Derivatives of 5-o-*Mercaptophenyl*-3-*methyl*-1-*phenylpyrazole.*

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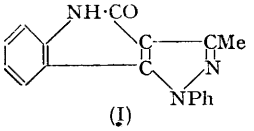
[Reprint Order No. 4455.]

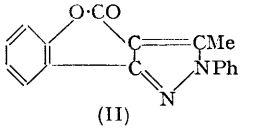
Some new *ortho*-substituted phenylpyrazoles are described, in which ring-closure has been effected between substituent groups to form a new polycyclic system (VII).

Comparatively few polycyclic systems containing the pyrazole nucleus have been described, and only two, *e.g.* (I) (Knorr and Jödicke, *Ber.*, 1885, **18**, 2260) and (II) (Minnuni and Lazarini, *Gazzetta*, 1925, **55**, 536), have been prepared by ring closure between one substituent in the pyrazole nucleus and another in an adjoining benzene ring.

These compounds resemble the lactone of 8-mercapto-1-naphthoic acid (Friedlander and Woroshzow, *Annalen*, 1912, **388**, 21). In each of these compounds the lactone ring is opened by alkalis and re-formed by mineral acids. 5-*o*-Mercaptophenyl-3-methyl-1-phenylpyrazole-4-carboxylic acid (IV; R = SH, R′ = CO_2H) has been shown to form a lactone with similar properties, and a study has been made of a number of related compounds in the hope of elucidating the nature of the products formed during the reductive degradation of thionaphthenopyrazole dioxides (as III; R = Me, R′ = Ph; Barry and McClelland, *J.*, 1935, 471). This account is concerned mainly with the preparation and properties of derivatives of 5-*o*-mercaptophenyl-3-methyl-1-phenylpyrazole (IV; R = SH, R′ = H).



(I)



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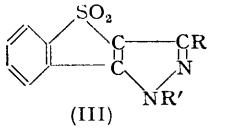

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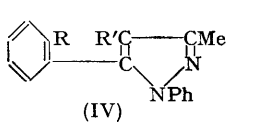
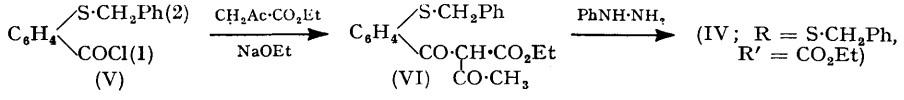


(IV)

Ethyl α-*o*-benzylthiobenzoylacetoacetate (VI), prepared by condensation of *o*-benzylthiobenzoyl chloride (V) with sodioacetoacetic ester, gave, on treatment with phenylhydrazine, ethyl 5-*o*-benzylthiophenyl-3-methyl-1-phenylpyrazole-4-carboxylate (IV; R = S·CH_2Ph, R′ = CO_2Et). Hydrolysis and decarboxylation gave the corresponding pyrazole (IV; R = S·CH_2Ph, R′ = H).



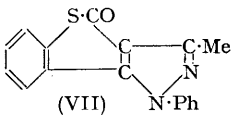
Debenzylation of the ester (IV; R = S·CH_2Ph, R′ = CO_2Et) by chlorine in moist acetic acid (cf. Zincke and Rose, *Annalen*, 1914, **406**, 127; Baker, Dodson, and Riegel, *J. Amer. Chem. Soc.*, 1946, **68**, 2616) gave ethyl 5-*o*-chlorosulphonylphenyl-3-methyl-1-phenylpyrazole-4-carboxylate (IV; R = SO_2Cl, R′ = CO_2Et). The free acid (IV; R = S·CH_2Ph, R′ = CO_2H) and its decarboxylation product (IV; R = S·CH_2Ph, R′ = H), however, both gave the same compound, 4-chloro-5-*o*-chlorosulphonylphenyl-3-methyl-1-phenylpyrazole (IV; R = SO_2Cl, R′ = Cl) when similarly treated.

Reduction of ethyl 5-*o*-chlorosulphonylphenyl-3-methyl-1-phenylpyrazole-4-carboxylate (IV; R = SO_2Cl, R′ = CO_2Et) with zinc and mineral acid gave, according to conditions, the sulphino-ester (IV; R = SO_2H, R′ = CO_2Et), the free acid (IV; R = SO_2H, R′ = CO_2H), the corresponding thiol (IV; R = SH, R′ = CO_2H), or its lactone (VII): (IV; R = SO_2Cl, R′ = CO_2Et) ⟶ (IV; R = SO_2H, R′ = CO_2Et) ⟶ (IV; R = SO_2H, R′ = CO_2H) ⟶ (IV; R = SH, R′ = CO_2H).

The sulphinic acids were remarkably stable to atmospheric oxidation, remaining unchanged after several weeks' exposure. Attempts to decarboxylate the thiol resulted in the formation of the lactone.

In order to confirm the structure of the above compounds, an attempt was made to

remove the sulphur-containing substituents and so obtain pyrazoles of known structure. Accordingly, ethyl 5-*o*-chlorosulphonylphenyl-3-methyl-1-phenylpyrazole-4-carboxylate (IV; R = SO_2Cl, R′ = CO_2Et) was heated in a sealed tube with mineral acid; the chlorosulphonyl group was hydrolysed.



(VII)

Ethyl 5-*o*-benzylsulphonylphenyl-3-methyl-1-phenylpyrazole-4-carboxylate (IV; R = SO_2·CH_2Ph, R′ = CO_2Et), however, underwent hydrogenolysis with Raney nickel to give ethyl 3-methyl-1 : 5-diphenylpyrazole-4-carboxylate (IV; R = H, R′ = CO_2Et) (cf. Mozingo *et al.*, *J. Amer. Chem. Soc.*, 1943, **65**, 1013), thus confirming its structure. The sulphone (IV; R = SO_2·CH_2Ph, R′ = H), prepared either by direct oxidation of the sulphide, or by hydrolysis and decarboxylation of ethyl 5-*o*-benzylsulphonylphenyl-3-methyl-1-phenylpyrazole-4-carboxylate (IV; R = SO_2·CH_2Ph, R′ = CO_2Et), was reduced by sodium amalgam in ethanol (Dabby, Kenyon, and Mason, *J.*, 1952, 4881) to 3-methyl-1-phenyl-5-pyrazolylbenzene-*o*-sulphinic acid (IV; R = SO_2H, R′ = H), which was stable to mineral acids and was therefore not identical with the sulphinic acid formed during the reduction of the thionaphthenopyrazole dioxide (III; R = Me, R′ = Ph) (Barry and McClelland, *loc. cit.*).

Further work on these derivatives is in progress.

Experimental

o-*Benzylthiobenzoyl Chloride*.—*o*-Benzylthiobenzoic acid (Apitzsch, *Ber.*, 1913, **46**, 310) was heated for ½ hr. with thionyl chloride (2—3 mol.). The acid *chloride* (60%), recrystallised several times from benzene, melted at 121—122° (Found: Cl, 13·4. $C_{14}H_{11}OClS$ requires Cl, 13·2%).

α-o-*Benzylthiobenzoylacetoacetic Ester*.—The acid chloride (1·1 mol.) and ethyl acetoacetate (1 mol.) in sodium ethoxide (Claisen *Annalen*, 1896, **291**, 67) gave, on addition of water (1 vol.), *ethyl* o-*benzylthiobenzoate* (27%), which after crystallisation from ethanol had m. p. 68° alone or mixed with the product obtained by heating the acid chloride with excess of ethanol (Found: C, 70·0; H, 5·9; S, 12·2. $C_{16}H_{16}O_2S$ requires C, 70·6; H, 5·9; S, 11·8%).

Acidification of the filtrate gave the diketo-ester (73%), m. p. 65° (from ethanol). This gave a red colour with ferric chloride. The *copper* derivative formed bluish-green crystals from chloroform–ligroin [Found: C, 62·0; H, 5·0; S, 8·1; Cu, 7·9. $(C_{20}H_{19}O_4S)_2Cu$ requires C, 62·1; H, 4·9; S, 8·3; Cu, 8·1%].

Estimation of copper. An ethereal suspension of the derivative was shaken with 3N-sulphuric acid until all the solid matter had decomposed. The blue aqueous layer was separated and the cupric ion estimated iodimetrically.

Ethyl 5-o-*Mercaptophenyl*-3-*methyl*-1-*phenylpyrazole*-4-*carboxylate*.—The diketo-ester (1 mol.), heated with phenylhydrazine (1·1 mol.) in acetic acid for 2 hr. at 100°, yielded the *pyrazole-carboxylate* (83%), as needles (from ethanol), m. p. 121—122°, which gave Knorr's pyrazoline test (Found: C, 72·4; H, 5·5; N, 6·7; S, 7·5. $C_{26}H_{24}O_2N_2S$ requires C, 72·9; H, 5·6; N, 6·5; S, 7·5%).

Oxidation. The pyrazolecarboxylate, hydrogen peroxide (10 ml.; 100 vol.), and acetic acid (25 ml.) were heated at 100° for 1 hr., and then diluted and cooled. The *sulphone* (1 g.) had m. p. 162° after crystallisation from acetic acid (Found: C, 67·5; H, 5·3; N, 6·2; S, 6·9. $C_{26}H_{24}O_4N_2S$ requires C, 67·8; H, 5·2; N, 6·1; S, 7·1%).

5-o-*Benzylthiophenyl*-3-*methyl*-1-*phenylpyrazole*-4-*carboxylic Acid*.—The pyrazole-carboxylate (1 g.) was heated for 2 hr. on the steam-bath with alcoholic potassium hydroxide (10%; 25 ml.), and the solution then acidified. The *acid* (0·8 g.), after recrystallisation from acetic acid, had m. p. 236° (decomp.) (Found: C, 71·2; H, 5·0; N, 6·8; S, 8·3. $C_{24}H_{20}O_2N_2S$ requires C, 72·0; H, 5·0; N, 7·0; S, 8·0%).

Decarboxylation. Heating of the acid for 1—1½ hr. at 250—255° gave 5-o-*benzylthiophenyl*-3-*methyl*-1-*phenylpyrazole* (60% yield), m. p. 110° (from ethanol) (Found: S, 9·2. $C_{23}H_{20}N_2S$ requires S, 9·0%).

Ethyl 5-o-*Chlorosulphonylphenyl*-3-*methyl*-1-*phenylpyrazole*-4-*carboxylate*.—Chlorine was passed into a solution of the pyrazole-carboxylate (40 g.) in acetic acid (AcOH, 1000 ml.; H_2O, 25 ml.) for ½ hr. at 0°, which was then set aside for 10 min. The *sulphonyl chloride* (36 g.) was precipitated by addition of ice water (500 ml.); after crystallisation from acetic acid it had m. p. 155—156° [Found: Cl, 8·2, 9·3 (Volhard). $C_{19}H_{17}ClO_4N_2S$ requires Cl, 8·7%].

Anilide. The sulphonyl chloride (1 g.) was heated with aniline (5 ml.) in benzene (25 ml.)

and then cooled. The *anilide* (1 g.) had m. p. 157·5° (from benzene) (Found: N, 9·5. $C_{19}H_{19}O_4N_3S$ requires N, 9·1%).

4-*Chloro*-5-o-*chlorosulphonylphenyl*-3-*methyl*-1-*phenylpyrazole*.—Similar chlorination of either the carboxylic acid or the pyrazole gave the *chloro*-compound (80%), m. p. 145° (after crystallisation from acetic acid), alone or when mixed (Found: C, 52·1; H, 3·2; N, 7·2; Cl, 19·3; S, 9·1. $C_{16}H_{12}O_2Cl_2N_2S$ requires C, 52·3; H, 3·3; N, 7·6; Cl, 19·3; S, 8·7%).

Ethyl 3-*Methyl*-1-*phenyl*-5-o-*sulphinophenylpyrazole*-4-*carboxylate*.—Concentrated hydrochloric acid (20 ml.) was added to a suspension of zinc dust (10 g.) in acetic acid (100 ml.) containing ethyl 5-*o*-chlorosulphonylphenyl-3-methyl-1-phenylpyrazole-4-carboxylate (12 g.), and the mixture set aside for 12 hr. at room temperature. More hydrochloric acid (20 ml.) was then added, and 1 hr. later sufficient water to produce a faint turbidity. Next morning the *sulphinic acid* was obtained as needles (9·5 g.), which crystallised from ethanol as large rhombs, m. p. 186° (sealed tube), giving Smiles's test (Found: C, 62·4; H, 4·8; N, 7·4; S, 8·5. $C_{19}H_{18}O_4N_2S$ requires C, 61·6; H, 4·9; N, 7·6; S, 8·6%).

Hydrolysis with 10% alcoholic potassium hydroxide for ½ hr. gave the corresponding *carboxylic acid* (82% yield), m. p. 244° (sealed tube) (after recrystallisation from ethanol (Found: N, 7·7; S, 9·2. $C_{17}H_{14}O_4N_2S$ requires N, 8·2; S, 9·3%).

5-o-*Mercaptophenyl*-3-*methyl*-1-*phenylpyrazole*-4-*carboxylic Acid Lactone*.—*Method* 1. Zinc dust (25 g.) was added portionwise to a boiling solution of ethyl 3-methyl-5-*o*-sulphinophenylpyrazole-4-carboxylate (10 g.) in acetic acid (100 ml.)–sulphuric acid (3N; 100 ml.) during 1½ hr. Dilution precipitated the *lactone* (2—3 g.), m. p. 208—210° (from butanol) (Found: C, 69·5; H, 4·2; N, 9·6; S, 11·2. $C_{17}H_{12}ON_2S$ requires C, 69·9; H, 4·1; N, 9·6; S, 11·0%).

Method 2. The lactone was similarly produced when concentrated hydrochloric acid was slowly added to a boiling solution of the ester in acetic acid, containing granulated zinc.

Hydrolysis of the Lactone (VII).—Boiling of the lactone for a few minutes with 20% ethanolic potassium hydroxide and acidification produced the thiol, which after recrystallisation from ethanol, melted at 158—160°, frothing and resolidifying to melt again at 208—210°. The thiol gave a white precipitate with mercuric chloride, and a yellow one with lead acetate. Addition of a few drops of concentrated hydrochloric acid to a boiling solution of the thiol in ethanol immediately regenerated the lactone, m. p. 208—210°. Warming the thiol, excess of 10% sodium carbonate solution, and a few drops of benzyl chloride for a few minutes, followed by acidification, produced the benzyl derivative, m. p. 235—236° (from acetic acid) alone or mixed with a specimen of 5-*o*-benzylthiophenyl-3-methyl-1-phenylpyrazole-4-carboxylic acid (IV; R = S·CH_2Ph, R′ = CO_2H).

5-o-*Benzylsulphonylphenyl*-3-*methyl*-1-*phenylpyrazole*.—*Method* 1. Ethyl 5-*o*-benzylthiophenyl-3-methyl-1-phenylpyrazole-4-carboxylate (IV; R = SO_2·CH_2Ph, R′ = CO_2Et) (7·5 g.) was heated for 15 min. with alcoholic potassium hydroxide (10%; 100 ml.); and the mixture acidified. The acid (5·2 g.), m. p. 238—240° (from ethanol) was heated at 250—270° for 1½ hr., giving an amber-coloured resin, m. p. 182—183° after recrystallisation from ethanol (Found: S, 8·2. $C_{23}H_{20}O_2N_2S$ requires S, 8·25%).

Method 2. 5-*o*-Benzylthiophenyl-3-methyl-1-phenylpyrazole (IV; R = S·CH_2Ph, R′ = H) (0·75 g.) in acetic acid (10 ml.) containing hydrogen peroxide (30%; 3 ml.) was heated for 1 hr. at 100°. Dilution with water produced the *sulphone* (0·5 g.), m. p. 180° alone (from ethanol) or 180—183° in admixture with the compound from method 1.

Reduction. The sulphone (1 g.) was heated with sodium amalgam (5%; 25 g.) in ethanol (25 ml.) for 3½ hr.; the odour of toluene was soon detected. Evaporation of the solvent, extraction with boiling water (charcoal), and acidification precipitated 3-methyl-1-phenyl-5-pyrazolylbenzene-*o*-sulphinic acid (IV; R = SO_2H, R′ = H). This was soluble in sodium hydrogen carbonate solution and was reprecipitated by acid; it gave Smiles's sulphinic acid test. The compound was characterised by treatment with benzyl chloride (1 ml.) in excess of potassium carbonate in 50% ethanol for 6 hr. at 100°. Dilution of the mixture and crystallisation of the oil from ethanol gave the sulphone, m. p. and mixed m. p. 180—182°.

Hydrogenolysis with Raney nickel. Ethyl 5-*o*-benzylsulphonylphenyl-3-methyl-1-phenylpyrazole-4-carboxylate (IV; R = SO_2·CH_2Ph, R′ = CO_2Et) (1 g.) was refluxed with Raney nickel (10 g.) in ethanol (50 ml.) for 9 hr. giving, after filtration, ethyl 3-methyl-1 : 5-diphenylpyrazole-4-carboxylate, m. p. 119—121° alone or mixed with an authentic specimen prepared from benzoylacetoacetic ester and phenylhydrazine (Knorr and Blank, *Ber.*, 1885, **18**, 312). The identity of this compound was also confirmed by hydrolysis to the carboxylic acid, m. p. 205°.

NORTHERN POLYTECHNIC, HOLLOWAY, LONDON, N.7. [*Received, July 3rd,* 1953.]