroxyl*-1-*phenylpyrazol*-5-*one* [from ethyl α-oxo-β-phenylhydrazonosuccinate [14] (*C*)], needles (77%) (from ethyl acetate), m. p. 163°, $\lambda_{max.}$ 239, 357 mμ (ε 10,660, 17,720) (Found: C, 57·7; H, 4·7; N, 11·3. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·9; N, 11·3%). Acetylation with acetic anhydride at 50° gave prisms, from benzene–light petroleum, of the *acetate*, m. p. 74—75°, $\lambda_{max.}$ 253 mμ (ε 10,170), $\lambda_{infl.}$ 275 mμ (ε 5700) (Found: C, 57·9; H, 4·7; N, 9·4. $C_{14}H_{14}O_5N_2$ requires C, 57·9; H, 4·9; N, 9·7%).

3-*Ethoxycarbonyl*-4-*hydroxy*-1-p-*nitrophenylpyrazol*-5-*one* [from ethyl α-oxo-β-*p*-nitrophenylhydrazonosuccinate [15] (*C*)], pale yellow prisms (50%) (from ethanol), m. p. 198° (decomp.), $\lambda_{max.}$ 228, 373 mμ (ε 11,400, 28,020) (Found: C, 48·7; H, 3·8; N, 14·5. $C_{12}H_{11}O_6N_3$ requires C, 49·1; H, 3·8; N, 14·3%).

3-*Cyano*-4-*hydroxy*-1-*phenylpyrazol*-5-*one* [from ethyl β-cyano-α-oxo-β-phenylhydrazonopropionate [16] (*C*)], needles (57%) (from nitromethane), m. p. 167° (decomp.), $\lambda_{max.}$ 252, 344 mμ (ε 14,100, 6300) (Found: C, 59·3; H, 3·7; N, 20·8. $C_{10}H_7O_2N_3$ requires C, 59·7; H, 3·5; N, 20·9%).

4-*Hydroxy*-3-1′-*hydroxyethyl*-1-*phenylpyrazol*-5-*one* [from ethyl αγ-dioxo-β-phenylhydrazonovalerate [17] (*C*)], prisms (26%) (from ethanol), m. p. 161° (decomp.), $\lambda_{max.}$ 241, 397 mμ (ε 14,800, 9750), pK_a' 7·9 in 50% ethanol (Found: C, 59·8; H, 5·5. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5%).

3-*Ethoxycarbonyl*-4-*hydroxy*-2-*methyl*-1-*phenylpyrazol*-5-*one*.—3-Ethoxycarbonyl-4-hydroxy-1-phenylpyrazol-5-one (50 g.), methyl iodide (28·4 g.), and methanol (50 ml.) were heated together in an autoclave at 105° for 16 hr. and, after cooling, the solid was filtered off and air-dried. Crystallisation from 50% aqueous ethanol (700 ml.) afforded needles of the N-*methylpyrazolone* (37 g.), m. p. 164°, $\lambda_{max.}$ 284, 331 mμ (ε 11, 210, 8110), pK_a' 6·4 in 50% methanol (Found: C, 59·6; H, 5·7; N, 10·8; active H, 0·37. $C_{13}H_{14}O_4N_2$ requires C, 59·5; H, 5·4; N, 10·7; 1 active H, 0·38%). Treatment with acetic anhydride gave the *acetate* as needles (from benzene–light petroleum), m. p. 71—72°, $\lambda_{max.}$ 237, 252, 317 mμ (ε 7330, 7710, 6910) (Found: C, 59·1; H, 5·3; N, 9·5. $C_{15}H_{16}O_5N_2$ requires C, 59·2; H, 5·3; N, 9·2%), whilst interaction with the appropriate acid chloride in the presence of pyridine yielded the following esters: *benzoate*, needles (from benzene–light petroleum), m. p. 115—116° (Found: C, 65·6; H, 4·8; N, 7·7. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 5·0; N, 7·7%); *diphenylacetate*, plates (from benzene–light petroleum), m. p. 120—121° (Found: C, 70·6; H, 5·2; N, 6·4. $C_{27}H_{24}O_5N_2$ requires C, 71·0; H, 5·3; N, 6·1%); p-*nitrobenzoate*, pale yellow prisms (from 50% aqueous ethanol), m. p. 151° (Found: C, 58·0; H, 4·2; N, 9·9. $C_{20}H_{17}O_7N_3$ requires C, 58·4; H, 4·2; N, 10·2%). Hydrogenation of the last ester with palladised strontium carbonate gave the p-*aminobenzoate*, pale yellow needles (from ethanol), m. p. 186° (Found: C, 60·5; H, 4·8; N, 10·8. $C_{20}H_{19}O_6N_3$ requires C, 60·5; H, 4·8; N, 10·6%).

3-*Carboxy*-4-*hydroxy*-2-*methyl*-1-*phenylpyrazol*-5-*one*.—The ester (IV; R = H, R′ = OEt) (2 g.) in warm ethanol (35 ml.) was treated overnight with 2N-sodium hydroxide (2 mol.); after concentration *in vacuo* the solution was acidified with 2N-hydrochloric acid and the resulting solid filtered off. Crystallisation from aqueous ethanol gave needles of the *acid* (1·8 g.), m. p. 134° (decomp.), $\lambda_{max.}$ 269, 298 mμ (ε 10,070, 6980), pK_a' 3·2 and 10·2 in 50% methanol (Found: C, 56·3; H, 4·9; N, 11·5. $C_{11}H_{10}O_4N_2$ requires C, 56·4; H, 4·3; N, 12·0%). The acid was heated to 200° (bath) until the evolution of carbon dioxide had stopped and, on cooling, the melt solidified. Crystallisation from toluene yielded 4-*hydroxy*-2-*methyl*-1-*phenylpyrazol*-5-*one* as needles, m. p. 191—192°, $\lambda_{max.}$ 242, 247, 283 mμ (ε 9950, 10,100, 9100), pK_a' 9·3 in 50% methanol (Found: C, 63·1; H, 5·4; N, 14·7. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%).

4-*Hydroxy*-2-*methyl*-1-*phenyl*-3-N-*phenylcarbamoylpyrazol*-5-*one*.—The ester (IV; R = H, R′ = OEt) (1 g.) in dioxan (10 ml.) was added to a suspension of anilinomagnesium iodide

[12] Reissert, *Ber.*, 1889, **22**, 2928.
[13] Parkes, *J.*, 1934, 1861.
[14] Rabischong, *Bull. Soc. chim. France*, 1904, **31**, 78.
[15] Chattaway, *J.*, 1933, 1389.
[16] Fleischauer, *J. prakt. Chem.*, 1893, **47**, 382.
[17] Beyer and Claisen, *Ber.*, 1888, **21**, 1697.

(2 mol.) in ether (30 ml.) (Hardy's method [18]), the *anilide* being obtained as needles (0·3 g.) (from aqueous ethanol), m. p. 231—232° (decomp.), $\lambda_{max.}$ 294, 340 mμ (ε 20,800, 11,300), pK_a' 5·5 in 50% dimethylacetamide (Found: C, 66·3; H, 4·7; N, 13·2. $C_{17}H_{15}O_3N_3$ requires C, 66·0; H, 4·9; N, 13·6%).

4-Benzyloxy-3-ethoxycarbonyl-2-methyl-1-phenylpyrazol-5-one.—Benzyl chloride (12·7 g.) and the ester (IV; R = H, R′ = OEt) (13 g.) in ethyl methyl ketone (1 l.) were refluxed with stirring in the presence of anhydrous potassium carbonate (27 g.) for 16 hr. The mixture was cooled and filtered, the filtrate evaporated to dryness, and the residue crystallised from light petroleum, to give needles of the *benzyl ether* (16·5 g.), m. p. 84—85°, $\lambda_{max.}$ 265, 319 mμ (ε 8800, 7880) (Found: C, 68·1; H, 5·7; N, 8·1. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 8·0%). Hydrolysis as previously yielded nacreous plates (from aqueous ethanol) of *4-benzyloxy-3-carboxy-2-methyl-1-phenylpyrazol-5-one*, m. p. 171° (decomp.), $\lambda_{max.}$ 260 mμ (ε 10,000), $\lambda_{infl.}$ 253, 293 mμ (ε 8450, 8410), pK_a' 3·4 in 50% methanol (Found: C, 66·7; H, 4·9. $C_{18}H_{16}O_4N_2$ requires C, 66·7; H, 5·0%). The acid was decarboxylated as before, to *4-benzoyloxy-2-methyl-1-phenylpyrazol-5-one* which separated from benzene–light petroleum as needles, m. p. 125—126°, $\lambda_{max.}$ 245, 282 mμ (ε 8750, 8750), $\lambda_{infl.}$ 268 mμ (ε 7430) (Found: C, 72·3; H, 5·6. $C_{17}H_{16}O_2N_2$ requires C, 72·8; H, 5·8%).

3-Carbamoyl-4-hydroxy-2-methyl-1-phenylpyrazol-5-one.—The ether (IV; R = Ph·CH_2, R′ = OEt) (0·5 g.) in methanol (15 ml.) at 0° was treated with dry ammonia for 5 hr. Removal of the solvent by distillation and crystallisation of the residue from aqueous ethanol furnished needles of *4-benzyloxy-3-carbamoyl-2-methyl-1-phenylpyrazol-5-one* (0·45 g.), m. p. 120·5—121·5° (Found: N, 13·0. $C_{18}H_{17}O_3N_3$ requires N, 13·0%). This compound (0·75 g.) in absolute ethanol (20 ml.) was hydrogenated in the presence of palladised strontium carbonate in the usual manner, to give the *hydroxy-amide* (0·2 g.), m. p. 246° (decomp.), $\lambda_{max.}$ 282, 330 mμ (ε 8880, 5890), pK_a' 6·0 in 50% methanol (Found: C, 56·7; H, 4·8; N, 17·6. $C_{11}H_{11}O_3N_3$ requires C, 56·7; H, 4·8; N, 18·0%), as needles from aqueous ethanol.

Hydrazide of 3-Carboxy-4-hydroxy-2-methyl-1-phenylpyrazol-5-one.—4-Benzyloxy-3-ethoxycarbonyl-2-methyl-1-phenylpyrazol-5-one (1 g.) in ethanol (10 ml.) was refluxed for 3 hr. with hydrazine hydrate (2 ml.; 90% w/w). On concentration to a small volume and addition of water (5 ml.) the crude *hydrazide* separated; it crystallised from water as needles (0·6 g.), m. p. 115° (Found: N, 16·4. $C_{18}H_{18}O_3N_4$ requires N, 16·6%). Hydrogenation as above gave, on crystallisation from aqueous alcohol, the *hydroxy-hydrazide* as plates (0·2 g.), m. p. 214° (decomp.), $\lambda_{max.}$ 289, 344 mμ (ε 12,450, 7850) (Found: C, 53·4; H, 4·8; N, 22·3. $C_{11}H_{12}O_3N_4$ requires C, 53·2; H, 4·9; N, 22·6%).

3-Ethoxycarbonyl-4-methoxy-2-methyl-1-phenylpyrazol-5-one.—The ester (IV; R = H, R′ = OEt) (13 g.) was added portionwise to a stirred solution at 10° of diazomethane (3 mol.) in ether (500 ml.) and after all the solid had dissolved acetic acid was added dropwise until no more effervescence occurred. The solution was washed with 2N-potassium carbonate, then water, and dried. Distillation to dryness and crystallisation of the residue from light petroleum yielded needles of the *methoxy-ester* (11·6 g.), m. p. 77°, $\lambda_{max.}$ 263, 318 mμ (ε 8090, 6590) (Found: C, 60·9; H, 6·1. $C_{14}H_{16}O_4N_2$ requires C, 60·9; H, 5·8%). Hydrolysis of the latter (6 g.) in the usual manner afforded *3-carboxy-4-methoxy-2-methyl-1-phenylpyrazol-5-one* as needles (from aqueous ethanol) (4·6 g.), m. p. 185° (decomp.), $\lambda_{max.}$ 259 mμ (ε 8800), $\lambda_{infl.}$ 295 mμ (ε 7120) (Found: C, 57·8; H, 5·1. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·9%). Heating the acid at 185° gave *4-methoxy-2-methyl-1-phenylpyrazol-5-one*, prisms (from benzene–light petroleum), m. p. 118—120°, $\lambda_{max.}$ 245, 251, 281 mμ (ε 10,100, 9720, 9990) (Found: C, 64·7; H, 5·8. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%), also obtained by the action of diazomethane on 4-hydroxy-2-methyl-1-phenylpyrazol-5-one.

3-Hydroxymethyl-4-methoxy-2-methyl-1-phenylpyrazol-5-one.—To a stirred suspension of lithium borohydride [19] (2 mol.) in tetrahydrofuran (25 ml.) was added dropwise the methoxy-ester (IV; R = Me, R′ = OEt) (7 g.) in ether (50 ml.) and after 30 min. the mixture was poured into water (100 ml.). Distillation to dryness *in vacuo* and crystallisation of the residue from water yielded needles of the *methoxy-alcohol* (4·1 g.), m. p. 155°, $\lambda_{max.}$ 247, 282 mμ (ε 10,800, 11,000) (Found: C, 61·5; H, 6·0. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0%).

3-Carbamoyl-4-methoxy-2-methyl-1-phenylpyrazol-5-one.—Dry ammonia was bubbled through a solution of the methoxy-ester (IV; R = Me, R = OEt) (10 g.) in methanol (30 ml.) at 0° for

[18] Hardy, *J.*, 1936, 398.
[19] Paul and Joseph, *Bull. Soc. chim. France*, 1953, 758.

4 hr. Evaporation to dryness and crystallisation of the residue from water furnished prisms of the *amide* (6·7 g.), m. p. 125° (Found : C, 58·4; H, 5·3. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·3%).

3-*Cyano*-4-*methoxy*-2-*methyl*-1-*phenylpyrazol*-5-*one*.—The foregoing amide (1 g.) and phosphoric oxide (1 g.) were mixed and distilled at atmospheric pressure over a free flame. The distillate, on crystallisation from light petroleum, afforded the *nitrile* as plates (0·5 g.), m. p. 89—90° (Found : C, 63·2; H, 5·0. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8%).

3-*Ethoxycarbonyl*-4-*hydroxy*-2-*methyl*-1-p-*nitrophenylpyrazol*-5-*one*.—3-Ethoxycarbonyl-4-hydroxy-1-*p*-nitrophenylpyrazol-5-one (2 g.), methyl iodide (15 g.), and methanol (5 ml.) were heated in a sealed tube at 110° for 15 hr. and, after cooling and filtration from unchanged material (0·2 g.), the filtrate was boiled with ethanol (15 ml.) and cooled. Filtration and crystallisation from ethanol gave yellow-brown cubes of the N-*methyl compound* (0·3 g.), m. p. 225—256° (decomp.), $\lambda_{max.}$ 314 mμ (ε 16,800) (Found : C, 50·6; H, 4·3. $C_{13}H_{13}O_6N_3$ requires C, 50·8; H, 4·3%). It formed an *acetate*, pale yellow prisms (from benzene–light petroleum), m. p. 117·5—118° (Found : C, 51·2; H, 4·2. $C_{15}H_{15}O_7N_3$ requires C, 51·6; H, 4·3%).

3-*Hydroxymethyl*-4-*methoxy*-2-*methyl*-1-*phenylpyrazolid*-5-*one*.—The methoxy-ester (IV; R = Me, R′ = OEt) (19 g.) in benzene (150 ml.) was added dropwise during 15 min. to a stirred and cooled suspension of lithium aluminium hydride (2·75 g.) in ether (100 ml.). The mixture was refluxed for 4 hr., then decomposed with water in the usual manner, and distillation yielded the *pyrazolidone* (8·8 g.), b. p. 149—151°/0·2 mm., n_D^{20} 1·5600 (Found : C, 61·4; H, 6·9. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8%).

2 : 3-*Dimethyl*-1-*phenyl*-Δ^3-*pyrazoline*.—Antipyrine (100 g.) in benzene (1·1 l.) was reduced with lithium aluminium hydride (20 g.) in ether (500 ml.) as in the previous example, and the crude product fractionally distilled, to give the *pyrazoline* (60 g.), b. p. 58°/0·2 mm., n_D^{20} 1·5708, pK_a' 3·72 in 66% ethanol (Found : C, 75·4; H, 8·2; N, 16·7. $C_{11}H_{14}N_2$ requires C, 75·8; H, 8·1; N, 16·1%). This formed a *sulphate* which, crystallised from ethanol–ether, had m. p. 160° (Found : C, 48·3; H, 5·9. $C_{11}H_{14}N_2,H_2SO_4$ requires C, 48·5; H, 5·9%). The pyrazoline on hydrogenation in the presence of palladised charcoal furnished 2 : 3-dimethyl-1-phenylpyrazolidine,[20] b. p. 68·5°/0·3 mm., n_D^{20} 1·5511, pK_a' 4·28 in 66% ethanol (Found : C, 74·7; H, 9·0; N, 16·1. Calc. for $C_{11}H_{16}N_2$: C, 75·0; H, 9·2; N, 15·9%). Dihydroantipyrine[21] was also isolated from the above reduction as a viscous liquid (14 g.), b. p. 112—114°/0·4 mm., n_D^{20} 1·5571, $\lambda_{max.}$ 253 mμ (ε 8130), pK_a' 9·05 in 66% ethanol (Found : C, 69·8; H, 7·6. Calc. for $C_{11}H_{14}ON_2$: C, 69·4; H, 7·4%).

N-*Anilinomandelamidine*.—Hydrogenation of 2-nitro-1-phenyl-2-phenylhydrazonoethanol (5·4 g.) in absolute ethanol (100 ml.) in the presence of palladised charcoal gave the *amidine* as prisms (from 50% aqueous ethanol) (3 g.), m. p. 132—134°, $\lambda_{max.}$ 267 mμ (ε 12,000), pK_a' 7·92 in 50% ethanol (Found : C, 70·0; H, 6·5; N, 17·3. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3; N, 17·4%). The base was heated in 2N-hydrochloric acid and cooled : the *hydrochloride* separated as needles, m. p. 210° (decomp.) (Found : C, 60·1; H, 6·0; N, 15·0. $C_{14}H_{15}ON_3,HCl$ requires C, 60·5; H, 5·8; N, 15·1%). This salt was also obtained when ethyl mandelimidate hydrochloride[2] (43 g.) and phenylhydrazine (21·6 g.) were refluxed together in absolute ethanol (200 ml.) for 30 min. After cooling and filtration from ammonium chloride (4 g.) the filtrate was diluted with ether to yield the salt (35 g.).

erythro- *and* threo-α-*Amino*-β-*hydroxybutyric Acid*.—Ethyl β-hydroxy-α-phenylhydrazonobutyrate (4·8 g.) in absolute ethanol (35 ml.) was hydrogenated at atmospheric pressure with Raney nickel W.6. Removal of the catalyst and evaporation of the filtrate to dryness afforded a residue to which was added water (25 ml.), and the suspension was refluxed for 4 hr. The resulting solution was then concentrated to dryness *in vacuo* and the residue crystallised from aqueous ethanol, to give the threonine mixture (15%), m. p. 222—224° (decomp.) (Found : C, 40·1; H, 7·5; N, 11·9. Calc. for $C_4H_9O_3N$: C, 40·3; H, 7·6; N, 11·8%). A microbiological assay (by Dr. O. D. Bird of the Nutrition Department, Parke, Davis & Company, Detroit, U.S.A.) showed the mixture to contain 23·6% of L-threonine.

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[20] Thoms, *Annalen*, 1923, **434**, 296.
[21] Knorr, *Ber.*, 1892, **25**, 759.