Studies on the Synthesis of Heterocyclic Compounds. Part X. One-Step Route to 1,2-Dimethyl-3-*R*-5-salicyloylimino-3-pyrazolines

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This communication outlines the development of a direct synthetic route to 1,2-dimethyl-3-*R*-5-salicyloylimino-3-pyrazolines, starting from readily available 3(5)-aminopyrazoles **1a, b, c** and methyl salicylate. The structures of the new compounds **3a, b, c** were determined on the basis of analytical and spectroscopic data as well as on the acid hydrolysis products.

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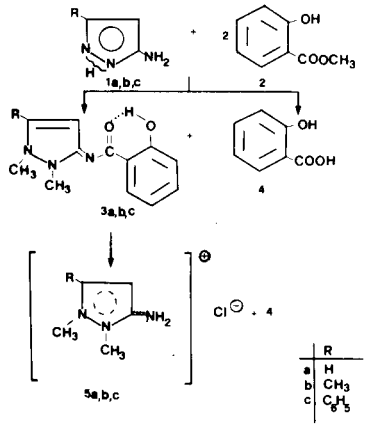
Pyrazolone derivatives and several salicylates have acquired considerable importance because of their use as analgesic, antipyretic and anti-inflammatory agents. It was therefore, thought of interest to synthesize novel compounds possessing all the above two moieties in one system and screen these for their pharmacological properties.

Considering our previous paper [1] that some *N*-phenyl-5-aminopyrazoles, on treatment with methylsalicylate, yield two kinds of new products formulated as *N*-(1-phenyl-3-*R*-pyrazol-5-yl)-2-methoxybenzamides and 1-phenyl-2-methyl-3-*R*-5-salicyloylimino-3-pyrazolines, this simple synthetic approach might be envisaged as a novel general route which enables the incorporation of salicyloyl moiety into the pyrazole nucleus. On the other hand, this finding prompted a further study on aminopyrazoles having endocyclic nitrogen atom free. Thus, refluxing the 3(5)-amino-5(3)-*R*-pyrazoles **1a, b, c** in methyl salicylate afforded the corresponding 1,2-dimethyl-3-*R*-salicyloylimino-3-pyrazolines, as the main products, and salicylic acid.

In the case of 3(5)-amino-5(3)-methylpyrazole (**1b**), the reaction led also in very low yield to a product formulated as *N*-(1,5-dimethylpyrazol-3-yl)-2-hydroxybenzamide (**6**), whereas we are unable to isolate any product from 3(5)-aminopyrazoles **1a, c**.

The structures of all the new products **3a, b, c** were established by analytical data and spectroscopic means, as well as by their hydrolysis products.

The nmr spectra of 1,2-dimethyl-3-*R*-5-salicyloylimino-3-pyrazolines **3a, b, c** exhibited two N-CH_3 (6H) resonances in the range of δ 3.6-3.8 and a signal at *ca.* δ 15 (1H) exchangeable with deuterium oxide, due to the hydroxyl group. The chemical shift of OH at very low field and the low frequency infrared band at 1610 cm^{-1} agree with a structure which is very strongly intramolecularly hydrogen bonded. Moreover, these compounds underwent acid hydrolysis to give quantitatively salicylic acid and 5-iminoantipyrine hydrochloride derivatives **5a, b, c**, the structures of which were consistent with spectral and analytical data.



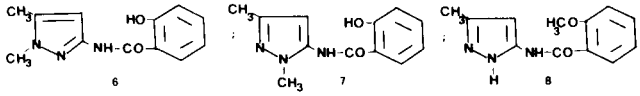
Table

1,2-Dimethyl-3-*R*-5-salicyloylimino-3-pyrazolines **3**

Compound	R	Mp °C	Molecular Formula	Analyses % Calcd. C	H	N	Found C	H	N
3a	H	187-189	$C_{12}H_{13}N_3O_2$ (a)	62.32	5.67	18.17	62.30	5.52	18.15
3b	CH_3	243-245	$C_{13}H_{15}N_3O_2$ (b)	63.66	6.16	17.13	63.62	6.20	17.18
3c	C_6H_5	208-210	$C_{18}H_{17}N_3O_2$ (c)	70.34	5.58	13.67	70.21	5.40	13.56

(a) ms: m/e 231 (M^+); ir: cm^{-1} 3300-3600 (broad, OH), 1610 (CO); nmr: δ 3.77 (s, CH_3, 3H), 3.88 (s, CH_3, 3H), 6.70-8.00 (a set of signals, H-3, H-4 and C_6H_4), 15.44 (s, OH, 1H, exchangeable). (b) ms: m/e 245 (M^+); ir: cm^{-1} 3300-3600 (broad, OH), 1610 (CO); nmr: δ 2.48 (s, CH_3, 3H), 3.70 (overlapped singlets, 2 × CH_3, 6H), 6.70-7.98 (a set of signals, H-4 and C_6H_4, 5H), 15.57 (s, OH, 1H, exchangeable). (c) ms: m/e 307 (M^+); ir: cm^{-1} 3300-3600 (broad, OH), 1610 (CO); nmr: δ 3.79 (s, CH_3, 3H), 3.88 (s, CH_3, 3H), 6.70-8.00 (a set of signals, H-4, C_6H_5 and C_6H_4, 10H), 15.32 (s, OH, 1H, exchangeable).

The product **6** had a molecular weight of 231 (mass spectrum) and a molecular formula $C_{12}H_{13}N_3O_2$ (analytical data). Among three possible isomers **6**, **7** and **8**, the one obtained is assumed to be the *N*-(1,5-dimethylpyrazol-3-yl)-2-hydroxybenzamide (**6**). The assumption was confirmed by the following considerations: (a) the structure *N*-(1,3-dimethylpyrazol-5-yl)-2-hydroxybenzamide (**7**) was eliminated by the fact that the isolated product was quite different (mp, R_f) from **7**, previously described by P. Giori and coworkers [2], (b) the presence in the ir spectrum of the characteristic OH broad bands around 3000 cm^{-1} and the presence in the mass spectrum of an intense peak of m/e 121, attributable to the salicyloyl fragment, eliminate the structure **8**.



The *N*(1), *N*(2) dimethylation and the amidolysis of 3(5)-aminopyrazoles **1a, b, c** are in agreement with the well established fact that methyl salicylate is a methylating and salicyloylating agent towards substrates such as 5-aminopyrazoles [1].

Although the yield in the reported cases ranges from 11-20%, we believe this synthesis to be interesting due to the fact that it accomplishes the dimethylation and amidolysis in only one step, starting from easily available materials 3(5)-aminopyrazoles and methyl salicylate.

The biological activity of the 1,2-dimethyl-3-*R*-salicyloylimino-3-pyrazolines **3a, b, c** will be communicated later on as it is under investigation.

EXPERIMENTAL

Melting points were determined on a Buchi-Tottoli apparatus and are uncorrected. The ir spectra were determined in hexachlorobutadiene with a Perkin-Elmer 299 spectrophotometer. A Jeol-JMS-01-SG-2 mass spectrometer was employed for determination of low resolution 75 eV mass spectra. The nmr spectra were determined in DMSO-d_6 solution with a Varian FT80A 80 Hz spectrometer (TMS as internal reference).

Reaction of 3(5)-Aminopyrazoles **1a, b, c** with Methyl Salicylate. General Procedure.

A mixture of **1a, b,** [3], **c** [4] (5 g) and methyl salicylate, in the molar ratio 1:5, was heated under reflux for 1.5 hours.

After cooling the reaction mixture was chromatographed on a column of silica gel (385 g) using diethyl ether as eluent.

In the case of **1a**, the first 4.6 ℓ and the successive fractions 1-50 (each 50 ml, diethyl ether-ethanol 1:1 as eluent) were discarded. Further elution with diethyl ether-ethanol 1:3 (fractions 55-109, each 50 ml) afforded a residue which was stirred with water at room temperature for 30 minutes, filtered, air dried and then crystallized from benzene. The solid was identical in all respects with an authentic sample of salicylic acid. Fractions 110-117 and the successive 118-250 (each 50 ml, ethanol as eluent) were collected, the solvent removed and the residue stirred with water (50 ml) at room temperature for 30 minutes. The solid was filtered off, air dried and recrystallized from ethyl acetate to give 1,2-dimethyl-5-salicyloylimino-3-pyrazoline (**3a**), yield 11% (see Table).

In the case of **1b**, the first 1.6 ℓ were neglected and the successive fractions 1-69 (each 50 ml) were evaporated to leave a residue, which was refluxed in ethyl acetate (70 ml). The resulting suspension was filtered and the solution evaporated to a small volume left the *N*-(1,5-dimethylpyrazol-3-yl)-2-hydroxybenzamide (**6**). The product melted at 238-240° (ethyl acetate), yield 0.5 g; ms: m/e 231 (M^+); ir: cm^{-1} 3300-2480 (multiplet broad bands, NH and OH), 1670 (CO); nmr: δ 2.25 (s, CH_3, 3H), 3.70 (s, CH_3, 3H), 6.44 (s, CH, 1H), 7.00-8.13 (multiplet, C_6H_4, 4H), 10.72 (broad, NH and OH, exchangeable).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.09; H, 5.83; N, 17.98.

Fractions 70-103 (each 50 ml, diethyl ether-ethanol 1:1 as eluent) were discarded and the combined successive fractions 103-114 (each 50 ml) and 115-143 (each 50 ml, diethyl ether-ethanol 1:3 as eluent) were collected, the solvent removed and the residue extracted several times with boiling benzene. The combined extracts were evaporated to a small volume when a crystalline material separated out. The product was identical in all respects with an authentic specimen of salicylic acid (0.3 g).

Fractions 143-195 (each 50 ml) and 196-221 (each 50 ml, ethanol as eluent) were discarded. Further elution with ethanol (fractions 222-312, each 50 ml) afforded a residue, which was stirred with water (50 ml) at room temperature for 30 minutes. The solid was filtered, air dried and crystallized from ethyl acetate to give 1,2,3-trimethyl-5-salicyloylimino-3-pyrazoline (**3b**), yield 20% (see Table).

In the case of **1c**, the first 5 ℓ were discarded. The successive eluates (diethyl ether-ethanol 1:1 as eluent) (2.5 ℓ) and (diethyl ether-ethanol 1:3 as eluent) (4 ℓ) were evaporated to give a solid identified as salicylic acid (mp, M^+, ferric chloride test). Further elution with ethanol (fractions 1-34, each 50 ml) afforded a residue, which was stirred with water at room temperature, filtered, air dried and then crystallized from ethyl acetate to give 1,2-dimethyl-3-phenyl-5-salicyloylimino-3-pyrazoline (**3c**), yield 16% (see Table).

Hydrolysis of 1,2-Dimethyl-3-*R*-5-salicyloylimino-3-pyrazolines. General Procedure.

Compounds **3a, b, c** (1 g) were refluxed with aqueous 2.4 *N* hydrochloric acid (20 ml) for 8 hours. After standing overnight a crystalline material, identified as salicylic acid (mp, R_f, ir, ferric chloride test), was separated out. The remaining solution was washed with diethyl ether (3 × 50 ml) and evaporated to dryness under reduced pressure. The residue was crystallized from anhydrous ethanol-diethyl ether to give quantitatively the 1,2-dimethyl-3-*R*-5-iminopyrazolium chlorides **5a, b, c**.

1,2-Dimethyl-5-iminopyrazolium Chloride (**5a**).

The product melted at 80-82°; ms: m/e 111 (M^+ of free base); ir: cm^{-1} 2700-3500 (multiple bands, ammonium); nmr: δ 3.82 (s, CH_3, 3H), 3.90 (s, CH_3, 3H), 5.90 (d, H-4, 1H, J = *ca.* 3 Hz), 7.40 (s, NH_2, 2H).

Anal. Calcd. for $C_5H_{10}ClN_3$: C, 40.67; H, 6.67; N, 28.47. Found: C, 40.48; H, 6.86; N, 28.49.

1,2,3-Trimethyl-5-iminopyrazolium Chloride (**5b**).

The product melted at 263-265°; ms: m/e 125 (M^+ of free base); ir: cm^{-1} 2700-3500 (multiple bands, ammonium); nmr: δ 2.27 (s, CH_3, 3H), 3.64 (s, CH_3, 3H), 3.73 (s, CH_3, 3H), 5.69 (s, H-4, 1H), 7.31 (s, NH_2, 2H).

Anal. Calcd. for $C_5H_{12}ClN_3 \cdot H_2O$: C, 39.66; H, 7.77; N, 23.14. Found: C, 39.51; H, 7.87; N, 22.89.

1,2-Dimethyl-3-phenyl-5-iminopyrazolium Chloride (**5c**).

The product melted at 235-236°; ms: m/e 187 (M^+ of free base); ir: cm^{-1} 2700-3500 (multiple bands, ammonium); nmr: δ 3.76 (s, CH_3, 3H), 3.98 (s, CH_3, 3H), 6.20 (s, H-4, 1H), 7.30-8.20 (a set of signals, NH_2 and C_6H_5, 7H).

Anal. Calcd. for $C_{11}H_{14}ClN_3 \cdot 2H_2O$: C, 54.65; H, 5.84; N, 17.39. Found: C, 54.71; H, 5.62; N, 17.39.

REFERENCES AND NOTES

[1] G. Daidone and S. Plescia, *J. Heterocyclic Chem.*, **18**, 747 (1981).

[2] P. Giori, M. Guarnieri, D. Mazzotta, G. Vertuani and G. Branca, *Il Farmaco, Ed. Sci.*, **4**, 277 (1979).

[3] E. Alcade, J. de Mendoza, J. M. Garcia-Marquina, C. Almera and J. Elguero, *J. Heterocyclic Chem.*, **11**, 423 (1974).

[4] V. Meyer, *J. Prakt. Chem. [2]*, **90**, 8 (1914).