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# A NOVEL PROCEDURE FOR THE PREPARATION OF 3-SUBSTITUTED 4-HYDROXYPYRAZOLE-5-CARBOXYLIC ACIDS AS AN APPROACH TO PYRAZOMYCIN

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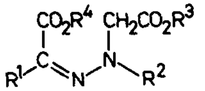
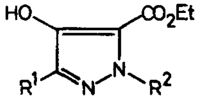
**As a part of our program directed toward the synthesis of C-nucleosides we have devised a general method for the synthesis of 3-substituted 4-hydroxypyrazole-5-carboxylic acids as a route to pyrazomycin[1].**



*Ia* $R^1 = Me; R^2 = H; R^3 = R^4 = Et$
*Ib* $R^1 = R^2 = R^3 = Me; R^4 = Et$
*Ic* $R^1 = Ph; R^2 = H; R^3 = Et; R^4 = Me$
*Id* $R^1 = R^3 = Me; R^2 = Ph; R^4 = Et$
*Ie* $R^1 = R^2 = Ph; R^3 = R^4 = Me$
*If* $R^1 = t\text{-}Bu; R^2 = H; R^3 = Et; R^4 = Me$



*IIa* $R^1 = Me; R^2 = H$
*IIb* $R^1 = R^2 = Me$
*IIc* $R^1 = Ph; R^2 = H$
*IId* $R^1 = Me; R^2 = Ph$
*IIe* $R^1 = R^2 = Ph$
*IIf* $R^1 = t\text{-}Bu; R^2 = H$

We have found that α-keto ester 2-carboalkoxymethylhydrazones undergo the Dieckmann reaction[2] to give 4-hydroxypyrazole-5-carboxylic acids. (In an analogous manner, some derivatives of β-hydroxypyrrole[3] and β-hydroxythiophene[4] have been prepared.) The starting hydrazones Ia-If were obtained by treatment of appropriate methyl or ethyl α-ketocarboxylic acid esters with ethyl hydrazinoacetate (preparation of Ia, Ic and If), with (1-methylhydrazino)-acetic acid or with (1-phenylhydrazino)acetic acid, followed by esterification with diazomethane (preparation of Ib and Id, Ie, resp.), as chromatographically homogenous oils. The Dieckmann cyclisation of Ia-If into 4-hydroxypyrazole-5-carboxylic acid esters IIa-IIf was carried out by refluxing 0.01 mole of the starting hydrazones in 40 ml 0.5 N sodium ethoxide in ethanol for two hours. After neutralisation of the reaction mixture, the product was isolated on a column of silicagel. UV spectra of IIa-IIf exhibit a characteristic bathochromic shift due to formation of the enolate ion. The IR spectra of IIa-IIf provide evidence of keto-enol equilibria in chloroform solution, with prevailing enol form. IIa-IIf give a positive ferric chloride test.

TABLE

Physical Properties of Ethyl 3-Substituted 4-Hydroxypyrazole-5-carboxylates

| Comp. | Yield | Melting point | λ max in nm | (log ε ) | IR ($CHCl_3$) | | ν in cm$^{-1}$ | |
|---|---|---|---|---|---|---|---|---|
| | % | °C (solvent) | 0.1 N HCl | 0.1 N NaOH | (C=O)[a] | (C=O)[b] | (OH) | (NH) |
| IIa | 50 | 174-175<br>water | 224 (3.87)<br>273 (3.75) | 237 (3.83)<br>317 (3.87) | 1692 | 1722 | 3539 | 3448 |
| IIb | 52 | 34-35<br>ether-p.ether[c] | 235 (4.01)<br>279 (3.79) | 242 (3.86)<br>323 (3.87) | 1676 | 1725 | 3521<br>3400 | |
| IIc | 39 | 171-172<br>ether-p.ether[c] | 218 (4.22)[d]<br>237 (4.20)<br>281 (3.90) | 228 (4.15)<br>333 (3.95) | 1693 | 1720i | 3440<br>3370 | 3390<br>3100 |
| IId | 45 | oil distilled<br>at 120 (0.05 mm) | 236 (3.97)<br>288 (3.87) | 251 (3.83)<br>331 (4.06) | 1671 | 1721<br>1731 | 3505<br>3380 | |
| IIe | 85 | 95-97<br>p.ether[c] | 225 (4.23)[d]<br>240 (4.19)<br>304 (3.98) | 228 (4.23)<br>347 (4.10) | 1673 | 1720<br>1737 | 3480<br>3330 | |
| IIf | 41 | 124-125<br>10% aq. acetic acid | 223 (3.84)<br>272 (3.70) | 237 (3.80)<br>320 (3.91) | 1687 | 1721i | 3525 | 3450<br>3140 |

[a] Enolic β-keto ester. [b] Non-enolic β-keto ester. [c] Petroleum ether b.p. 60-70°C.
[d] Measured in 0.1 N HCl in 10% ethanol.

All compounds described gave satisfactory elemental analyses and their mass spectra fragmentation patterns are compatible with the assigned structures.

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