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Preparation of Esters of 4-Hydroxypyrazole-3,5-dicarboxylic Acid

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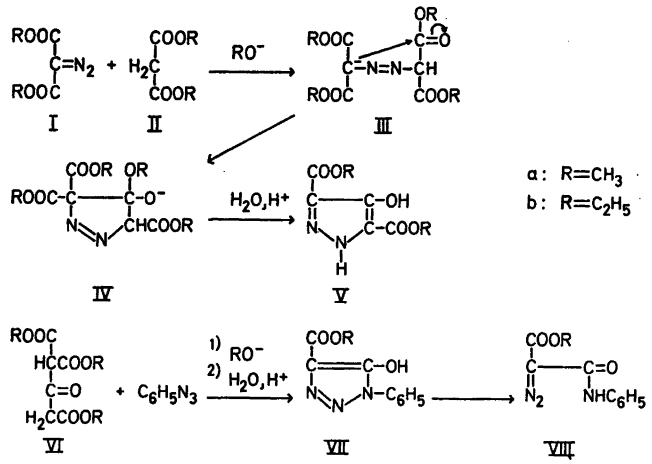
The base catalyzed reaction of dimethyl diazomalonate with dimethyl malonate gives a high yield of dimethyl 4-hydroxypyrazole-3,5-dicarboxylate. The corresponding diethyl ester was obtained in low yield only. The mechanism of the formation of dimethyl 4-hydroxypyrazole-3,5-dicarboxylate as a byproduct in the reaction of phenyl azide with dimethyl malonate is discussed.

Bertho and Nüssel [1] have described the preparation of a number of 4-hydroxypyrazole derivatives by the reaction of malonic esters with ethyl diazoacetate in the presence of sodium ethoxide. Thus they claimed to obtain diethyl 4-hydroxypyrazole-3,5-dicarboxylate (Vb) in 25 % yield from diethyl malonate and ethyl diazoacetate. Although the yields reported by Bertho and Nüssel were rather low the method seemed attractive because the starting materials are readily available. However, in spite of numerous attempts conducted under various conditions, we have been unable to reproduce any of the results reported by Bertho and Nüssel. The reaction of diethyl malonate with ethyl diazoacetate in ethanolic sodium ethoxide gives, in our hands, an untractable tar from which only traces of diethyl 4-hydroxypyrazole-3,5-dicarboxylate (Vb) can be isolated. Attempts to use the corresponding methyl esters were equally unsuccessful.

Presumably the ethyl diazoacetate decomposes under the strongly alkaline conditions used in this reaction [2] and it was therefore decided to investigate the reaction of the more stable esters of diazomalonic acid with malonic esters to see whether 4-hydroxypyrazole derivatives could be prepared by this route. Esters of diazomalonic acid are readily prepared by the method of Regitz.[3]

When diethyl diazomalonate (Ib) was reacted with diethyl malonate (IIb) in ethanolic sodium ethoxide diethyl 4-hydroxypyrazole-3,5-dicarboxylate (Vb) was indeed obtained. However, the yield (7 %) was low and could not be increased by variation of the reaction conditions. The corresponding methyl esters (Ia) and (IIa), on the other hand, gave a good yield (83 %) of dimethyl



4-hydroxypyrazole-3,5-dicarboxylate (Va) when allowed to react in methanolic sodium methoxide. The reaction probably proceeds *via* the condensation product (III) [4,5] which by ring closure gives (IV) and, subsequently, the 4-hydroxypyrazole (V).

Dimethyl 4-hydroxypyrazole-3,5-dicarboxylate (Va) was first described by Dimroth [6] who obtained this compound as a byproduct in the synthesis of methyl 1-phenyl-5-hydroxy-1,2,3-triazole-4-carboxylate (VIIa) from phenyl azide and dimethyl malonate in the presence of methanolic sodium methoxide. Dimroth assumed that the pyrazole (Va) was formed from trimethyl acetonetricarboxylate (VIa) which had been shown by Willstätter [7] to be formed in low yield from dimethyl malonate and sodium. This mechanism has now been checked by preparing triethyl acetonetricarboxylate (VIb) according to Willstätter [7] and treating it with phenyl azide in ethanolic sodium ethoxide. This gave as the main product ethyl 1-phenyl-5-hydroxy-1,2,3-triazole-4-carboxylate (VIIb), which was isolated as the ring-opened product (VIII);[6] no pyrazole could be detected in the reaction product. The mechanism proposed by Dimroth [6] must therefore be incorrect.

A different mechanism has been proposed by Fusco [8] to explain the formation of the pyrazole (Va) from phenyl azide and malonic ester. This mechanism involves the intermediate formation of a triazoline which decomposes to give diazoacetic ester. The latter is then assumed to react with malonic ester according to the scheme of Bertho and Nüssel [1] to give the pyrazole (Va). Since, however, we have been unable to reproduce the results of Bertho and Nüssel the mechanism proposed by Fusco appears to be highly unlikely.

Since it has now been found that dimethyl diazomalonate gives a high yield of the pyrazole (Va) on reaction with dimethyl malonate it would be reasonable to assume that the diazomalonic ester (I) is an intermediate in the formation of (Va) in the Dimroth reaction. The diazomalonic ester (Ia) would then be assumed to be formed by a diazogroup transfer from phenyl azide to malonic ester analogous to the reaction taking place between tosyl azide and malonic ester.[3]

EXPERIMENTAL

Dimethyl 4-hydroxypyrazole-3,5-dicarboxylate (Va). A solution of sodium (1.52 g) in anhydrous methanol (39 ml) was cooled in an ice-salt bath and dimethyl malonate (2.93 g) was added. The mixture was stirred and dimethyl diazomalonate [3] (3.48 g) was added in the course of *ca.* 5 min, the temperature being kept below 0°. The mixture was then stirred for 30 min at 0°, the ice-bath was removed, and the stirring was continued for an additional 30 min during which time a yellow precipitate formed. The mixture was then heated to gentle reflux for 2 h. After cooling the precipitate was filtered off and washed with ether (2×30 ml) and then stirred for 5 min with 2 N hydrochloric acid (36 ml). Filtration gave the crude dimethyl 4-hydroxypyrazole-3,5-dicarboxylate (Va) as yellow crystals, m.p. 228—230° (decomp.), yield 3.65 g (83 %). The product was dissolved in a boiling mixture of methanol (300 ml) and water (50 ml); on cooling to −30° the pure compound precipitated, m.p. 235—237° (reported [6] 232°). The infrared spectrum of the product was identical with that of a sample prepared according to Dimroth.[6]

Diethyl 4-hydroxypyrazole-3,5-dicarboxylate (Vb) was prepared by the procedure described above from sodium (0.37 g) in anhydrous ethanol (11 ml) by addition of diethyl malonate (0.78 g) and diethyl diazomalonate [3] (0.99 g). After the 2 h reflux period almost no precipitate was formed. The ethanol was then removed *in vacuo* and ether (70 ml) was added to the residue. The solid was filtered off and dissolved in 1 N hydrochloric acid (22 ml). The solution was evaporated to dryness *in vacuo* and the residue was extracted with boiling ether (4×25 ml). Evaporation of the ether gave a residue which was extracted with chloroform (4×5 ml) leaving an insoluble residue which consisted mainly of malonic acid. The chloroform was evaporated and the residue was dissolved in ether and the solution was filtered through activated carbon. The ether solution was concentrated to 5 ml and kept at −30° for 2 days thereby precipitating 75 mg (7 %) of diethyl 4-hydroxypyrazole-3,5-dicarboxylate (Vb) with m.p. 109—111°. Recrystallization from ether gave the pure compound as colourless crystals, m.p. 131—132°. Its melting point and infrared spectrum were identical with those of a sample obtained in very low yield by the method of Bertho and Nüssel.[1] The latter authors reported the m.p. to be 151°; however, the compound is apparently dimorphic. Several unsuccessful attempts were made to improve the yield obtained in this preparation by variation of the amount of ethanol used as solvent or by varying the reaction temperature.

Triethyl acetonetricarboxylate was prepared according to Willstätter.[7] In a number of experiments the yield varied between 1 and 10 %. The product was purified by distillation *in vacuo* and was obtained as a colourless liquid, b.p. 113° (0.05 mm). (Found: C 52.50; H 6.68. Calc. for $C_{12}H_{18}O_7$: C 52.57; H 6.62). The cupric chelate was prepared, m.p. 84—86° (reported [7] 83—85°). (Found: C 47.40; H 5.76. Calc. for $C_{24}H_{34}Cu$, 2 H_2O: C 47.63; H 5.86).

Reaction of triethyl acetonetricarboxylate with phenyl azide. To a solution of sodium (26 mg) in ethanol (1 ml) was added triethyl acetonetricarboxylate (0.30 g) and phenyl azide (0.12 ml). The mixture was heated to reflux for 1 h in an oil bath and then kept over night at room temperature. The ethanol was then evaporated with a stream of air, and water (2 ml) was added to the residue. The aqueous solution was washed twice with ether and then acidified with 4 N hydrochloric acid. A brown oil separated which crystallized when the mixture was kept for several days at +5°. The product was recrystallized from ether-pentane to give 70 mg (30 %) of ethyl diazomalonate monoanilide (VIII) as yellow crystals, m.p. 71—72°. An infrared spectrum proved its identity with an authentic sample prepared according to Dimroth.[6] No pyrazole could be detected in the mother liquor from the above mentioned product.

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