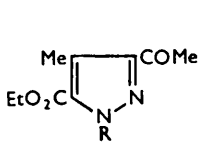
## 506. *Dipyrazolyls from C-Acetylpyrazoles.*

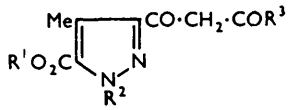
By E. G. Brain and I. L. Finar.

3-Acetylpyrazoles have been converted into pyrazolyl substituted β-diketones and benzylideneacetylpyrazoles. Both types of product have been used to prepare substituted dipyrazolyls: 3 : 5′-, 5 : 5′-, and 3 : 3′-dipyrazolyl have been obtained.

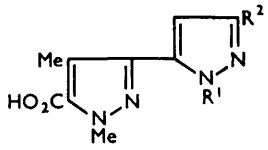
3 : 3′- and 3 : 5′-Dipyrazolyls have usually been prepared [1,2] from hydrazines and 1 : 3 : 4 : 6-tetraketones. The disadvantage of this method is that an unsymmetrical tetraketone can theoretically yield four dipyrazolyls, and a symmetrical tetraketone three. In one case [2] the intermediate pyrazolyl β-diketone was isolated and its structure elucidated. Since only two possible isomers can arise from a β-diketone and a hydrazine (cf. Finar and Simmonds [3]), the structures of the dipyrazolyls obtained from a pyrazolyl β-diketone can be ascertained more readily.



| | R |
|---|---|
| I | Me |
| II | H |

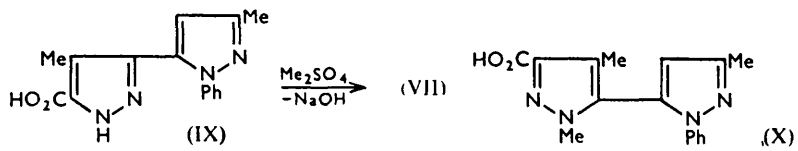


| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| III | H | Me | Me |
| IV | Et | H | Me |
| V | Et | Me | Ph |



| | $R^1$ | $R^2$ |
|---|---|---|
| VI | H | Me |
| VII | Ph | Me |
| VIII | Ph | Ph |

Attempts to convert the ester group of ethyl 3-acetyl-1 : 4-dimethylpyrazole-5-carboxylate (I) into a β-dicarbonyl side-chain were unsuccessful but, when treated with ethyl acetate and sodium ethoxide, this ester gave 3-acetoacetyl-1 : 4-dimethylpyrazole-5-carboxylic acid (III). Under similar conditions the product from ethyl 5-acetyl-4-methylpyrazole-3-carboxylate (II) was the diketone ester (IV). When the ester (I) was condensed with ethyl benzoate the product was also a diketone ester (V).




With hydrazine, the acetoacetyl compound (III) gave 1 : 4 : 3′-trimethyl-3 : 5′-dipyrazolyl-5-carboxylic acid (VI). The product obtained by condensation with phenylhydrazine was assumed to have the structure (VII) by analogy with the formation of 3-methyl-1 : 5-diphenylpyrazole from benzoylacetone.[4]

Bromination of compound (VII) led to the 4′-bromo-derivative which, from molecular models, would be expected to be optically resolvable owing to restricted rotation about the C–C bond joining the pyrazole rings. An attempt to resolve this bromo-acid by means of the brucine salt was, however, unsuccessful. The alternative structure (XII) for the parent compound can, therefore, not be discounted.

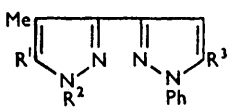
Ethyl 3-acetoacetyl-4-methylpyrazole-5-carboxylate (IV) also condensed with phenylhydrazine to give, after hydrolysis, a dipyrazolylcarboxylic acid (IX). This gave, on methylation, a mixture of the acid (VII) and its isomer (X). The orientation of the phenyl-substituted pyrazole ring in (IX) must therefore be as in (VII).

[1] Claisen and Roosen, *Annalen*, 1894, **278**, 294.
[2] Finar, *J.*, 1955, 1205.
[3] Finar and Simmonds, *J.*, 1958, 200.
[4] Drumm, *Proc. Roy. Irish Acad.*, 1931, **40**, *B*, 106.

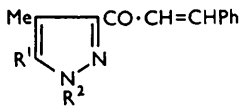
When ethyl 3-benzoylacetyl-1 : 4-dimethylpyrazole-5-carboxylate (V) was condensed with phenylhydrazine two products (VIII) and (XI) were obtained after hydrolysis. 1 : 4-Dimethyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl-5-carboxylic acid (XI) was synthesised by an unambiguous method and was found to be identical with the minor product of the condensation. The major product is therefore 1 : 4-dimethyl-1′ : 3′-diphenyl-3 : 5′-dipyrazolyl-5-carboxylic acid (VIII). This is in contrast with the case of the pyrazolyl β-diketone previously quoted [2] which gave the 3 : 3′-dipyrazolyl as its major condensation product with phenylhydrazine.

The monobromo-derivative of the acid (VIII) could not be resolved by means of its brucine salt since the latter was obtained only as an uncrystallisable resin.

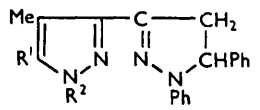
The unambiguous synthesis of 1 : 4-dimethyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl-5-carboxylic acid (XI) was carried out in the following way. 3-Benzylideneacetyl-1 : 4-dimethylpyrazole-5-carboxylic acid (XV) was obtained by a Claisen–Schmidt reaction with the ethyl acetyldimethylpyrazolecarboxylate (I) and benzaldehyde. It did not react



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| XI | $CO_2H$ | Me | Ph |
| XII | $CO_2H$ | Me | Me |
| XIII | $CO_2H$ | H | Ph |
| XIV | H | Me | Ph |



| | $R^1$ | $R^2$ |
|---|---|---|
| XV | $CO_2H$ | Me |
| XVI | H | Me |
| XVII | $CO_2H$ | H |



| | $R^1$ | $R^2$ |
|---|---|---|
| XVIII | $CO_2Me$ | Me |
| XIX | H | Me |

satisfactorily with phenylhydrazine, the product being a mixture containing much unchanged starting material. Its methyl ester, however, afforded pure methyl 4′ : 5′-dihydro-1 : 4-dimethyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl-5-carboxylate (XVIII). This was oxidised and then hydrolysed, to give the dipyrazolyl acid (XI).

In the same way, ethyl acetylmethylpyrazolecarboxylate (II) gave benzylideneacetylmethylpyrazolecarboxylic acid (XVII), which was condensed with phenylhydrazine and then oxidised to give 4-methyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl-5-carboxylic acid (XIII).

The decarboxylation product (XVI) of the acid (XV) reacted with phenylhydrazine more completely than either the parent acid or its methyl ester, and the dihydrodipyrazolyl (XIX) was obtained. This gave 1 : 4-dimethyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl (XIV) on oxidation.

## Experimental

*3-Acetoacetyl-1 : 4-dimethylpyrazole-5-carboxylic Acid.*—Ethanol-free sodium ethoxide (2 mol., from 3·4 g. of sodium) was suspended in a refluxing mixture of ether (300 c.c.) and ethyl acetate (80 c.c.; excess) for 5 min., then ethyl 3-acetyl-1 : 4-dimethylpyrazole-5-carboxylate (15·6 g., 1 mol.) was added, and refluxing with stirring was maintained for 3 hr. A further 2 mol. of sodium ethoxide were then added, and refluxing and stirring were continued for another 3 hr. The mixture, which then contained a pale yellow precipitate, was extracted with water (200 c.c.) and then with N-sodium hydroxide (2 × 100 c.c.). The combined extracts were washed with ether and acidified with hydrochloric acid. From the sticky solid which was precipitated were obtained cream-coloured crystals of *3-acetoacetyl-1 : 4-dimethylpyrazole-5-carboxylic acid* by recrystallisation twice from benzene containing 5% of ethanol (yield 6·5 g., 39%; m. p. 179—180°) (Found: C, 53·1; H, 5·6; N, 12·7. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%).

If, instead of refluxing, the reactants were mixed and set aside at room temperature for 12 hr. the reaction failed. Low yields were obtained when the second addition of sodium ethoxide was omitted.

*Ethyl 3-Benzoylacetyl-1 : 4-dimethylpyrazole-5-carboxylate.*—The procedure given above was

repeated with ethyl benzoate instead of ethyl acetate. A yellow precipitate was formed during the refluxing but this was insoluble in water. It was therefore filtered off at the end of the reaction and then washed, first with ether, then with water. The pasty solid was shaken with ether (100 c.c.) and 4N-hydrochloric acid (30 c.c.). The ethereal layer was washed with water, dried ($Na_2SO_4$), and evaporated, leaving a solid. After three recrystallisations from ligroin pure *ethyl* 3-*benzoylacetyl*-1 : 4-*dimethylpyrazole*-5-*carboxylate* was obtained (5 g., 32%; m. p. 109°) (Found: C, 65·0; H, 5·9; N, 8·5. $C_{17}H_{18}O_4N_2$ requires C, 65·0; H, 5·7; N, 8·9%).

*Ethyl* 3-*Acetoacetyl*-4-*methylpyrazole*-5-*carboxylate.*—Claisen condensation with ethyl 5-acetyl-4-methylpyrazole-3-carboxylate and ethyl acetate was carried out as above but the proportion of ethyl acetate to ether used as solvent was kept high (approx. 50% by vol.) since larger amounts of ether resulted in the precipitation of the *N*-sodium salt of the acetylpyrazole. The product was worked up as for 3-acetoacetyl-1 : 4-dimethylpyrazole-5-carboxylic acid but, after recrystallisation from benzene, the product was found to be the *ester* (28%; m. p. 121—123°). A further recrystallisation from benzene raised the m. p. to 123—124° (Found: C, 55·8; H, 6·0; N, 12·0. $C_{11}H_{14}O_4N_2$ requires C, 55·5; H, 5·9; N, 11·8%).

*Condensation of* 3-*Acetoacetyl*-1 : 4-*dimethylpyrazole*-5-*carboxylic Acid with Hydrazine.*—A mixture of the diketone (2·0 g., 1 mol.), 60% hydrazine hydrate (0·82 g., 1·1 mol.), and ethanol (30 c.c.) was heated for 30 min. on the steam-bath. Water was added and the solution was cooled. A brown mass of crystals was deposited. When twice recrystallised from water this yielded pure 1 : 4 : 3′-*trimethyl*-3 : 5′-*dipyrazolyl*-5-*carboxylic acid*, m. p. 247—248° (decomp.) (Found: C, 54·3; H, 5·5; N, 25·7. $C_{10}H_{12}O_2N_4$ requires C, 54·5; H, 5·45; N, 25·45%).

*Condensation of* 3-*Acetoacetyl*-1 : 4-*dimethylpyrazole*-5-*carboxylic Acid with Phenylhydrazine.*—The diketone (2 g., 1 mol.), phenylhydrazine (1·9 g., 2 mol.) and acetic acid (25 c.c.) were refluxed together for 2·5 hr. Water (20 c.c.) was added. 1 : 4 : 3′-*Trimethyl*-1′-*phenyl*-3 : 5′-*dipyrazolyl*-5-*carboxylic acid* slowly separated. This was recrystallised, first from benzene–ligroin, then twice from dilute ethanol and had m. p. 212—213° (1·1 g.) (Found: C, 64·5; H, 5·4; N, 18·7. $C_{16}H_{16}O_2N_4$ requires C, 64·8; H, 5·4; N, 18·9%).

The acid was brominated in chloroform solution and the resulting 4′-*bromo*-1 : 4 : 3′-*trimethyl*-1′-*phenyl*-3 : 5′-*dipyrazolyl*-5-*carboxylic acid* was obtained as white crystals, m. p. 201·5—202·5°, from hot dilute ethanol (Found: C, 51·7; H, 4·0; N, 15·0; Br, 21·5. $C_{16}H_{15}O_2N_4Br$ requires C, 51·2; H, 4·0; N, 14·95; Br, 21·35%). A hydrated product, m. p. 110° (decomp.), is obtained from cold dilute ethanol.

*Condensation of Ethyl* 3-*Acetoacetyl*-4-*methylpyrazole*-5-*carboxylate with Phenylhydrazine.*—This was carried out as described for the *N*-methyl derivative, but the product, an oil, was saponified with ethanolic potassium hydroxide, to yield, on acidification with dilute hydrochloric acid, 4 : 3′-*dimethyl*-1′-*phenyl*-3 : 5′-*dipyrazolyl*-5-*carboxylic acid* which, recrystallised from dilute ethanol and then ethanol, had m. p. 250—251° (Found: C, 63·7; H, 4·8; N, 19·8. $C_{15}H_{14}O_2N_4$ requires C, 63·8; H, 4·95; N, 19·85%). No other product was isolated.

This acid (2·3 g.) was treated with methyl sulphate (1 mol.) and sodium hydroxide (2·5 mol.) in aqueous solution at 90°. After 1 hr. the solution was acidified. The precipitated oil solidified and was dried, giving a buff powder (2·15 g.), m. p. *ca.* 60—90°. This was recrystallised twice from benzene (100 c.c.), to give white needles of 1 : 4 : 3′-trimethyl-1′-phenyl-5 : 5′-dipyrazolyl-3-carboxyiic acid, m. p. 232·5—233° (Found: C, 64·5; H, 5·1; N, 18·8. $C_{16}H_{16}O_2N_4$ requires C, 64·8; H, 5·4; N, 18·9%). Concentration of the original benzene mother-liquor gave a second crop consisting of a mixture of the above compound together with blunt crystals of the already known 1 : 4 : 3′-trimethyl-1′-phenyl-3 : 5′-dipyrazolyl-5-carboxylic acid. The fine needles were mechanically removed from the blunt crystals by a stream of light petroleum. The blunt crystals were then recrystallised from benzene–ligroin and from dilute ethanol, having m. p. 210·5—212°, mixed m. p. 212—213° with an authentic specimen.

*Condensation of Ethyl* 3-*Benzoylacetyl*-1 : 4-*dimethylpyrazole*-5-*carboxylate with Phenylhydrazine.*—This was carried out by the usual method. In this case also the product was an oil and was therefore saponified to give the solid dipyrazolyl acid. The yield of crude acid (m. p. 185—190°) was 91·5%. This was recrystallised four times from benzene containing 10% of ligroin: pure 1 : 4-*dimethyl*-1′ : 3′-*diphenyl*-3 : 5′-*dipyrazolyl*-5-*carboxylic acid* (52%) had m. p. 193—194° (Found: C, 70·2; H, 5·2; N, 15·6. $C_{21}H_{18}O_2N_4$ requires C, 70·3; H, 5·0; N, 15·65%).

The recrystallisation liquors were worked up by the usual procedure for fractional crystallisation and a more soluble fraction (m. p. 184—212°; 8·4%) was thus obtained. After two

recrystallisations from ethanol 1 : 4-dimethyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl-5-carboxylic acid (0·3%), m. p. and mixed m. p. 256—256·5°, was obtained.

*3-Benzylideneacetyl-1 : 4-dimethylpyrazole-5-carboxylic Acid.*—A mixture of ethyl 3-acetyl-1 : 4-dimethylpyrazole-5-carboxylate (2·0 g., 0·95 mol.), benzaldehyde (1·06 g., 1 mol.), 10% aqueous sodium hydroxide (20 c.c.; excess), and ethanol (50 c.c.) was set aside for 20 hr., then acidified. The white precipitate of the *benzylideneacetyldimethylpyrazolecarboxylic acid* (1·7 g.), recrystallised from ethanol, had m. p. 267—268° (decomp.) (1·3 g., 46%) (Found: C, 66·4; H, 5·2; N, 10·5. $C_{15}H_{14}O_3N_2$ requires C, 66·7; H, 5·2; N, 10·4%).

This acid was refluxed for 30 hr. with methanol (40 c.c.) and saturated methanolic hydrogen chloride (20 c.c.). The mixture was then cooled and the solid filtered off. Three recrystallisations from ethanol gave the *methyl ester*, m. p. 177—178° (Found: C, 67·7; H, 5·85; N, 9·6. $C_{16}H_{16}O_3N_2$ requires C, 67·5; H, 5·65; N, 9·85%).

The acid was heated at 280° for 25 min. The tarry product was washed in ether with aqueous sodium hydroxide and passed through alumina. The crude *3-benzylideneacetyl-1 : 4-dimethylpyrazole* then obtained by evaporation was recrystallised from ligroin (63%; m. p. 90—92°). Two more recrystallisations raised the m. p. to 92·5—93·5° (Found: C, 74·1; H, 6·1; N, 12·8. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%).

Benzylideneacetyldimethylpyrazole was condensed with phenylhydrazine by the method used for the diketone. 1 : *2-Dihydro-1′ : 4′-dimethyl-1 : 5-diphenyl-3 : 3′-dipyrazolyl* was obtained; it formed colourless crystals, m. p. 141—142° (50%), from ligroin (Found: C, 75·8; H, 6·3; N, 17·3. $C_{20}H_{20}N_4$ requires C, 75·9; H, 6·3; N, 17·7%). Solutions of this substance in ligroin gave a strong blue fluorescence in ultraviolet light. Oxidation with potassium permanganate in acetone then gave 1 : *4-dimethyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl* which, when twice recrystallised from ligroin, melted at 139—141° (mixed m. p. with the precursor 117—127°) (Found: C, 76·6; H, 5·8; N, 18·0. $C_{20}H_{18}N_4$ requires C, 76·4; H, 5·7; N, 17·8%).

*Methyl 4′ : 5′-Dihydro-1 : 4-dimethyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl-5-carboxylate.*—Methyl 3-benzylideneacetyl-1 : 4-dimethylpyrazole-5-carboxylate was condensed with phenylhydrazine by the usual method but with refluxing for 8 hr. The *product* was obtained by recrystallisation from ethanol as blunt crystals, m. p. 174—175°, strongly fluorescent in ultraviolet light (Found: C, 70·6; H, 5·8; N, 15·0. $C_{22}H_{22}O_2N_4$ requires C, 70·6; H, 5·9; N, 15·0%).

Oxidation with potassium permanganate in 90% aqueous pyridine gave the fully aromatic dipyrazolyl ester, m. p. 128—129°, which was hydrolysed by ethanolic potassium hydroxide to 1 : 4-dimethyl-1′ : 5′-diphenyl-3 : 3′-dipyrazolyl-5-carboxylic acid, m. p. 255—256° (decomp.) (from ethanol) (Found: C, 69·9; H, 4·9; N, 15·2. $C_{21}H_{18}O_2N_4$ requires C, 70·3; H, 5·0; N, 15·65%).

*5-Benzylideneacetyl-4-methylpyrazole-3-carboxylic Acid.*—Ethyl 5-acetyl-4-methylpyrazole-3-carboxylate was condensed with benzaldehyde by the method previously used, but the reaction was allowed to proceed for 1·5 days. The *benzylideneacetylmethylpyrazole acid*, crystallised from acetic acid, had m. p. 231·5—233° (Found: C, 66·0; H, 4·3; N, 11·1. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7; N, 10·95%).

*4′-Methyl-1 : 5-diphenyl-3 : 3′-dipyrazolyl-5′-carboxylic Acid.*—The above benzylidene compound was condensed with phenylhydrazine by the general method and refluxed for 7 hr. The crude product was not purified but oxidised directly by permanganate–pyridine. The final pyridine solution was evaporated and the residue dissolved in a little water and then acidified. The precipitated *acid* had m. p. 273·5—274° (decomp.) (from acetic acid) (Found: C, 69·25; H, 5·4; N, 16·1. $C_{20}H_{20}O_2N_4$ requires C, 69·0; H, 5·75; N, 16·1%).

One of us (E. G. B.) thanks the D.S.I.R. for a maintenance grant.

THE NORTHERN POLYTECHNIC,
HOLLOWAY ROAD, LONDON, N.7.

[*Received, February 4th*, 1958.]