451. *The Preparation and Properties of Some Pyrazolylacetic Acids.*

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Some pyrazoles containing the acetic acid side-chain have been prepared by means of the Willgerodt reaction, and their activity in the wheat cylinder test has been investigated.

Ethyl 3-acetyl-4-methylpyrazole-5-carboxylate [1] (I) was subjected to the Kindler [2] modification of the Willgerodt reaction employing sulphur and morpholine,[3] but the product was uncrystallisable. Attempts to isolate an acid from this by hydrolysis failed, but a crystalline thionmorpholide hydrochloride (II) was obtained and hydrolysed to the corresponding acetic acid (III). The same acetic acid derivative was obtained from 3-acetyl-4-methylpyrazole-5-carboxylic acid (IV): the mixture resulting from the action of sulphur and morpholine on this compound was water-soluble, and the thionmorpholide acid (V) was obtained as a solid on acidification. This also yielded the acid (III) on hydrolysis.

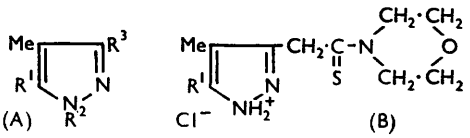
Methylation of the ester (I) gave only the 3-acetyl compound and none of the 5-acetyl isomer (VI*a*), as was shown by hydrolysis to a sterically hindered acid (VII) which was only slowly esterified by methanolic hydrogen chloride. The Willgerodt reaction with (VI) gave a crystalline 5-ethoxycarbonyl-1 : 4-dimethyl-3-pyrazolyl(thioacetmorpholide) (VIII) which was hydrolysed to the acetic acid derivative (IX).

Decarboxylation of the acid (VII) yielded a ketone (X), but the Willgerodt reaction on this failed to give the desired 1 : 4-dimethyl-3-pyrazolylacetic acid (XI). This acid, however, was obtained as its methyl ester (XIII) by decarboxylating the monomethyl ester (XII).

The Willgerodt reaction on 3-acetyl-4-methylpyrazole (XIV), followed by treatment of

[1] Klages, *J. prakt. Chem.*, 1902, **65**, 387.
[2] Carmack and Spielman, "Organic Reactions," Wiley, New York, 1946, Vol. III, p. 85.
[3] Schwenk and Papa, *J. Org. Chem.*, 1946, **11**, 798.

the product with hydrochloric acid, yielded a crystalline 4-methyl-3-pyrazolyl(thioacetmorpholide) hydrochloride (XV) which, on hydrolysis, gave the 4-methyl-3-pyrazolylacetic acid (XVI) in poor yield.



(A) (B)

		R^1	R^2	R^3
I	A	CO_2Et	H	Ac
II	B	CO_2Et		
III	A	CO_2H	H	$CH_2{\cdot}CO_2H$
IV	A	CO_2H	H	Ac
V	A	CO_2H	H	$CH_2{\cdot}CS{\cdot}N{<}C_4H_8{>}O$
VI	A	CO_2Et	Me	Ac
VI*a*	A	Ac	Me	CO_2Et
VII	A	CO_2H	Me	Ac
VIII	A	CO_2Et	Me	$CH_2{\cdot}CS{\cdot}N{<}C_4H_8{>}O$

		R^1	R^2	R^3
IX	A	CO_2H	Me	$CH_2{\cdot}CO_2H$
X	A	H	Me	Ac
XI	A	H	Me	$CH_2{\cdot}CO_2H$
XII	A	CO_2H	Me	$CH_2{\cdot}CO_2Me$
XIII	A	H	Me	$CH_2{\cdot}CO_2Me$
XIV	A	H	H	Ac
XV	B	H		
XVI	A	H	H	$CH_2{\cdot}CO_2H$

The acids, as sodium salts, were subjected to the wheat cylinder test, the percentage elongations of wheat coleoptiles in solutions of the sodium salts being given in the Table. The compounds showed slight activity at concentrations rather close to those causing toxicity. In the pea curvature test all the acids were inactive at concentrations up to 500 p.p.m.

Elongation (%) of wheat coleoptiles in solutions of sodium salts of the pyrazolylacetic acids.

	Compound			
Concn. (p.p.m.)	III	IX	XI	XVI
0·1	100	102	99	99
1·0	100	102	104	102
10	104	101	102	102
100	115	102	102	109
500	Toxic	106	130	Toxic

Experimental

Orientation of 3-Acetyl-1 : 4-dimethylpyrazole-5-carboxylic Acids.—The total crude product (17·5 g.) obtained by methylating and then hydrolysing 3-acetyl-4-methylpyrazole-5-carboxylic ester [4] (19·6 g.) was refluxed for 3 hr. with 1% methanolic hydrogen chloride (500 g.), and the solution then rapidly evaporated. The residue was dissolved by shaking it with ether and aqueous sodium hydrogen carbonate. Unchanged acid was liberated from the aqueous solution with acid (14·5 g., 83%). The ethereal layer was evaporated, the residue hydrolysed, and the acid isolated (3·0 g., 17%). This acid was refluxed for 3 hr. with 1% methanolic hydrogen chloride (100 g.), and the unchanged acid separated from the ester by the above process (unchanged acid, 1·1 g., 37%; ester, 1·4 g., 45%); the ester (from dilute alcohol) melted at 157—158°, or at 155—156° when mixed with authentic methyl 3-acetyl-4-methylpyrazole-5-carboxylate (m. p. 155—157°) (Klages [4] gives m. p. 152°).

The recovered acid (14·5 g.) was refluxed for 3 hr. with 1% methanolic hydrogen chloride (400 g.), and the extraction repeated as before. The unchanged acid had m. p. 189—191° (Klages [4] gives 185—186°) (11·0 g., 76%). The methyl ester was obtained as needles, m. p. 110—111° (1·5 g., 97%).

Willgerodt Reaction of Ethyl 3-Acetyl-1 : 4-dimethylpyrazole-5-carboxylate. 5-Ethoxycarbonyl-1 : 4-dimethyl-3-pyrazolyl(thioacetmorpholide).—Ethyl 3-acetyl-1 : 4-dimethylpyrazole-5-carboxylate [4] (m. p. 85—86°; 5·0 g., 0·024 mole), sulphur (1·1 g., 0·033 g.-atom), and morpholine (7 c.c.; excess) were refluxed for 1 hr. at 150°. After cooling, the solidified mass was triturated with water, then dilute hydrochloric acid, then again water, and recrystallised from methanol (yield 3·72 g., 50%). The *morpholide* is obtained as pale cream needles, m. p. 103—104°, on rapid cooling, or as rhombs or platelets, m. p. 107—108°, by keeping the needles

[4] Klages and Rönneburg, *Ber.*, 1903, **36**, 1128.

in contact with the mother-liquor for several days (Found : C, 53·7; H, 6·9; N, 13·8; S, 10·5. $C_{14}H_{21}O_3N_3S$ requires C, 54·0; H, 6·8; N, 13·5; S, 10·3%). Suspensions of the two forms in Nujol had different infrared absorption spectra but the spectra of 5% solutions in carbon tetrachloride were identical. 5-Ethoxycarbonyl-1 : 4-dimethyl-3-pyrazolyl(thioacetmorpholide) (5 g.) was refluxed for 5 hr. with 10% ethanolic potassium hydroxide (75 c.c.). Water (100 c.c.) was then added and the mixture evaporated to 50 c.c. to remove morpholine. 3N-Hydrochloric acid (50 c.c.) was next added and the mixture again evaporated to 50 c.c. (to remove hydrogen sulphide). On cooling (charcoal), the *pyrazolylacetic acid* crystallised as white needles (2·6 g., 82%), m. p. 197° (Found : C, 49·1; H, 5·3; N, 13·8. $C_8H_{10}O_4N_2$ requires C, 48·6; H, 5·1; N, 14·15%).

Willgerodt Reaction of Ethyl 5-Acetyl-4-methylpyrazole-3-carboxylate.—The procedure followed was as above, but the product could not be obtained solid, and no product could be obtained on hydrolysis. Treatment of the product from 4·0 g. of ester with concentrated hydrochloric acid (10—15 c.c.) gave a clear solution from which, on cooling, yellow crystals of *ethoxycarbonylmethylpyrazolyl(thioacetmorpholide) hydrochloride*, m. p. 158—161°, were obtained after washing with hydrochloric acid (3—5 c.c.) and drying *in vacuo*. Recrystallisation from chloroform–benzene gave crystals, m. p. 160—161° (Found : S, 9·9; Cl, 10·8. $C_{13}H_{20}O_3N_3ClS$ requires S, 9·6; Cl, 10·65%).

5-Carboxy-4-methyl-3-pyrazolylacetic Acid.—3-Ethoxycarbonyl-4-methyl-3-pyrazolyl(thioacetomorpholide) hydrochloride (1 g.) was refluxed for 3 hr. with 3N-aqueous sodium hydroxide. After cooling, some yellow amorphous material was filtered off. The solution was acidified and white needles of the *pyrazolylacetic acid*, m. p. 245—258°, formed in spherical agglomerates after 2—3 days. After two recrystallisions from hot water the m. p. was 265—267° (Found : C, 45·7; H, 4·55; N, 15·0. $C_7H_8O_4N_2$ requires C, 45·7; H, 4·4; N, 15·2%).

5-Carboxy-4-methyl-3-pyrazolyl(thioacetmorpholide).—The Willgerodt reaction on 5-acetyl-4-methylpyrazole-3-carboxylic acid (4·2 g.) yielded a water-soluble resin. A solution of this in water (100 c.c.) was slowly acidified (stirring) with dilute hydrochloric acid. The *morpholide* separated as a yellow precipitate, m. p. 235—236° (decomp.), but could not be recrystallised from the usual solvents; purified by reprecipitation (hydrochloric acid) from aqueous sodium hydrogen carbonate, it had m. p. 235—236° (decomp.) (Found : C, 48·8; H, 5·3; N, 15·8; S, 11·9. $C_{11}H_{15}O_3N_3S$ requires C, 49·0; H, 5·6; N, 15·6; S, 11·9%).

This morpholide (3 g.) was hydrolysed as described above. The carboxymethylpyrazolylacetic acid crystallised slowly from water in pale yellow rosettes, m. p. 264—266° (1·9 g., 91%). Recrystallisation from ethanol gave white crystals, m. p. 265—267°.

3-Acetyl-1 : 4-dimethylpyrazole.—3-Acetyl-1 : 4-dimethylpyrazole-5-carboxylic acid (15 g.) was heated at 240° ± 10° until vigorous ebullition ceased. The crude *acetyldimethylpyrazole* (10·4 g.) was then rapidly distilled off under reduced pressure and redistilled at 0·1 mm., the fraction boiling at 63—65° being collected (8·7 g., 76·5%). This solidified at 19—20° (Found : C, 60·9; H, 7·1; N, 20·0. $C_7H_{10}ON_2$ requires C, 60·8; H, 7·3; N, 20·3%).

Methyl 5-Carboxy-1 : 4-dimethylpyrazole-3-acetate.—5-Carboxy-1 : 4-dimethylpyrazole-3-acetic acid (1·55 g.) was refluxed for 3 hr. with 1% methanolic hydrogen chloride (250 c.c.), then evaporated to dryness, dissolved in aqueous sodium hydrogen carbonate, and extracted with ether. The aqueous solution was acidified and the *monoester* (1·5 g., 90%) filtered off; it had m. p. 141—142° (Found : equiv., 216. $C_8H_{11}O_2N_2{\cdot}CO_2H$ requires equiv., 212).

Methyl 1 : 4-Dimethyl-3-pyrazolylacetate.—Methyl 5-carboxy-1 : 4-dimethylpyrazole-3-acetate (2·0 g.) was heated at 200—240° for 1 hr. The product was distilled at 0·05—0·08 mm. and the fraction boiling at 76—78° was collected; this remained an oil (1·1 g., 70%).

1 : 4-Dimethyl-3-pyrazolylacetic Acid.—The preceding ester (1·0 g.) was saponified with ethanolic potassium hydroxide for 1 hr., and the solution was acidified, diluted with water, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated; the residual solid, twice recrystallised from benzene–light petroleum and finally from benzene, had m. p. 107—109° (0·45 g.; 49%) (Found : C, 54·7; H, 6·6; N, 17·8. $C_7H_{10}O_2N_2$ requires C, 54·6; H, 6·6; N, 18·2%).

4-Methyl-3-pyrazolyl(thioacetmorpholide) Hydrochloride.—Crude 4-methyl-3-acetylpyrazole [4] (6·75 g.; m. p. 97—100°) was subjected to the Willgerodt reaction as in previous experiments but, after the reaction, excess of morpholine was removed at 120—130° under reduced pressure. To the remaining resin was added concentrated hydrochloric acid (10—20 c.c.) until it gave a paste of pale yellow crystals of the *morpholide hydrochloride*. This was cooled and filtered, and

the solid was washed with a small amount of concentrated hydrochloric acid, then dried on porous tile (yield, 7 g., 43%). Recrystallisation from ethanol gave white crystals, m. p. 206° (decomp.) (Found: N, 15·9; S, 12·15; Cl, 13·2. $C_{10}H_{16}ON_3ClS$ requires N, 16·0; S, 12·25; Cl, 13·6%).

4-*Methylpyrazolyl*-3-*acetic Acid*.—The preceding salt (7 g.) was hydrolysed by the normal method, but the aqueous solution, after filtration, was evaporated at 130°/20 mm. The dry residue was extracted with boiling ethanol, and the extract evaporated. The resinous residue (4·5 g.) was dissolved in aqueous sodium hydrogen carbonate, and the solution washed with benzene. The aqueous solution was acidified and extracted with ether (10 × 100 c.c.). The combined extracts gave a white crystalline residue on evaporation (0·4 g.), but further ether extracts yielded only negligible amounts of residue. The solid, after recrystallisation from benzene, consisted of white needles of the 4-*methylpyrazolyl*-3-*acetic acid*, m. p. 116—117° (0·22 g.) (Found: C, 51·8; H, 5·9; N, 20·2. $C_6H_8O_2N_2$ requires C, 51·5; H, 5·7; N, 20·0%).

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