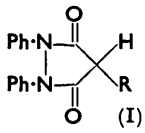
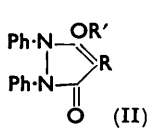
208. 3 : 5-*Dioxo*-1 : 2-*diphenylpyrazolidines. The* 4-*Hydroxy- and Certain* 4-*Alkoxy- and* 4-*Alkylamino-analogues.*

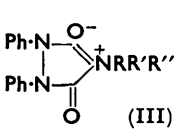
By (Mrs.) K. M. Hammond, N. Fisher, E. N. Morgan and (Miss) E. M. Tanner, with (in part) C. S. Franklin.

Dimethyl tetrahydropyranyloxymalonate reacts with hydrazobenzene to give 3 : 5-dioxo-1 : 2-diphenyl-4-tetrahydropyranyloxypyrazolidine. Removal of the tetrahydropyranyl group afforded 4-hydroxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidine. A series of 4-alkoxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidines has been prepared by interaction of alkoxymalonic esters with hydrazobenzene. 4-Alkoxy-3-hydroxy-1 : 2-diphenylpyrazolin-5-ones were isolated directly from condensations utilising diethyl methoxy- and ethoxymalonic esters; these are converted into the isomeric 4-alkoxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidines. Condensations of *N*-benzyl-*N*-*n*-butyl- and *N*-benzyl-*N*-methyl-aminomalonates with hydrazobenzene and debenzylation of the resultant products gave the corresponding 4-*n*-butylamino- and 4-methylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidines.

Recent investigations into the anti-inflammatory activities of the 4-acyl-,[1] 4-alkyl-,[2,3] and 4-aminoalkyl-3 : 5-dioxo-1 : 2-diphenylpyrazolidines [1] have emphasised the high degree of specificity associated with the phenylbutazone structure (I; R = Bu^n). Syntheses are described, below, of the hitherto unknown 4-hydroxy-analogue (I; R = OH) and certain 4-alkoxy- (I; R = OMe, OEt, OPr^n, and OBu^n) and 4-alkylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidines (III; R = R′ = H, R″ = Me and Bu^n; R = H, R′ = R″ = Me).

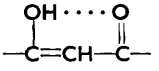
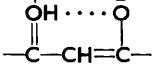

(I)


(II)


(III)

Condensation of dimethyl tetrahydropyranyloxymalonate [4] with hydrazobenzene in presence of sodium ethoxide [5] at 160—170° gave 3 : 5-dioxo-1 : 2-diphenyl-4-tetrahydropyranyloxypyrazolidine. This was converted by toluene-*p*-sulphonic acid in ethanol at room temperature into 4-hydroxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (I; R = OH). An earlier attempt at the synthesis of the 4-hydroxy-analogue, utilising diethyl benzyloxymalonate in the initial condensation, failed owing to decomposition of the latter.

Under comparable conditions, diethyl methoxymalonate condensed with hydrazobenzene to give 3-hydroxy-4-methoxy-1 : 2-diphenyl-3-pyrazolin-5-one (II; R = OMe, R′ = H). This 4-methoxy- and the corresponding 4-ethoxy-pyrazolinone (II; R = OEt, R′ = H), similarly prepared, were comparatively unstable, and only the latter could be

(IV)   (V)

readily purified by recrystallisation. Their infrared spectra (Table) bore strong resemblances to those of the enolisable β-diketones, in having low OH frequencies (2700—2300 cm.$^{-1}$) and carbonyl frequencies as low as 1596 cm.$^{-1}$. Resonance between the forms (IV) and (V) is believed to be the reason for these anomalous frequencies in the enolisable

[1] Logemann, Lauria, and Zamboni, *Chem. Ber.*, 1955, **88**, 1353.
[2] Bavin, Drain, Seymour, and Waterhouse, *J. Pharm. Pharmacol.*, 1955, **7**, 1022.
[3] Budziarek, Drain, McCrae, McLean, Newbold, Seymour, Spring, and Stansfield, *J.*, 1955, 3158.
[4] Davoll and Laney, *J.*, 1956, 2124.
[5] Ruhkopf, *Ber.*, 1940, **73**, 820.

β-diketones,[6] and a similar effect is presumably operative in these 4-alkoxy-3-hydroxy-1 : 2-diphenyl-3-pyrazolin-5-ones. Characterisation of the acidic 4-methoxy- and 4-ethoxy-pyrazoline was achieved by conversion into the corresponding enol ethers (II; R = OMe, R′ = Me; R = OEt, R′ = Me) with ethereal diazomethane. In the double-bond region of their infrared spectra the strongest band, which is probably due to the amide-carbonyl group, is near 1635 cm.$^{-1}$, and the weaker, near 1690 cm.$^{-1}$, is due to the C=C double bond, although the latter is surprisingly high. This effect is not due to crystal structure as it persists in chloroform solution. Phenylbutazone reacts with ethereal diazomethane in a comparable manner, to give an enol ether (II; R = Bu^n, R′ = Me) with very similar infrared spectral characteristics.

Conversion of the enolic 4-methoxy- and 4-ethoxy-pyrazolines into the corresponding 4-alkoxy-3 : 5-dioxopyrazolidines (I; R = OMe and OEt) was achieved by recrystallisation from acetic acid.

In contrast, condensation of diethyl *n*-propoxy- and *n*-butoxy-malonate with hydrazobenzene furnished 3 : 5-dioxo-1 : 2-diphenyl-4-*n*-propoxy- (I; R = OPr^n) and 4-*n*-butoxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (I; R = OBu^n) directly. The corresponding enolic pyrazolines were not encountered.

The neutral 4-alkoxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidines do not react with ethereal diazomethane, and are not titratable, and their infrared spectra (Table) show carbonyl frequencies within the narrow range 1741—1747 cm.$^{-1}$ with a weaker component between 1754 and 1761 cm.$^{-1}$. Confirmation of their structure is found in the spectrum of the 4-*n*-butyl-4-methyl analogue where the tautomeric shift is blocked. The infrared spectrum of 4-hydroxy-3 : 5-dioxo-1 : 2-diphenylpyrazolidine closely resembles those of the 4-alkoxy-analogues although this compound exhibits anomalous behaviour on potentiometric titration and on treatment with ethereal diazomethane. The infrared spectrum of phenylbutazone [1] is similar to those of the 4-alkoxy-pyrazolidines although the C=O frequency is somewhat lower than in the latter.

Infrared spectra (*Nujol mulls*) (*cm.*$^{-1}$).

R	R′	R″	OH–NH region		Double-bond region					
4-Alkoxy-derivs., (a) *Pyrazolidines* (I)										
OH			3380		1763s	1713s		1598		1493
OMe					1761sh	1747s		1598		1490
OEt					1754sh	1747s		1595		1487
OPr^n					1754sh	1742s		1591		1484
OBu^n					1757sh	1741s		1591		1484
4-*n*-Butyl-4-methyl-					1754	1731s		1592		1481
(b) *Pyrazolines* (II)										
OMe	H		2715	2355	1742w	1710w	1641	1596s		1485
OEt	H		2730	2365	1751w	1715w	1636sh	1596s		1484
OMe	Me					1696	1635s	1591		1490
OEt	Me					1686	1636s	1591		1484
Bu^n	Me					1687	1640s	1594		1493
4-Amino-derivs. (III)										
H	H	H	2605w	2355w, 2045w		1710w	1675sh	1602s	1556, 1526sh	1493sh
H	H	Ac	3320		1772	1721s	1676s	1598	1496sh	1484sh
H	H	Me	2480	2370w	1946w		1696w	1604s	1583s	1496sh
H	H	Bu^n	2550, 2480	2370w			1691w	1601sh	1565s	1484
H	Me	Me	2690	2130w	1925w		1691w	1615s	1594sh	1482sh
Me	Me	Me					1682w	1615s	1598sh	1482sh

s = strong band; sh = shoulder; w = very weak band.

Ultraviolet absorption spectra of the 4-alkoxypyrazolidines in alcohol have their absorption maxima between 236 and 242 mμ, with only slight shifts with changes of pH; 4-ethoxy-3-hydroxy-1 : 2-diphenylpyrazolin-5-one shows a shift of maxima towards the longer wavelengths in 0·1N-sodium hydroxide, as would be expected.

Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.

The introduction of certain basic substituents into the 4-position of the 3 : 5-dioxo-1 : 2-diphenylpyrazolidine nucleus gave compounds possessing very different properties. A study of their behaviour on potentiometric titration revealed that the 4-amino-, 4-dimethylamino-, and 4-methylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidines had pK_a' values of 2·5 and 7·20; 2·5 and 8·57; and 2·5 and 8·17, respectively. These values closely resemble those of glycine (2·4 and 9·8). Additionally, the 4-dimethylamino-analogue reacted with ethereal diazomethane to give a neutral betaine;[7] and absence of strong infrared bands in the range 1741—1747 cm.$^{-1}$ and presence of other bands in the double-bond region comparable with those shown by the pyrazolines suggest that these compounds are best represented by the zwitterionic formula (III).

3 : 5-Dioxo-1 : 2-diphenylpyrazolidine (I; R = H), coupled with benzenediazonium chloride, furnished the 4-phenylazo-derivative (I; R = N:NPh). This could be reduced (i) catalytically with palladium–charcoal to the known 4-amino-compound[8] (III; R = R′ = R″ = H) or (ii) with zinc in acetic acid–acetic anhydride to the 4-acetamido-derivative (III; R = R′ = H, R″ = Ac). Condensation of diethyl dimethylaminomalonate with hydrazobenzene gave 4-dimethylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (III; R = H, R′ = R″ = Me) and this with ethereal diazomethane afforded a neutral betaine (III; R = R′ = R″ = Me). In a comparable manner, diethyl *N*-benzyl-*N*-methylamino- and diethyl *N*-benzyl-*N*-*n*-butylamino-malonate with hydrazobenzene gave 4-*N*-benzyl-*N*-methylamino- (III; R = H, R′ = CH_2Ph, R = Me) and 4-*N*-benzyl-*N*-*n*-butylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (III; R = H, R′ = CH_2Ph, R″ = Bu^n), respectively. Debenzylation of these compounds allowed the isolation of 4-methylamino- (III; R = R′ = H, R″ = Me) and 4-*n*-butylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (III; R = R′ = H, R″ = Bu^n) as pale orange, partially crystalline solids which were generally unstable, especially towards recrystallisation in bulk. Their ultraviolet spectra in alcohol were somewhat difficult to plot; results quoted were obtained by rapid measurement on freshly prepared solutions.

The compounds described in this paper were tested for anti-inflammatory activity by Dr. C. V. Winder of the Research Department, Parke, Davis & Co., Detroit. The tests did not reveal significant activity.

Experimental

Alkoxymalonic Esters.—Diethyl methoxymalonate was prepared from ethyl methoxyacetate, ethyl carbonate, and sodium ethoxide.[9] Similarly prepared were diethyl ethoxymalonate, *diethyl* n-*propoxymalonate*, b. p. 72—74°/0·2 mm., n_D^{20} 1·4228 (Found: C, 54·7; H, 8·2. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%), and *diethyl* n-*butoxymalonate*, b. p. 119—120°/3 mm., n_D^{20} 1·4253 (Found: C, 56·8; H, 8·5. $C_{11}H_{20}O_5$ requires C, 56·9; H, 8·7%).

Ethyl Benzyloxyacetate.—Benzyl alcohol (250 c.c.), potassium hydroxide (84 g.), and xylene (150 c.c.) were refluxed together with stirring until azeotropic removal of water was complete. To the resultant solution, ethyl chloroacetate (30 c.c.) was added at 120° (oil-bath) and the mixture refluxed until neutral. At the same temperature, 10N-sodium hydroxide (110 c.c.) was carefully added with stirring and reflux maintained for a further 1 hr. Then the mixture after dilution with water was steam-distilled, cooled, and extracted with ether. Subsequently, the aqueous phase was acidified and extracted with carbon tetrachloride. Evaporation of the solvent layer and distillation of the residue gave benzyloxyacetic acid (95 g.), b. p. 149—51°/1·5 mm., n_D^{23} 1·5280. Esterification furnished ethyl benzyloxyacetate (92%), b. p. 100—102°/1 mm., n_D^{22} 1·4970.

Diethyl Benzyloxymalonate.—Diethyl oxalate (73 g.) was added to a stirred suspension of sodium hydride (12 g.) in ether[10] (50 c.c.). To this, ethyl benzyloxyacetate (48·6 g.) was slowly (4 hr.) run in and the mixture refluxed for 1 hr. After cooling, the latter was poured into ice-water, acidified with acetic acid and extracted with ethyl acetate. Evaporation of the

[7] Kuhn and Brydowna, *Ber.*, 1937, **70**, 1333.
[8] Musante and Fabbrini, *Gazzetta*, 1954, **84**, 595.
[9] Ames and Bowman, *J.*, 1951, 1079.
[10] Soloway and La Forge, *J. Amer. Chem. Soc.*, 1947, **69**, 2677.

washed and dried solvent layer left an oil which was heated at 180—190° (oil-bath) under a vacuum for 8 hr. Final distillation gave *diethyl benzyloxymalonate* (18·6 g.), b. p. 134—138°/0·4 mm., n_D^{21} 1·4915 (Found: C, 63·0; H, 6·8. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%). The *diamide*, m. p. 226° (decomp.), crystallised from ethanol in needles (Found: C, 57·2; H, 5·9; N, 12·9. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%).

Aminomalonic Esters.—Diethyl *N*-benzyl-*N*-methylaminomalonate was prepared by the reaction of diethyl bromomalonate with *N*-benzylmethylamine in ethanol.[11] *Diethyl* N-*benzyl*-N-n-*butylaminomalonate*, b. p. 149—50°/0·3 mm., n_D^{20} 1·4845 (Found: C, 67·2; H, 8·4; N, 4·2. $C_{18}H_{27}O_4N$ requires C, 67·3; H, 8·5; N, 4·4%), was prepared in an analogous manner.

4-*Hydroxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (I; R = OH).—To a solution of sodium (0·04 g.-atom) in absolute ethanol (150 c.c.) was added dimethyl tetrahydropyranyloxymalonate (0·04 mole) and hydrazobenzene (0·04 mole). The ethanol was removed by distillation and the residue heated at 160—170° (oil-bath) under a vacuum for 2 hr. The crude product was extracted with ether and water, and the separated aqueous layer chilled and acidified with acetic acid (0·05 mol.). The white flocculent precipitate of 3 : 5-*dioxo*-1 : 2-*diphenyl*-4-*tetrahydropyranyloxypyrazolidine* (46%) which separated was filtered off and dried. It melted at ~60° but could not be recrystallised (Found: C, 67·7; H, 5·8; N, 8·0. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 8·0%).

The product (8·5 g.) was dissolved in warm absolute ethanol (250 c.c.), cooled, and treated with toluene-*p*-sulphonic acid (0·15 g.). Overnight there separated rectangular prisms of 4-*hydroxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine ethanol solvate* (3·75 g.), m. p. 201—203° (decomp.) (Found: C, 65·2; H, 5·7; N, 9·3. $C_{15}H_{12}O_3N_2,C_2H_5{\cdot}OH$ requires C, 65·0; H, 5·8; N, 8·9%). Recrystallisation of this from 2-methoxyethanol and drying at 100°/1 hr. in a high vacuum gave the parent 4-*hydroxy-compound*, m. p. 211—213° (decomp.) (Found: C, 67·1; H, 4·8; N, 10·0. $C_{15}H_{12}O_3N_2$ requires C, 67·2; H, 4·5; N, 10·4%). Ultraviolet absorption in EtOH: $\lambda_{max.}$ 235 mμ (ε 18,500).

4-*Methoxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (I; R = OMe).—Likewise, the crude product obtained from a condensation between diethyl methoxymalonate and hydrazobenzene was extracted with ether and water. Acidification of the aqueous layer gave a precipitate which when dried and recrystallised from aqueous ethanol gave microscopic flattened needles of 3-*hydroxy*-4-*methoxy*-1 : 2-*diphenylpyrazolin*-5-*one* (II; R = OMe, R′ = H), m. p. 130—131° (58%) (Found: C, 68·5; H, 5·2; N, 9·9. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0; N, 9·9%). The latter with ethereal diazomethane gave the 3-*methyl ether* (II; R = OMe, R′ = Me), m. p. 173—174° (Found: C, 69·1; H, 5·4; N, 9·7. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%), which separated in needles from aqueous ethanol. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 257 mμ (ε 17,900). Recrystallisation of the 3-hydroxy-compound from aqueous acetic acid and finally from 2-methoxyethanol furnished colourless hexagonal tablets of 4-*methoxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine*, m. p. 248—250° (decomp.) (Found: C, 68·4; H, 5·0; N, 10·0. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0; N, 9·9%). Ultraviolet absorption in EtOH: $\lambda_{max.}$ 236 mμ (ε 13,600). This compound does not react with ethereal diazomethane.

Similarly prepared, 4-*ethoxy*-3-*hydroxy*-1 : 2-*diphenylpyrazolin*-5-*one* (II; R = OEt, R′ = H), m. p. 148—150° (40%) (Found: C, 69·2; H, 5·5; N, 9·6. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%), recrystallised from aqueous ethanol in colourless flattened needles. The pK_a' in 50% aqueous EtOH was 3·55. Ultraviolet absorption max.: in EtOH, 237, 240, 273 (sh) mμ (ε 14,500, 14,500, and 8170); in 0·1N-sodium hydroxide, 265 mμ (ε 15,100). The derived 3-*methyl ether* (II; R = OEt, R′ = Me), m. p. 98—99° (Found: C, 69·7; H, 5·9; N, 9·0. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·9; N, 9·0%), separated in colourless needles from aqueous methanol. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 259 mμ (ε 17,300). Further recrystallisation of 4-ethoxy-3-hydroxy-1 : 2-diphenylpyrazolin-5-one from acetic acid converted it into 4-*ethoxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (I; R = OEt) which separated in stout needles, m. p. 240—242° (decomp.), from ethyl methyl ketone (Found: C, 68·9; H, 5·4; N, 9·6. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%). Ultraviolet absorption in EtOH: $\lambda_{max.}$ 238, 241 mμ (ε 13,600, 13,500).

3 : 5-*Dioxo*-1 : 2-*diphenyl*-4-n-*propoxypyrazolidine* (I; R = OPr^n), m. p. 228—229° (decomp.) (Found: C, 69·7; H, 5·7; N, 8·8. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·9; N, 9·0%), flattened needles from 2-methoxyethanol, and 4-n-*butoxy*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (I; R = OBu^n), m. p. 242—244° (decomp.) (Found: C, 70·7; H, 6·0; N, 8·7. $C_{19}H_{20}O_3N_2$ requires C,

[11] Hardegger and Corrodi, *Helv. Chim. Acta*, 1956, **39**, 980.

70·4; H, 6·2; N, 8·6%), flattened needles from ethyl methyl ketone, were prepared in an analogous manner. Ultraviolet absorptions in EtOH: $\lambda_{max.}$ 242 mμ (ε 14,300) and 242 mμ (ε 14,400) respectively. In the preparations of the 4-*n*-propoxy- and the 4-*n*-butoxy-analogue the enolic pyrazolines were not encountered.

4-n-*Butyl*-3-*methoxy*-1 : 2-*diphenyl*-3-*pyrazolin*-5-*one* (II; R′ = Me, R = Bu^n).—Treatment of phenylbutazone with ethereal diazomethane afforded, in the usual manner, the 3-*methyl ether*, m. p. 91—92° (Found: C, 74·3; H, 6·9; N, 8·8. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·9; N, 8·7%), which crystallised from light petroleum (b. p. 80—100°) in colourless plates. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 253 mμ (ε 15,800).

3 : 5-*Dioxo*-1 : 2-*diphenyl*-4-*phenylazopyrazolidine* (I; R = N:NPh).—To a stirred suspension of 3 : 5-dioxo-1 : 2-diphenylpyrazolidine (0·1 mole) in water (500 c.c.), containing sodium acetate (0·5 mole) at 5° were added chloroform (250 c.c.) and an aqueous solution of benzenediazonium chloride (0·1 mole). After 2 hr., the separated chloroform layer was combined with a chloroform washing of the aqueous layer and evaporated to dryness. Crystallisation of the residue from ethanol gave orange needles of 3 : 5-*dioxo*-1 : 2-*diphenyl*-4-*phenylazopyrazolidine*, m. p. 184—186° (94%) (Found: C, 71·0; H, 4·5. $C_{21}H_{16}O_2N_4$ requires C, 70·8; H, 4·5%).

4-*Amino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (III; R = R′ = R″ = H).—The foregoing azo-compound (3·5 g.) in absolute alcohol (60 c.c.) was shaken with 15% palladium–charcoal (1 g.) under normal conditions until uptake of hydrogen was complete. After addition of N-sodium hydroxide (10 c.c.), the mixture was again shaken for a few minutes, then the catalyst was filtered off. Addition of N-hydrochloric acid (10 c.c.) to the filtrate precipitated partially crystalline (needles), buff-coloured 4-amino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine, m. p. 229—230° (decomp.) (1·8 g.) (Found: C, 67·3; H, 5·4. Calc. for $C_{15}H_{13}O_2N_3$: C, 67·4; H, 4·9%). The values for pK_{a_1}' and pK_{a_2}' in 50% EtOH were 2·5 and 7·20 respectively. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 244, 252 (sh) mμ (ε 13,200, 12,600). This compound, for which Musante and Fabbrini [8] recorded m. p. 197—200° (decomp.), separated in yellowish needles from aqueous alcohol, when recrystallised in small amounts. The *isopropylidene derivative*, m. p. 201° (decomp.) (Found: C, 70·3; H, 5·8; N, 13·7. $C_{18}H_{17}O_2N_3$ requires C, 70·3; H, 5·6; N, 13·7%), prepared by refluxing the foregoing compound in acetone, separated in colourless needles from methanol. The *acetyl derivative*, m. p. 190° (Found: C, 65·3; H, 5·1. $C_{17}H_{15}O_3N_3$ requires C, 66·0; H, 4·9%), which crystallised from benzene in colourless prisms, was obtained by (i) direct acetylation (acetic anhydride) of the 4-amino-compound and (ii) by reduction of the 4-phenylazo-compound. A solution of the latter (1·8 g.) in acetic acid (25 c.c.) containing acetic anhydride (10 c.c.) was treated with zinc dust (6 g.), at <40°. After 1 hr. at room temperature, the mixture was filtered and the filtrate evaporated. Recrystallisation of the residue from benzene furnished the 4-acetamido-derivative, the mixed m. p. with the compound prepared by direct acetylation being undepressed.

4-*Dimethylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (III; R = H, R′ = R″ = Me).—Diethyl dimethylaminomalonate [12] (10·2 g.) in xylene (100 c.c.) was refluxed with sodium hydride (1·2 g.) for 0·5 hr. To the resultant suspension of diethyl sodiodimethylaminomalonate, hydrazobenzene (9·2 g.) in xylene (50 c.c.) was added and the mixture refluxed 2 hr. On cooling, the mixture was extracted with water and the combined aqueous extracts were acidified with dilute hydrochloric acid. Recrystallisation of the dried precipitate from aqueous acetic acid furnished colourless plates of 4-*dimethylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine*, m. p. 196—197° (decomp.) (Found: C, 69·2; H, 5·7. $C_{17}H_{17}O_3N_3$ requires C, 69·1; H, 5·8%). The values for pK_{a_1}' and pK_{a_2}' in 50% EtOH were 2·5 and 8·57. Ultraviolet absorption in EtOH: $\lambda_{max.}$ 253 mμ (ε 21,970).

Similarly prepared from the requisite malonic esters were 4-N-*benzyl*-N-*methylamino*- m. p. 179—180° (decomp.) (Found: C, 74·7; H, 5·8; N, 11·3. $C_{23}H_{21}O_2N_3$ requires C, 74·4; H, 5·7; N, 11·3%), tablets from ethyl methyl ketone, and 4-N-*benzyl*-N-n-*butylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine*, m. p. 184—185° (decomp.) (Found: 71·0; H, 6·2; N, 9·0. $C_{26}H_{27}O_3N_3,CH_3{\cdot}CO_2H$ requires C, 71·0; H, 6·6; N, 8·0%), tablets from aqueous acetic acid.

4-*Methylamino*-3 : 5-*dioxo*-1 : 2-*diphenylpyrazolidine* (III; R = R′ = H, R″ = Me).—The foregoing *N*-benzyl-*N*-methylamino-compound (5·6 g.), suspended in ethanol (100 c.c.), was shaken with 10% palladium–charcoal (2 g.) in hydrogen. The original solid slowly dissolved and when the uptake of hydrogen was complete the resulting fine white precipitate was redissolved by adding N-sodium hydroxide (15 c.c.), and the mixture filtered. Acidification of

[12] Jones and Wilson, *J.*, 1949, 550.

the filtrate with N-hydrochloric acid (15 c.c.) precipitated *4-methylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine*, m. p. 171—173° (decomp.), as a partially crystalline orange solid (2·7 g.) (Found : C, 68·6; H, 5·6; N, 14·4. $C_{16}H_{15}O_2N_3$ requires C, 68·3; H, 5·3; N, 14·9%). The pK_{a_1}' and pK_{a_2}' values in 50% EtOH were 2·5 and 8·17. Ultraviolet absorption in EtOH : $\lambda_{max.}$ 236, 238, 245 (sh) mμ (ε 15,000, 15,000, 14,300).

4-n-*Butylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine* (III; R = R′ = H, R″ = Bu^n), m. p. 190—191° (decomp.) (Found : C, 70·0; H, 6·6; N, 12·5. $C_{19}H_{21}O_2N_3$ requires C, 70·6; H, 6·6; N, 13·0%), was obtained in a comparable manner, as an orange, partially crystalline powder. Owing to instability and poor solubility potentiometric titrations were not completed. Ultraviolet absorption in EtOH : $\lambda_{max.}$ 237, 240 mμ (ε 16,500, 16,400).

5-Hydroxy-1 : 2-diphenyl-4-trimethylammoniopyrazol-3-one betaine (III; R = R′ = R″ = Me).—4-Dimethylamino-3 : 5-dioxo-1 : 2-diphenylpyrazolidine (5 g.), finely powdered and suspended in ether containing a little methanol, was treated with ethereal diazomethane, and the mixture kept overnight at room temperature. The insoluble material (1·6 g.) was filtered off and recrystallised from 2-methoxyethanol, to give hexagonal plates of the *betaine*, m. p. 267—268° (decomp.) (Found : C, 69·8; H, 6·0; N, 13·6. $C_{18}H_{19}O_2N_3$ requires C, 69·9; H, 6·2; N, 13·6%). This compound is not titratable between pH 2·5 and 11.

Infrared spectra were recorded with a Grubb-Parsons DBI/S3A spectrometer, and ultraviolet absorption measurements were made on a Unicam S.P.500 spectrophotometer.

The authors thank Mr. D. E. Seymour, of Smith & Nephew Research Ltd., for the sample of 4-*n*-butyl-4-methyl-1 : 2-diphenylpyrazolidine, and Dr. R. E. Bowman for many helpful discussions. Microanalyses are by Mr. A. J. Durre.

RESEARCH DEPARTMENT, PARKE, DAVIS & CO. LTD.,
HOUNSLOW, MIDDLESEX.

[*Received, October 17th*, 1956.]