ACTA CHEMICA SCANDINAVICA 16 (1962) 2395–2405

The Reaction between Thiohydrazides and Ethyl Benzoylchloroacetate

Part I. Formation of Ethyl 5-Phenylpyrazole-4-carboxylates

JAN SANDSTRÖM

Department of Organic Chemistry, University of Lund, Lund, Sweden

The reaction between thiohydrazides and ethyl benzoylchloroacetate in the presence of slightly less than one equivalent of sodium ethoxide leads to the formation of ethyl 5-phenylpyrazole-4-carboxylates. Thiohydrazides with free or benzyl substituted amino groups give hydroxy-dihydro-thiadiazines as unstable intermediates, whereas the 1-phenylthiohydrazides give more stable, ring-open intermediates. Both products are dehydrated by acids to red, unstable intermediates, probably thiadiazines which rapidly eliminate sulphur and give the pyrazole esters, usually in good yields. These esters, particularly the N-unsubstituted ones, are remarkably resistant to nucleophilic reagents. This has been explained by the electron donating effect of the pyrazole ring, which is most pronounced after ionization. This interpretation has been supported by a LCAO—MO calculation of the π electron distribution in a pyrazole-4-carboxylic ester and its anion. The acid dissociation constants are given for some N-unsubstituted pyrazole esters.

In previous investigations by the present author [1,2] and by Beyer and collaborators [3–5] it has been shown that thiohydrazides react with a variety of α-halogen carbonyl compounds to give labile 1,3,4-thiadiazines, which undergo ring-contraction with extrusion of sulphur to form pyrazoles. The reactions between thiohydrazides with free amino groups and α-chlorodesoxybenzoin has been shown to proceed *via* two intermediates that can be isolated, *viz.* a hydroxydihydro-thiadiazine and a thiadiazine [2]. The thiadiazine was comparatively stable, which was ascribed to conjugation with the phenyl group in the position 5. Previously [1,3] it had been found that electron attracting groups in the position 6 facilitated the ring contraction. The present investigation was undertaken in order to study the combined effect of a phenyl group in the position 5 and a carbethoxy group in the position 6. Each of the five thiohydrazides (I a—e) was dissolved in one equivalent of N sodium ethoxide and was made to react with one equivalent of ethyl benzoylchloroacetate. It was

observed that when a small excess of sodium ethoxide was employed, the reaction took an unexpected course with formation of benzoylhydrazones of ethoxycarbonylmethyl thiolcarboxylates, as will be described in Part II of this series. Only the 1-phenyl substituted thiohydrazides reacted according to expectation in the presence of an excess of base. When excess base was avoided, and the reaction was performed at room temperature, no intermediates could be isolated, and it could be shown by paper chromatography that pyrazoles appeared in the reaction mixtures already after a few minutes. However, if the reactants in absolute ethanol solution were mixed at −30°, crystalline products were obtained. The analytical results were in agreement with the expected hydroxy-dihydrothiadiazine structure (II), but infrared spectra (Fig. 1) showed that only the products from the thiohydrazides (I a—c) had this structure. In the spectra of the derivatives of the phenyl substituted thiohydrazides (I d) and (I e) two carbonyl bands appeared, one at 1730 cm^{-1}, originating from the ester carbonyl group, and one at 1680 cm^{-1} from a C-benzoyl group. Therefore, these intermediates must still be open, and have the general structure (III). A strong band at 1600 cm^{-1} may be due to a conjugated carbon-nitrogen double bond stretching mode. The compounds (II a—c) show only the ester carbonyl band near 1730 cm^{-1} in this region.

The intermediates (II) are rapidly decomposed at room temperature in an exothermic reaction, but they can be stored for some time at −30°. The intermediates (III) show a normal stability.

Attempts to isolate the intermediate thiadiazines (IV) have hitherto been in vain. Previously [2] the transformation of hydroxydihydrothiadiazines to thiadiazines could be effected by careful heating or by treatment with acetic

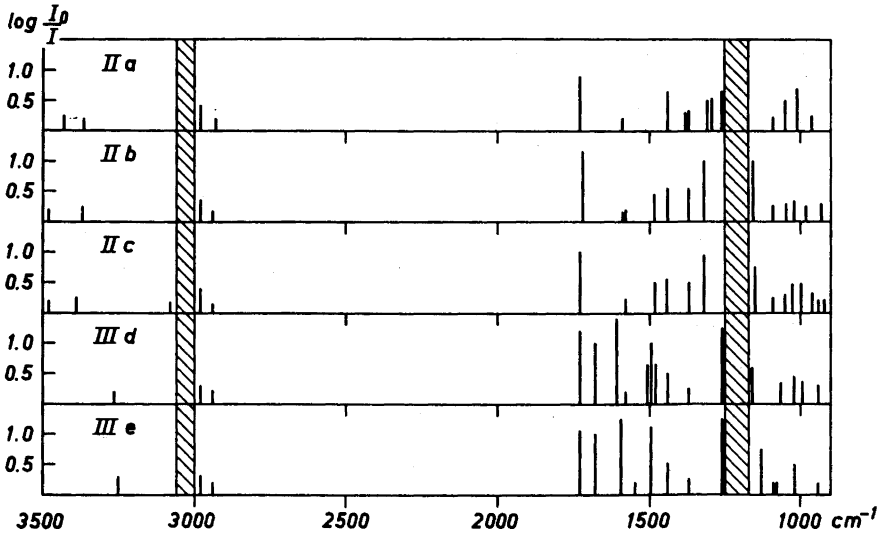
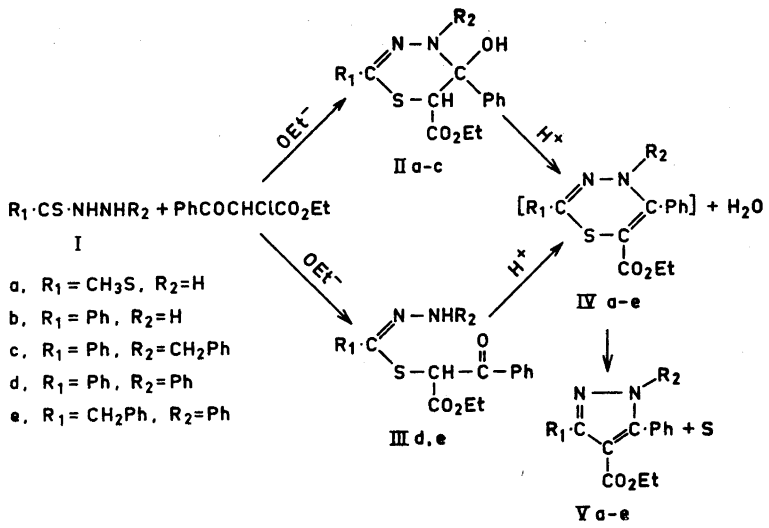
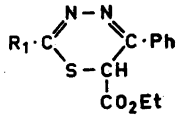


Fig. 1. Infrared spectra of the intermediates (II) and (III) in chloroform. The shaded areas indicate regions of high solvent absorption. $c = 0.15$.



anhydride or acids. However, the compounds described here were always directly transformed to pyrazoles and sulphur, no matter how carefully the solutions were heated up. On treatment with acetic anhydride or very dilute hydrochloric acid a red to reddish-yellow colour appeared, which soon faded under simultaneous precipitation of sulphur. The colour is probably due to the thiadiazines, since Beyer *et al.*[5] have found that the ethyl 2-methylthio-5-methyl-1,3,4-thiadiazine-6-carboxylate is red. The change could be followed spectrophotometrically. All compounds with the structures (II) and (III) in slightly acid medium developed absorption bands in the region 4000—4500 Å with an apparent extinction coefficient of about 1000 to 1700. The bands appeared very rapidly and reached the maximum absorption before any readings could be made. Thereafter they disappeared gradually in a rate, which increased with the concentration of acid. When attempts were made to repeat the experiments on a preparative scale, red, non-crystalline products were obtained. However, the colour of these substances faded in the course of the purification procedures, even during paper chromatography, and finally only pyrazoles and sulphur were obtained.

The thiadiazines derived from thiohydrazides with a free amino group can have either of the structures (IV) and (VI).



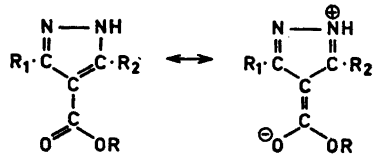
VI

The appearance of the very similar absorption maxima between 4000 and 4500 Å indicates that the red colour in all cases is due to the structure (IV), which is the only possible one for the thiadiazines from (II c), (III d), and (III e). Bulka *et al.*[6] have concluded, from the result of a reaction with *p*-nitrobenzaldehyde, that the structure corresponding to (VI) is the best representation of the thiadiazines. However, the two forms may well exist in equilibrium.

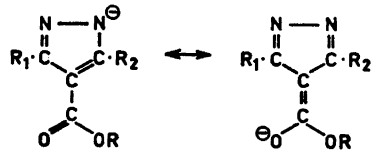
Thus, the results of this part of the investigation show, according to expectation, that the intermediate thiadiazines are considerably destabilised by the 6-carbethoxy group.

This reaction may be a convenient tool for the preparation of N-substituted pyrazoles with known constitution. The scope of the reaction has been considerably widened by the recent very extensive work of Jensen *et al.*[7–9], by which a wide variety of new thiohydrazides has become available.

As has been noticed previously [1], the pyrazole-4-carboxylic esters are remarkably stable to hydrolysis. This applies in particular to the esters with a free NH group. Thus ethyl 3,5-diphenylpyrazole-4-carboxylate (Vb) is not detectably hydrolysed after two hours reflux in two equivalents of 0.5 N ethanolic potassium hydroxide. Under the same conditions the 1-methyl analogue is hydrolysed to 51 % and the 1-phenyl analogue to 73 %. The slow hydrolysis of the pyrazole esters has been explained by the electron donating effect of the pyrazole ring [10] (VII), which increases the electron density around the carbonyl carbon atom and thereby impedes attacks by nucleophilic reagents. The greater reactivity of the 1-phenyl derivative was explained by a competing migration of electrons into the benzene ring. However, this effect can only explain the difference between the 1-phenyl and 1-methyl esters, but not the much greater difference between the 1-methyl and the 1-unsubstituted ones. It was observed during this investigation that the latter esters are



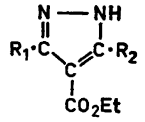
VII



VIII

considerably more acidic than the unsubstituted pyrazole (Table 1). Therefore, the esters are probably completely ionised under the conditions of hydrolysis. Qualitatively it is easily understood that the migration of π electrons from the ring to the carbethoxy group is facilitated by ionisation, since then it can take place without separation of charges (VIII). This effect has also been demonstrated in a more quantitative way by a LCAO-MO calculation of the π electron distribution in a simple pyrazole ester and its anion. The method of calculation employed is the interative procedure devised by Janssen [12]. Two sets of Coulomb and resonance integrals are used (Table 2) in order to show that the result is not too dependent on the choice of parameters. The β_{CN} and β_{NN} values of set II and the β_{CO} values are derived from the overlap integrals

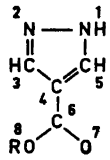
Table 1.

pK_a values for  at 20°C.

R_1	R_2	pK_a
C_2H_5O	CH_3[a]	11.8
C_2H_5S	CH_3[a]	11.4
CH_3S	C_6H_5	10.5
C_6H_5	C_6H_5	11.1
Pyrazole		14 [b]

[a] Ref.[1] [b] Ref.[11]

Table 2. Coulomb and resonance integrals for pyrazole-4-carboxylate and its anion.



	Acid		Anion	
	I	II	I	II
α_1	$\alpha + 1.5\beta$	$\alpha + 1.5\beta$	$\alpha + 0.5\beta$	$\alpha + 0.5\beta$
α_2	$\alpha + 0.5\beta$	$\alpha + 0.5\beta$	$\alpha + 0.5\beta$	$\alpha + 0.5\beta$
α_3	α	α	α	α
α_4	α	α	α	α
α_5	α	α	α	α
α_6	α	α	α	α
α_7	$\alpha + \beta$	$\alpha + \beta$	$\alpha + \beta$	$\alpha + \beta$
α_8	$\alpha + 2\beta$	$\alpha + 2\beta$	$\alpha + 2\beta$	$\alpha + 2\beta$
β_{12}	β	0.65β	β	0.65β
β_{23}	β	0.85β	β	0.90β
β_{34}	β	β	β	β
β_{45}	β	β	β	β
β_{15}	β	0.92β	β	0.90β
β_{46}	β	β	β	β
β_{67}	0.85β	0.85β	0.85β	0.85β
β_{68}	0.70β	0.70β	0.70β	0.70β

taken from the tables of Mulliken *et al.*[13] and under the assumption that the resonance integral of a bond is proportional to its overlap integral[14]. The carbon-nitrogen and nitrogen-nitrogen bond lengths in pyrazole are taken from the work of Ehrlich[15].

The carbon-oxygen bond lengths, 1.22 and 1.36 Å, are taken from methyl acetate[16]. In the anion both β_{CN} values are put equal to 0.90 β, and the π electron density of each nitrogen atom is given as 1.5 electrons at the start of the calculation, in order to do justice to the symmetry of the anion. The Coulomb integral for the nitrogen atom 2 is chosen as $\alpha + 0.5\ \beta$[17]. Since atom 1 gives up one electron more to the delocalised bond, the method of calculation requires that its Coulomb integral shall be $\alpha + 1.5\ \beta$. The value for the carbonyl oxygen atom is derived from the electronegativity differences[18], and the value for the alkoxy oxygen atom must be one unit of β higher.

The results of the calculation are given in Table 3. For comparison the calculated π electron distribution in a simple aliphatic ester is also given. The numbering of the atoms is according to Table 2. As could be expected, set I gives the greater separation of charges, but the differences for the carbethoxy group are insignificant. As was predicted by qualitative considerations, the π electron density is higher at the carbonyl carbon atom (atom 6) in a pyrazole-4-carboxylic ester than in a simple aliphatic ester, and this density is further increased on ionisation.

Table 3. π Electron distribution.

Atom No.	Acid		Anion		Simple ester
	I	II	I	II	
1	1.621	1.690	1.321	1.371	
2	1.152	1.187	1.321	1.371	
3	1.039	0.994	1.036	0.987	
4	1.095	1.081	1.122	1.114	
5	0.958	0.917	1.036	0.987	
6	0.825	0.825	0.832	0.836	0.784
7	1.384	1.380	1.405	1.407	1.303
8	1.926	1.926	1.928	1.929	1.912

Longuet-Higgins[19] has shown how differences in π electronic charge can be related to differences in acidity constants for the conjugate acids of aza-aromatic compounds. The same treatment can be applied to pyrazole and 4-carbethoxypyrazole. Assuming the same entropy of ionization for the two systems we obtain $2.3\ RT\ (pK_{a_1} - pK_{a_2}) = -\Delta q_N \cdot \Delta\alpha_N$, where Δq_N is the difference between the π electron densities of the imino nitrogen atoms of pyrazole and its ester, and $\Delta\alpha_N$ is the difference in Coulomb integral between $=N-H$ and $=N^{\ominus}$. In the present approximation $\Delta\alpha_N$ is one unit of β, and Δq_N is 0.22 and 0.25 with the parameter set I and II, respectively. We use 0.24 as a mean value for Δq_N. An estimation of $pK_{a_1} - pK_{a_2}$ requires the evaluation

of β in common energy units. If we use the old and much criticized [20] value of -20 kcal/mole, we obtain $pK_{a_1} - pK_{a_2} = 3.6$. The agreement must be regarded as fortuitous considering the uncertainty in the β value and the effect of the substituents in the pyrazole esters, but it is gratifying that the direction and order of magnitude of the effect of the 4-carbethoxy group are correctly reproduced.

The 1-unsubstituted esters were hydrolysed by dissolving in concentrated sulphuric acid at 110°. On dilution with water the acids were obtained in fair yields. Hydrazinolysis is very slow, and the 1-unsubstituted esters were recovered unchanged after two days in a great excess of boiling anhydrous hydrazine. The 1-substituted esters also react slowly, but from them hydrazides have been obtained.

The pyrazole-4-carboxylic acids were decarboxylated at their melting points to the corresponding 4-unsubstituted pyrazoles.

EXPERIMENTAL

Ethyl 2-methylthio-5-hydroxy-5-phenyl-Δ^2-dihydro-1,3,4-thiadiazine-6-carboxylate (IIa). Methyl dithiocarbazate [21] (I a, 2.6 g) in N sodium ethoxide (20 ml) and ethyl benzoylchloroacetate [22] (4.5 g) in absolute ethanol (10 ml) were mixed at $-30°$. Crystallization started at once, and on the following day colourless rods (3.9 g, 63 % yield) were collected and washed with water to remove the sodium chloride. By addition of water (20 ml) a further amount of the product (1.2 g, 20 % yield) was precipitated. The combined products crystallised from chloroform-light petroleum (b.p. 40–60°) as colourless rods, m.p. 80–85°. Drying, recrystallization and storing were performed at $-30°$. (Found: C 49.9; H 5.06; N 8.93; S 20.5. $C_{13}H_{16}N_2O_3S_2$ (312.40) requires C 50.0; H 5.16; N 8.97; S 20.5). Even at $-30°$ the product turns first reddish-yellow and then pale yellow due to decomposition. At room temperature the reaction can be vigorous with a considerable raise in temperature.

λ_{max}: 3130 Å with ε: 10 500, and 2060 Å with ε: 15 300, in absolute ethanol. When 1.0 ml of 10^{-2} N HCl in absolute ethanol was added to 9.0 ml of a 10^{-3} M solution of (II a) in absolute ethanol, an absorption maximum appeared at 4160 Å with a maximum apparent ε value of about 1000, which then fell to half of this value in about four minutes.

Ethyl 3-methylthio-5-phenyl-pyrazole-4-carboxylate (V a). The hydroxy-dihydrothiadiazine (II a, 3.1 g) was dissolved in ethanol (20 ml), and 2 N HCl in ethanol (10 ml) was added. The mixture turned deep red, but the colour soon faded, and a precipitate of pure sulphur was formed (0.27 g, 84 % yield). Water (50 ml) was added to the filtered solution, and colourless rods were precipitated (2.5 g, 96 % yield), m.p. 131–132° after recrystallization from toluene-heptane. (Found: C 59.5; H 5.34; N 10.6; S 12.1. $C_{13}H_{14}N_2O_2S$ (262.32) requires C 59.5; H 5.38; N 10.7; S 12.2).

In general the preparation of the pyrazole esters is most conveniently performed *via* the isolation of the intermediates (II) or (III). If the reaction is performed at room temperature, the isolation of the pyrazoles is rendered more difficult due to the formation of by-products.

3-Methylthio-5-phenyl-pyrazole-4-carboxylic acid. The ester (V a, 5.2 g) was dissolved in concentrated sulphuric acid (15 ml). The solution was kept at 110° for 20 min, and then it was poured into water (100 ml). A colourless solid separated, which was extracted with N sodium bicarbonate solution (40 ml) and gave a residue of unreacted ester (0.27 g, 5 %). On acidification, the sodium bicarbonate solution deposited a colourless powder (4.0 g, 87 % yield), which crystallised from ethanol as colourless, irregular prisms, m.p. 289–290° (decomp.). (Found: C 56.2; H 4.37; N 11.9; S 13.6; equiv.wt. 230. $C_{11}H_{10}N_2O_2S$ (234.27) requires C 56.4; H 4.30; N 12.0; S 13.7; equiv.wt. 234).

3-Methylthio-5-phenyl-pyrazole hydrochloride. The acid (0.46 g) was kept at 300° until the evolution of gas had ceased. The residue was dissolved in absolute ether (5 ml), and 4 N HCl in absolute ether (5 ml) was added. Colourless crystals separated at once (0.40 g, 89 % yield), m.p. 165–167°, consisting of the hydrochloride of the desired

pyrazole. (Found: C 52.8; H 5.00; Cl 15.8; N 12.4. $C_{10}H_{11}ClN_2S$ (226.73) requires C 53.0; H 4.89; Cl 15.6; N 12.4). When the hydrochloride was decomposed with water, a colourless oil was formed, which crystallised when cooled to −10° but melted again at room temperature.

Ethyl 2,5-diphenyl-5-hydroxy-Δ²-dihydro-1,3,4-thiadiazine-6-carboxylate (II b). Thiobenzhydrazide [23] (I b) in 0.95 equiv. of N sodium ethoxide was made to react with 1 equiv. of ethylbenzoylchloroacetate at −30° as in the preparation of (II a) and gave a total yield of 84 % of (II b), colourless rods from chloroform-light petroleum, m.p. 91−93°. (Found: C 62.8; H 5.38; N 8.17; S 9.20. $C_{18}H_{18}N_2O_3S$ (342.40) requires C 63.1; H 5.30; N 8.18; S 9.36). This compound is less labile than (II a), but it is completely transformed into pyrazole and sulphur after a few days at room temperature.

λ_{max}: 2940 Å with ε: 10 000, and 2070 Å with ε: 29 500, in absolute ethanol. In acid solution a transient absorption band appears at 4440 Å with a maximal apparent ε value of about 1000.

Ethyl 3,5-diphenyl-pyrazole-4-carboxylate (V b). This pyrazole was prepared like (V a) in 90 % yield and crystallised from toluene-heptane as colourless prisms, m.p. 141−142°. (Found: C 73.8; H 5.47; N 9.51. $C_{18}H_{16}N_2O_2$ (292.33) requires C 74.0; H 5.52; N 9.59).

3,5-Diphenyl-pyrazole-4-carboxylic acid. The ester (V b) was hydrolysed in sulphuric acid like (V a) and gave 12 % of unchanged ester and 82 % of crude acid, which crystallised from ethanol-dimethyl sulphoxide as colourless, rhombic plates, m.p. 289−290° (decomp.). (Found: C 72.6; H 4.77; N 10.6; equiv.wt. 268. $C_{16}H_{12}N_2O_2$ (264.28) requires C 72.7; H 4.58; N 10.6; equiv.wt. 264).

3,5-Diphenylpyrazole. Diphenylpyrazole-4-carboxylic acid (0.5 g) was kept at 300° until the evolution of gas had ceased. The residue was recrystallised from 50 % aqueous ethanol (10 ml) and gave colourless, irregular prisms (0.23 g, 54 % yield), m.p. 199−200°. (Found: C 81.6; H 5.67. $C_{15}H_{12}N_2$ (220.27) requires C 81.8; H 5.49). This compound has been described by several authors, and the reported data are in good agreement with those obtained in the present work.

Ethyl 2,5-diphenyl-4-benzyl-5-hydroxy-Δ²-dihydro-1,3,4-thiadiazine-6-carboxylate (II c). This compound was prepared as (II a) and (II b) from 1-benzylthiobenzhydrazide [24] (I c) and ethyl benzoylchloroacetate in 85 % yield, colourless rods from chloroform-light petroleum, m.p. 90−91°. (Found: C 69.2; H 5.44; N 6.45; S 7.40. $C_{25}H_{24}N_2O_3S$ (432.52) requires C 69.4; H 5.59; N 6.48; S 7.41).

λ_{max}: 3055 Å with ε: 10 000, and 2085 Å with ε: 33 500. In acid solution the transient absorption band appears at 4300 Å with a maximal apparent ε value of about 1000.

Ethyl 1-benzyl-3,5-diphenyl-pyrazole-4-carboxylate (V c). This pyrazole was prepared as (V a) and (V b) in 92 % yield. It crystallised from methanol as colourless rods, m.p. 86−87°. (Found: C 78.6; H 5.80; N 7.44. $C_{25}H_{22}N_2O_2$ (382.44) requires C 78.5; H 5.80; N 7.33).

(V c) was also prepared by benzylation of (V b). This compound (2.9 g) was dissolved in N NaOH (15 ml) and ethanol (30 ml). Benzyl chloride (1.3 ml) was added, and within a few minutes a colourless oil started to separate. It solidified on scratching (3.8 g, quantitative yield) and crystallised from methanol as colourless rods, m.p. 86−87°, undepressed on admixture with the product described above.

1-Benzyl-3,5-diphenyl-pyrazole-4-carboxylic acid. The pyrazole ester (V c, 3.8 g) was refluxed for 4 h in N ethanolic potassium hydroxide (20 ml). On acidification with N HCl (20 ml), a colourless solid separated (2.8 g, 79 % yield), which crystallised from ethanol as colourless rods, m.p. 207−208° (decomp.). (Found: C 77.7; H 5.23; N 7.93; equiv.wt. 354. $C_{23}H_{18}N_2O_2$ (354.39) requires C 77.9; H 5.12; N 7.91; equiv.wt. 354).

1-Benzyl-3,5-diphenylpyrazole. The carboxylic acid just described (0.5 g) was kept at 220° until the evolution of gas had ceased. The semisolid residue was dissolved in ethanol (5 ml). The solution was cooled to −20° and deposited colourless, irregular prisms, m.p. 91−92° (0.27 g, 60 % yield). (Found: C 84.8; H 5.78; N 9.00. $C_{22}H_{18}N_2$ (310.38) requires C 85.1; H 5.84; N 9.03).

Ethyl 1-methyl-3,5-diphenyl-pyrazole-4-carboxylate. The pyrazole (V b, 5.8 g) was dissolved in N NaOH (25 ml) and ethanol (50 ml), and methyl iodide (4.5 g) was added. The resulting clear solution soon turned cloudy, and on the following day a solid precipitate had formed (6.05 g, 99 % yield), which crystallised from heptane as colourless needles, m.p. 98−99°. (Found: C 74.3; H 5.83; N 9.18. $C_{19}H_{18}N_2O_2$ (306.35) requires C 74.5; H 5.92; N 9.15).

1-Methyl-3,5-diphenyl-pyrazole-4-carboxhydrazide. The pyrazole ester (6.1 g) was refluxed with absolute ethanol (10 ml) and anhydrous hydrazine (10 ml) for 96 h. Then the reaction mixture was poured into water (200 ml). A semisolid, colourless mass separated, which could not be induced to crystallise. It was then dissolved in chloroform (50 ml) and extracted with three successive portions of N HCl (50 ml each). The combined acid extracts were brought to pH 5 by the addition of solid sodium acetate, and a precipitate was formed (2.6 g, 45 % yield), which crystallised from 25 % aqueous ethanol as colourless rods, m.p. 181—182°. (Found: C 69.4; H 5.54; N 19.2. $C_{17}H_{16}N_4O$ (292.33) requires C 69.8; H 5.52; N 19.2). Evaporation of the chloroform solution gave unchanged starting material (3.1 g, 50 %).

S-[Benzoyl-ethoxycarbonyl-methyl]-1-phenyl-isothiobenzhydrazide (III d). 1-Phenylthiobenzhydrazide [25] (I d) and ethyl benzoylchloroacetate reacted in the usual way to give a reddish-yellow solid in 98 % yield, which crystallised from chloroform-light petroleum as pale yellow, rhombic prisms, m.p. 55—56°. (Found: C 68.8; H 5.27; N 6.60; S 7.64. $C_{24}H_{22}N_2O_3S$ (418.50) requires C 68.9; H 5.30; N 6.70; S 7.66).

λ_{max}: 3525 Å with ε: 16 000, 2920 Å with ε: 10 500, 2450 Å with ε: 25 100, and 2070 Å with ε: 29 000 in absolute ethanol. In acid solution a transient absorption maximum appeared at 4280 Å with a maximal apparent ε value of about 1700.

Ethyl 1,3,5-triphenyl-pyrazole-4-carboxylate (V d). The phenylhydrazone (III d, 4.2 g) was dissolved in absolute ethanol (30 ml), and 2 N HCl in absolute ethanol (5 ml) was added. The solution turned deep red, but the colour soon faded, and a precipitate of pyrazole and sulphur was formed. Purification was effected by successive recrystallizations from acetic acid (50 ml) and butanol (25 ml) and gave pale yellow rods (3.0 g, 82 % yield), m.p. 146—147°. (Found: C 77.9; H 5.29; N 7.68. $C_{24}H_{20}N_2O_2$ (368.42) requires C 78.2; H 5.47; N 7.61).

This ester has previously been described by Minunni and D'Urso [26], who report m.p. 145—146.5°.

1,3,5-Triphenylpyrazole-4-carboxylic acid. The pyrazole (V d, 3.7 g) was refluxed for 4 h with N ethanolic potassium hydroxide (20 ml). Acidification with N HCl (20 ml) gave a microcrystalline powder (2.4 g, 70 % yield), which crystallised from ethanol as colourless rods, m.p. 243—243.5° (decomp.). (Found: Equiv.wt. 342. $C_{22}H_{16}N_2O_2$ requires equiv.wt. 340). This acid has also been described by Minunni and D'Urso [26], who report m.p. 237—238°.

1,3,5-Triphenyl-pyrazole-4-carboxhydrazide. The pyrazole ester (V d, 3.7 g) was refluxed for 48 h with anhydrous hydrazine (25 ml) and absolute ethanol (25 ml). Then the mixture was poured into water (250 ml), and a colourless solid separated (3.1 g, 78 % yield), which crystallised from 70 % aqueous ethanol as colourless rods, m.p. 166—167°. (Found: C 74.2; H 5.24; N 15.6. $C_{22}H_{18}N_4O$ (354.39) requires C 74.6; H 5.12; N 15.8).

This hydrazide (0.7 g) and benzaldehyde (0.3 g) reacted in 70 % aqueous ethanol (10 ml) to give a colourless product (0.68 g, 78 % yield), which crystallised from butanol as colourless, long plates, m.p. 185—186°. (Found: C 78.4; H 5.30; N 12.6. $C_{29}H_{22}N_4O$ (442.50) requires C 78.7; H 5.01; N 12.7).

1,3,5-Triphenylpyrazole. Triphenylpyrazole-4-carboxylic acid (0.68 g) was kept at 250° until the evolution of gas had ceased. The liquid residue was dissolved in ethanol (5 ml), and N NaOH (2 ml) was added. A solid product separated (0.44 g, 74 % yield), which crystallised from butanol as colourless rods, m.p. 138—139°. (Found: C 84.9; H 5.60. $C_{21}H_{16}N_2$ (296.36) requires C 85.1; H 5.44).

Wislicenus [27] reports m.p. 136.5—137.5 for this pyrazole.

S-[Benzoyl-ethoxycarbonyl-methyl]-1-phenyl-isothiophenylacethydrazide (III e). 1-Phenylthiophenylacethydrazide [9] (I e) and ethyl benzoylchloroacetate reacted in the usual way to give 81 % of (III e), which crystallised from chloroform-light petroleum as pale yellow rods, m.p. 111—112°. (Found: C 69.6; H 5.59; N 6.36; S 7.37. $C_{25}H_{24}N_2O_3S$ (432.52) requires C 69.4; H 5.59; N 6.48; S 7.41).

λ_{max}: 2875 Å with ε: 17 500, 2480 Å with ε: 17 500, and 2075 Å with ε: 34 500 in absolute ethanol. In acid solution a transient absorption maximum appeared at 3990 Å with an apparent ε value of about 1500.

Ethyl 1,5-diphenyl-3-benzyl-pyrazole-4-carboxylate (V e). The phenylhydrazone (III e, 4.3 g) was dissolved in ethanol (40 ml), and 2 N HCl in ethanol (10 ml) was added. The mixture first turned red and then pale yellow and deposited a small amount of sticky material. Addition of water (200 ml) to the filtered solution precipitated a semisolid mass,

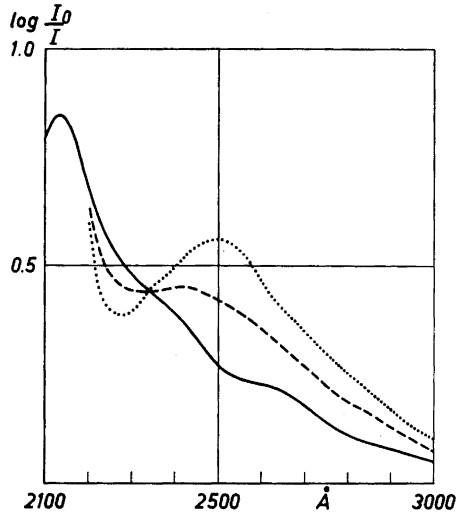


Fig. 2. Ultraviolet spectra of ethyl 3-ethylthio-5-methylpyrazole-4-carboxylate in water at pH 6 (———), pH 11.5 (– – –), and pH 13.7 (· · · · ·). $c = 5 \times 10^{-5}$.

which was dissolved in benzene (5 ml) and subjected to chromatography on alumina. Light petroleum eluted sulphur (0.16 g, 50 % yield), and benzene gave a colourless solid (1.6 g, 42 % yield), which crystallised from heptane as colourless rods, m.p. 111—112°. (Found: C 78.5; H 5.70; N 7.38. $C_{25}H_{22}N_2O_2$ (382.44) requires C 78.5; H 5.80; N 7.33).

Acid dissociation constants (Table 1). These were determined by standard spectrophotometric technique in 5×10^{-5} M solutions in water with 0.5 % of ethanol. All spectra showed a bathochromic displacement on ionisation (Fig. 2). The spectra of the anions were recorded in 0.5 N NaOH, in which solution even the weakest of the acids is ionised to more than 98 %. As a consequence of the solvent effect on the spectra, the K_a values calculated at different wavelengths differed with up to 5 %, but the values of K_a calculated from measurements at five different pH values around the pK_a value showed good agreement for each wavelength, and the average pK_a values are considered to be reliable up to 0.1 unit.

The ultraviolet spectra were recorded with a Beckman DU spectrophotometer with photomultiplier attachment except for the spectra of the compounds (II a—c) and (III d, e) in acid solution, which were recorded with a Perkin-Elmer Model 137 recording spectrophotometer.

The infrared spectra were recorded with a Perkin-Elmer Model 221 prism-grating instrument.

The LCAO-MO calculations were performed on the electronic digital computor "SMIL" at the Department of Numerical Analysis of the University of Lund.

Acknowledgements. The author is indebted to the *Swedish Natural Science Research Council* for financial support, to Miss Ingeborg Leutiger and Fil.kand. Kristina Arvidsson for skilful experimental assistance, and to Mrs Kerstin Kulle-Pettersson for recording the infrared spectra. The LCAO-MO calculations were programmed by Fil.kand. Leif Robertsson, and Laborator Carl-Erik Fröberg and Ingenjör Kjell Jönsson gave valuable advice concerning the use of the computor.

REFERENCES

1. Sandström, J. *Arkiv Kemi* **8** (1955) 523.
2. Sandström, J. *Arkiv Kemi* **15** (1960) 195.
3. Beyer, H. and Wolter, G. *Chem. Ber.* **89** (1956) 1652.
4. Beyer, H., Wolter, G. and Lemke, H. *Chem. Ber.* **89** (1956) 2550.
5. Beyer, H., Bulka, E. and Beckhaus, F. W. *Chem. Ber.* **92** (1959) 2593.
6. Bulka, E., Ahlers, K.-D. and Beyer, H. *Chem. Ber.* **94** (1961) 1122.
7. Jensen, K. A. *Acta Chem. Scand.* **15** (1961) 1067.
8. Jensen, K. A. and Pedersen, Chr. *Acta Chem. Scand.* **15** (1961) 1097.
9. Jensen, K. A., Baccaro, H. R., Buchardt, O., Olsen, G. E., Pedersen, Chr. and Toft, J. *Acta Chem. Scand.* **15** (1961) 1109.
10. Sandström, J. *Svensk Kem. Tidskr.* **68** (1956) 143.
11. Mason, S. F., cited in Albert, A. *Heterocyclic Chemistry*. Essential Books, Fair Lawn 1959, p. 143.
12. Janssen, M. J. *Rec. trav. chim.* **79** (1960) 1066.
13. Mulliken, R. S., Rieke, C. A., Orloff, D. and Orloff, H. *J. Chem. Phys.* **17** (1949) 1248.
14. Mulliken, R. S. *J. Chim. Phys.* **46** (1949) 712.
15. Ehrlich, H. W. W. *Acta Cryst.* **13** (1960) 946.
16. O'Gorman, J. M., Shand, Jr., W. and Shomaker, V. *J. Am. Chem. Soc.* **61** (1950) 4222.
17. Gerson, F. and Heilbronner, E. *Helv. Chim. Acta* **41** (1958) 2332.
18. Daudel, R., Lefebvre, R. and Moser, C. *Quantum Chemistry, Methods and Applications*. Interscience Publishers, New York 1959, p. 76.
19. Longuet-Higgins, H. C. *J. Chem. Phys.* **18** (1950) 275.
20. Streitwieser, A., Jr. *Molecular Orbital Theory for Organic Chemists*. John Wiley and Sons, New York 1961, p. 241.
21. Busch, M. and Starke, M. *J. prakt. Chem.* [2] **93** (1916) 59.
22. Peratoner, A. *Gazz. chim. ital.* **22 II** (1892) 41.
23. Holmberg, B. *Arkiv Kemi, Mineral. Geol.* **17 A** (1944) N:o 23, p. 7.
24. Forsgren, B. and Sandström, J. *Acta Chem. Scand.* **14** (1960) 789.
25. Holmberg, B. *Arkiv Kemi* **7** (1954) 517.
26. Minunni, G. and D'Urso, S. *Gazz. chim. ital.* **58** (1928) 691.
27. Wislicenus, J. *Ann.* **308** (1899) 253.

Received June 7, 1962.