# Studies on the Synthesis of Heterocyclic Compounds. Part VI. The Action of Methyl Salicylate on Some 5-Aminopyrazoles



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Some 1-phenyl-3-*R*-5-aminopyrazoles reacted with methyl salicylate to give *N*-(1-phenyl-3-*R*-pyrazol-5-yl)-2-methoxybenzamides (**3a,b,c**), 1-phenyl-2-methyl-3-*R*-salicyloilimino-3-pyrazolines (**4a,b,c**) together with 1-phenyl-3-*R*-5-methylamino pyrazoles (**5a,b,c**). The structures of the new compounds **3** and **4** were determined on the basis of analytical and spectroscopic data as well as on the acid hydrolysis products.

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As part of series of studies on the chemistry of the pyrazole ring and with the intent to synthesize derivatives of potential biological interest incorporating the salicyloyl moiety, we reacted some 1-phenyl-3-*R*-5-aminopyrazoles with methyl salicylate.

By refluxing amines **1a,b,c** with **2**, two kind of new products, **3a,b,c** and **4a,b,c**, formulated as *N*-(1-phenyl-3-*R*-pyrazol-5-yl)-2-methoxybenzamides and 1-phenyl-2-methyl-3-*R*-5-salicyloylimino-3-pyrazolines, together with poor quantities of 1-phenyl-3-*R*-5-methylaminopyrazoles (**5a,b,c**) were obtained (Scheme I). The structures of products **3a,b,c** and **4a,b,c** were deduced by spectroscopic methods, analytical data and by their hydrolysis products. Nmr spectra of **3a,b,c** showed a methoxy proton resonance at $\delta$ 3.49-3.72 (3H) and a signal at $\delta$ 10.27-10.33, exchangeable with deuterium oxide, attributable to the amidic NH group.

Significantly, these compounds underwent acid hydrolysis to afford quantitatively the starting 5-aminopyrazoles **1a;b;c** and 2-methoxybenzoic acid. On the other hand, upon acid hydrolysis, compounds **4a,b,c** gave salicylic acid and 5-iminoantipyrine hydrochlorides **6a,b**, the structures of which were consistent with spectral and analytical data (see Experimental). Furthermore, the melting point of **6b** was identical to that reported in the literature for 1-phenyl-2,3-dimethyl-5-imino-3-pyrazoline (1).

Nmr spectra of products **4a,b,c** exhibited an N-C$H_3$ resonance at $\delta$ 3.37-3.58 (3H) and a signal at $\delta$ 13.93-14.31 (1H), exchangeable with deuterium oxide, due to the hydroxyl group. The chemical shift of the hydroxylic proton of **4a,b,c** at very low field and the low frequency infrared band at 1620-1625 cm$^{-1}$ agree with a structure which is very strongly intramolecularly hydrogen bonded.

SCHEME I

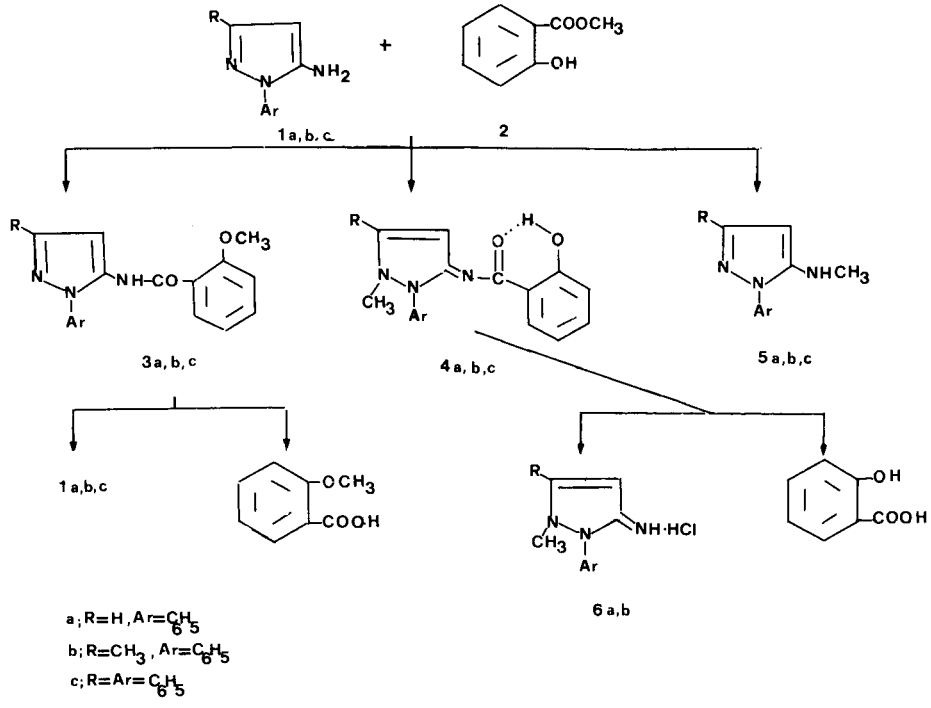


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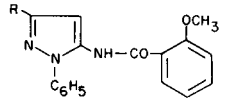
Table I

*N*-(1-Phenyl-3-*R*-pyrazol-5-yl)-2-methoxybenzamides



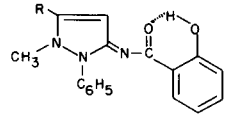
**3 a,b,c**

| Compound No. (a) | R | Mp °C | Formula | Analyses Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **3a** | H | 151-153° | $C_{17}H_{15}N_3O_2$ (a) | 69.61 | 5.15 | 14.33 | 69.68 | 5.27 | 14.33 |
| **3b** | $CH_3$ | 155-157° | $C_{18}H_{17}N_3O_2$ (b) | 70.34 | 5.58 | 13.67 | 70.36 | 5.65 | 13.79 |
| **3c** | $C_6H_5$ | 184-186° | $C_{23}H_{19}N_3O_2$ (c) | 74.78 | 5.18 | 11.38 | 74.68 | 5.48 | 11.41 |

(a) Compound **3a** had ir: 3315 (NH), 1665 $cm^{-1}$ (CO); nmr (deuterochloroform): δ 3.52 (3H, s, $CH_3$), 6.83-8.33 (11H, m, $C_6H_5$, $C_6H_4$, $H_3$ and $H_4$), 10.33 (1H, s, NH, exchangeable); ms: m/e 293 ($M^+$). Compound **3b** had ir: 3340 (NH), 1680 $cm^{-1}$ (CO); nmr (deuterochloroform): δ 2.33 (3H, s, $CH_3$), 3.49 (3H, s, $CH_3$), 6.79-8.30 (10H, m, $C_6H_5$, $C_6H_4$ and $H_4$), 10.27 (1H, s, NH, exchangeable); ms: m/e 307 ($M^+$). Compound **3c** ir: 3300 (NH), 1670 $cm^{-1}$ (CO); nmr (deuterochloroform): δ 3.72 (3H, s, $CH_3$), 7.10-7.95 (15H, m, 2 x $C_6H_5$, $C_6H_4$ and $H_4$), 10.33 (1H, s, NH, exchangeable); ms: m/e 369 ($M^+$).

Table II

1-Phenyl-2-methyl-3-*R*-5-salicyloilimino-3-pyrazolines



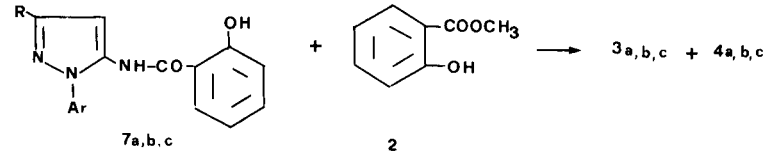
**4 a,b,c**

| Compound No. (a) | R | Mp °C | Formula | Analyses Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **4a** | H | 234-236° | $C_{17}H_{15}N_3O_2$ (a) | 69.91 | 5.15 | 14.33 | 69.54 | 5.17 | 14.39 |
| **4b** | $CH_3$ | 236-238° | $C_{18}H_{17}N_3O_2$ (b) | 70.34 | 5.58 | 13.67 | 70.26 | 5.50 | 13.62 |
| **4c** | $C_6H_5$ | 215-217° | $C_{23}H_{19}N_3O_2$ (c) | 74.78 | 5.18 | 11.38 | 74.74 | 5.15 | 11.29 |

(a) Compound **4a** had ir: 3300-3600 $cm^{-1}$ (multiple bands, OH); nmr (DMSO-$d_6$): δ 3.58 (3H, s, $CH_3$), 7.09-8.24 (11H, m, $C_6H_5$, $C_6H_4$, $H_3$ and $H_4$), 14.23 (1H, s, OH, exchangeable); ms: m/e 293 ($M^+$). Compound **4b** had nmr (DMSO-$d_6$): δ 2.41 (3H, s, $CH_3$), 3.40 (3H, s, $CH_3$), 7.00-7.63 (10H, m, $C_6H_5$, $C_6H_4$ and $H_4$), 14.31 (1H, s, OH, exchangeable); ms: m/e 307 ($M^+$). Compound **4c** had ir: 3300-3600 $cm^{-1}$ (multiple bands, OH); nmr (DMSO-$d_6$) δ 3.37 (3H, s, $CH_3$), 6.68-8.11 (15H, m, 2 x $C_6H_5$, $C_6H_4$ and $H_4$), 13.93 (1H, s, OH, exchangeable); ms: m/e 369 ($M^+$).

A review of literature indicated that Kametani, *et al.* (2), previously reported the reaction of various amines with methyl salicylate in a solvent affording sometimes the corresponding amides as the main products and sometimes *N*-methylated amines and quaternary ammonium compounds. However, these authors did not find methylated forms of their amidolysis products. The main difference between this previously reported data and our findings is that 5-aminopyrazoles **1a,b,c** did not react with methyl salicylate in a solvent such toluene or xylene, but rather they required more severe reaction conditions.

SCHEME II



**7a,b,c** **2**

a; R=H, Ar=$C_6H_5$
b; R=$CH_3$, Ar=$C_6H_5$
c; R=Ar=$C_6H_5$

The simplest mechanism to explain the formation of compounds **3a,b,c** and **4a,b,c** would involve the initial formation of amides **7a,b,c**, which are then *O*- and *N*(2)-methylated by the excess of methyl salicylate. Thus, in order to support this hypothesis, we reacted the amides **7a,b,c** with **2**. Products **3a,b,c** and **4a,b,c**, identical with the compounds formed from amines **1a,b,c**, were obtained (see Scheme II). However, the observation that the ratio of **3a,b** to **4a,b** was appreciably altered by varying the starting materials, amines or amides, and the recovery of unreacted **7c** in bulk quantity, led us to conclude that the mechanistic pathway involved in the reaction of amines **1a,b,c** with methyl salicylate was a more complex one.

## EXPERIMENTAL

Melting points were determined on Buchi-Tottoli apparatus are are uncorrected. Ir spectra were determined in nujol mulls (unless otherwise specified) with a Perkin-Elmer infrared 299 spectrophotometer. Nmr spectra were obtained with a Varian EM-390 90 MHz spectrometer (TMS as internal reference). A Jeol-JMS-01-SG-2 mass spectrometer was employed for determination of low resolution 75 eV mass spectra.

Reaction of 1-Phenyl-5-aminopyrazole (**1a**) and 1-Phenyl-3-methyl-5-aminopyrazole (**1b**) with Methyl Salicylate (**2**).

A solution of **1a** (3), **b** (4) (10 mmoles) and 7.6 g. of methyl salicylate was refluxed for 1.5 hours. After adding water (10 ml.) and petroleum ether (bp 40-70°) (10 ml.) two layers were obtained, the lower was extracted with a 10 ml. of petroleum ether and the ethereal extracts were neglected. The remaining solution was shaken with chloroform (50 ml.). Evaporation of the dried (sodium sulfate) chloroform extract left a residue, which was recrystallized from ethyl acetate to give **4a** (yield 12%), **4b** (yield 31%). These products are listed in Table II.

The mother liquors from crystallization, taken to dryness under reduced pressure, afforded a residue which was extracted with boiling ether (50 ml.) for 1 hour. After cooling, the ethereal extract was washed with aqueous 1*N* hydrochloric acid (2 x 50 ml.), with water, then dried (sodium sulfate) and concentrated under reduced pressure to dryness to give a residue which was crystallized from ethyl acetate to give **3a** (yield 7%), **3b** (yield 10%). These products are listed in the Table I.

The acidic inorganic layer was basified with aqueous sodium hydroxide and extracted with ether (3 x 30 ml.). The combined extracts, upon tlc on silica gel (chloroform as eluent), revealed the presence of the 5-methylaminopyrazoles **5a,b**, which were identified by comparison with an authentic sample (5,6).

Reaction of 1,3-Diphenyl-5-aminopyrazole (**1c**) with Methyl Salicylate (**2**).

A solution of **1c** (7) and 7.6 g. of methyl salicylate was refluxed 1.5 hours and then diluted with petroleum ether (b.p. 40-70°) (80 ml.), the separated solid was filtered and recrystallized to give **3c** (yield 30%). The mother liquors from crystallization were taken to dryness under reduced pressure. The resulting residue was chromatographed on a column (3 x 150 cm) of silica gel (400 g.) with chloroform. The fractions 1-57 (each 50 ml.) were neglected, the combined fractions 58-60 (each 50 ml.) gave 1,3-diphenyl-5-methylpyrazole (**5c**) (yield 12%), identical with an authentic sample (6). Further elution with chloroform (fractions 62-63 (each 50 ml.) afforded 600 mg. of the starting 1,3-diphenyl-5-aminopyrazole. The combined fractions 79-148 (each 50 ml.) gave **4c**, which was purified by preparative tlc (silica gel, ethyl acetate as eluent) (yield 8%) (Table II).

Hydrolysis of *N*-(1-Phenyl-3-*R*-pyrazol-5-yl)-2-methoxybenzamides.

A suspension of **3a,b,c** (1 g.) in ethanol (20 ml.) was treated with aqueous concentrated hydrochloric acid (20 ml.) and the mixture was refluxed for 12 hours. The solution was concentrated to a small volume, the resutling oleus residue was treated with water (10 ml.) and the mixture was basified with aqueous potassium hydroxide (30%).

In the case of **3a** and **3c** the precipitate separated out was filtered off and crystallized. The products were identical with authentic specimens of 1-phenyl-5-aminopyrazole (3) and 1,3-diphenyl-5-aminopyrazole (7), respectively (ms, ir, Rf, m.p. and mixed m.p.). In the case of **3b**, the oil which separated was extracted with ethyl ether. Evaporation of the organic layer left an oil identical with an authentic sample of 1-phenyl-3-methyl-5-aminopyrazole (ms, ir, Rf) (4).

The remaining alkaline solution was acidified and extracted with ethyl ether (3 x 30 ml.). The organic layer was washed with water and dried (sodium sulfate). Following evaporation, a crystalline product, identical in all respects with an authentic sample of 2-methoxybenzoic acid, was formed.

Hydrolysis of 1-Phenyl-2-methyl-3-*R*-salicyloylimino-3-pyrazolines.

Compounds **4a,b** (1 g.) were refluxed with aqueous 2.4*N* hydrochloric acid (20 ml.) for 8 hours. The suspension was extracted with ethyl ether (3 x 30 ml.) and the organic layer washed with water (2 x 90 ml.). Evaporation of the ethereal extracts afforded quantitatively a white crystalline product, which was identical with an authentic sample of salicylic acid (ir, $R_f$, m.p. by mixed fusion).

The aqueous solution was evaporated under reduced pressure and the residue was crystallized from absolute ethanol-absolute ether (yield 80%) to give the 1-phenyl-2-methyl-3-*R*-5-iminopyrazolium chlorides **6a,b**. In the case of **6b**, filtration was not possible, because of its extremely high hygroscopic character. Therefore, the solvent was decanted and the product was washed with absolute ethyl ether and stored in a dissicator.

Compound **6a**.

The product melted at 238-240°; ms m/e 173 ($M^+$ − HCl); ir (hexachlorobutadiene): 3600-2800 $cm^{-1}$ (broadened bands, aminic and ammonium groups); nmr (DMSO-$d_6$): δ 3.46 (3H, s, $CH_3$), 6.03 (1H, d, H-4, J = 2.0 Hz), 7.38 (2H, s, $NH_2$, exchangeable), 7.70-7.79 (5H, large s, aromatic protons), 8.48 (1H, d, H-3, J = 2.0 Hz).

*Anal.* Calcd. for $C_{10}H_{12}ClN_3$: C, 57.29; H, 5.79; N, 20.04. Found: C, 57.35; H, 5.72; N, 19.96.

Compound **6b**.

The product melted at 190-192° [lit. (1) m.p. 192°]; ms: m/e 187 ($M^+$ − HCl); nmr (DMSO-$d_6$): δ 2.37 (3H, s, $CH_3$), 3.32 (3H, s, $CH_3$), 5.89 (1H, s, pyrazolic H), 7.18 (2H, s, $NH_2$, exchangeable), 7.61-7.71 (5H, m, $C_5H_5$).

*N*-(1-Phenylpyrazol-5-yl)-2-hydroxybenzamide (**7a**).

This compound was prepared by a route reported in the literature (8). Thus, to a refluxed solution of equimolecolar amounts (23 mmoles) of 1-phenyl-5-aminopyrazole (**1a**) (3) and acetylsalicyloyl chloride (9) in 50 ml. of dry chloroform was added triethylamine (3.2 ml.) in four portions, each 1.6 ml., 0.8 ml. and 2 X 0.4 ml., respectively, over a period of 4 hours. The solution was evaporated under reduced pressure. The residue was mixed with water (100 ml.) and extracted with ethyl ether (3 X 150 ml.). The organic layer was shaken with 1*N* hydrochloric acid (3 X 100 ml.) and washed with a satured aqueous sodium bicarbonate solution (2 X 100 ml.) followed by water (2 X 100 ml.) and dried (sodium sulfate). The ethereal extracts were evaporated, leaving an oil, which was stirred room temperature with 200 ml. of 1*N* sodium hydroxide for 1 hour. The filtered solution was adjusted to *p*H 6 by adding aqueous hydrochloric acid (10%). The resulting suspension was then extracted with ethyl acetate (2 X 100 ml.); evaporation of the dried (sodium sulfate) extracts left *N*-(1-phenylpyrazol-5-yl)-2-hydroxybenzamide (**7a**) (yield 50%), m.p. 166-168° (benzene); ir (hexachlorobutadiene): multiple bands in the 3 μ region (NH, OH), 1680 $cm^{-1}$ (CO); nmr (DMSO-$d_6$): δ 6.73-8.00 (11H, m, $C_6H_5$, $C_6H_4$, H-3 and H-4), 10.76-11.62 (2H, broad, NH and OH, exchangeable).

*Anal.* Calcd. for $C_{10}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.75; H, 4.81; N, 15.34.

Reaction of *N*-(1-Phenyl-3-*R*-pyrazol-5-yl)-2-hydroxybenzamides (**7a,b,c**) with Methyl Salicylate (**2**).

Compounds **7a,b** (8), **c** (8) (1 mmole) and methyl salicylate (1.2 g.) were refluxed for 1.5 hours. In the case of **7a** and **7b**, products **3a** (yield 36%) and **3b** (yield 62%), respectively, were isolated and identified from the reaction mixture by preparative tlc on silica gel using chloroform as an eluent. Using methanol as an eluent, products **4a** (yield 5%) and **4b** (yield 29%), respectively, were detected and identified.

In the case of **7c**, the reaction mixture was chromatographed over a column (3 cm diameter) of silica gel (30 g.) using petroleum ether as eluent 500 ml.) and then chloroform (500 ml.). The ethereal eluate and the first 250 ml. of chloroform were neglected. The remaining 250 ml. of chloroform were evaporated under reduced pressure, the resulting residue was shaken at room temperature with 1.5 ml. of aqueous 1*N* sodium hydroxide for 1 hour. By acidifing the alkaline solution, 200 mg. of unreacted **7c** separated. The insoluble material was recrystallized from ethyl acetate to give **3c** (15%). Further elution with methanol (500 ml.) afforded **4c**, which was purified by preparative tlc (ethyl acetate as eluent) (yield 5.5%). All of the products isolated (**3** and **4**) were identical with those obtained by the above described method (m.p., and mixed m.p., Rf).

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