A NEW SYNTHESIS OF γ-YLIDENE-α,β-BUTENOLIDES FROM 2-NITRO-5-FURANCARBALDEHYDE AND PYRAZOLES

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Abstract - A new and rapid synthesis of 5-pyrazolylmethylene-2(5H)furanones by the reaction of 2-nitro-5-furancarbaldehyde (I) with different substituted pyrazoles (IIa-f) in acetic acid-acetic anhydride is described.

In the last years much interest has been focused on the synthesis of molecules containing the butenolide moiety, which are synthons of pharmacologically important α-methylene-γ-lactones[1,2].

In this paper we report a new interesting reaction of 5-nitro-2-furancarbaldehyde (I) which leads directly to the synthesis of γ-ylidene-α,β-butenolides. Moreover we found an easy way for linking a heterocyclic ring (e.g. pyrazole) to the ω-position of these unsaturated systems.

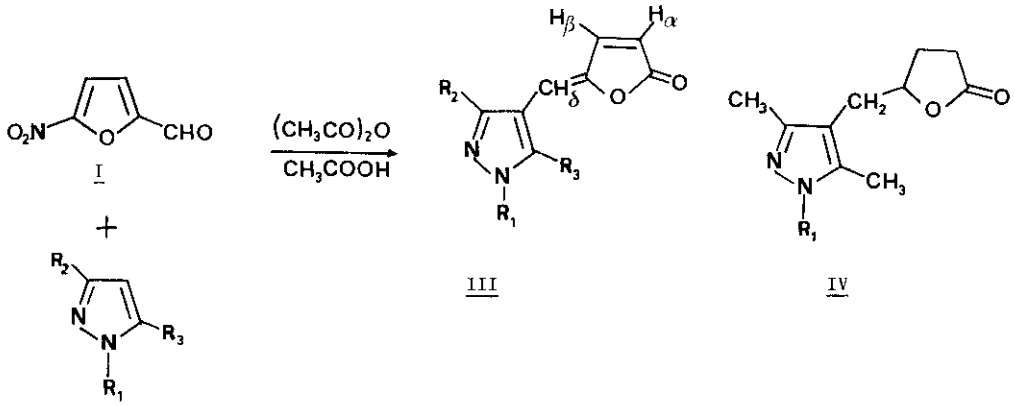
The reaction of I and methyl substituted heterocycles in acidic medium is very well known to yield 5-nitro-2-vinylfurans[3] through the expected aldol like condensation between the formyl and the 'activated methyl groups'.

To our surprise however when I and 1,2,3-trimethylpyrazole (IIa) were heated to reflux in a solution of glacial acetic acid-acetic anhydride we did not obtain any condensation products. A yellow crystalline solid could be isolated in 20% yield[4] after work up of the dense black polymeric reaction mixture and was identified as 5-(1',3',5'-trimethyl-4'-pyrazolylmethylene)-2(5H)-furanone (IIIa). Thus the elemental analysis and the mass spectrum m/z 204(M^+) indicated the molecular formula $C_{11}H_{12}N_2O_2$ which is consistent with the formal loss of HNO_2 from the reactants. The IR spectrum of IIIa revealed bands at 1820 and 1770 cm^{-1} assignable to the unsaturated γ-lactone ring and a C=C absorption band at 1658 cm^{-1}.

The PMR spectrum of IIIa in $CDCl_3$ showed signals of three methyl groups at δ2.30 and 2.38(C-Me) and δ3.72 (N-Me) in addition to three olefinic protons signals at δ5.88 (d, $J_{\delta-\alpha}$ <1Hz, H_δ), δ6.06 (dd, $J_{\delta-\alpha}$ <1Hz, $J_{\alpha-\beta}$=5.3 Hz, H_α) and δ7.56 (d, $J_{\alpha-\beta}$=5.3 Hz, H_β). These findings and the absence of the pyrazole H_4 singlet in the PMR of IIIa confirmed that all the methyl groups on the heterocyclic ring had remained untouched during the reaction and that a butenolide moiety had been linked through a -CH= group, to the C_4 position of the pyrazole ring. As expected, on hydrogenation with two moles of hydrogen over 5% Pd-C catalyst in EtOH, IIIa was converted into the saturated γ-butyrolactone derivative IVa, whose structure was fully supported by its spectroscopic data (see experimental section).

This reaction of (I) was then extended to other 3-methylpyrazoles(IIb-f)and was shown to be general, yielding in all cases 5-(4'-pyrazolylmethylene)-2(5H)-furanones (IIIb-f) through an aromatic substitution reaction.

The structures of these products accounted for their elemental analysis and spectroscopic and chemical properties. In particular IR and PMR spectral data, which were very similar to those discussed for IIIa, clearly indicated the presence of the butenolide systems on C_4 (IR and PMR spectra are reported in the Table).

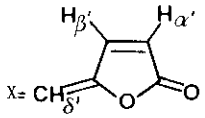


II

	R_1	R_2	R_3
a	CH_3	CH_3	CH_3
b	C_6H_5	CH_3	CH_3
c	C_6H_5	CH_3	NH_2
d	C_6H_5	CH_3	H
e	H	CH_3	CH_3
f	H	CH_3	H

	R_1	R_2	R_3
a	CH_3	CH_3	CH_3
b	C_6H_5	CH_3	CH_3
c_1	C_6H_5	CH_3	$NHCOCH_3$
c_2	C_6H_5	CH_3	$N(COCH_3)_2$
d	C_6H_5	CH_3	H
e	X	CH_3	CH_3
f	X	CH_3	H

	R_1
a	CH_3
b	C_6H_5



Hydrogenation of IIIb over 5% Pd-C in EtOH yielded the saturated γ-lactone IVb, in accordance with its structure as 5-(3',5'-dimethyl-1'-phenyl-4'-pyrazolylmethylene)-2(5H)-furanone.

The reaction of IIc with I occurred with partial acetylation of the free 5-amino group on the pyrazole ring. Two crystalline products were isolated from the reaction mixture and were identified as 5-(5'-acetylamino-3'-methyl-1'-phenyl-4'-pyrazolylmethylene)-2(5H)-furanone [$IIIc_1$: δ2.05 (3H, s, $\underline{CH_3}CONH$-) and δ8.08 (1H, broad, $CH_3\underline{CONH}$)] and 5-(5'-diacetylamino-3'-methyl-1'-phenyl-4'-pyrazolylmethylene)-2(5H) furanone [$IIIc_2$: δ2.25 (6H, s, $-N(\underline{COCH_3})_2$)] respectively.

On treatment with acetic anhydride and pyridine $IIIc_1$ was readily converted into the N-diacetyl derivative $IIIc_2$. Furthermore oxidation of $IIIc_1$ with $KMnO_4$ in acetone at room temperature gave the expected 5-acetylamino-3-methyl-1-phenylpyrazol-4-carboxylic acid which upon exposure to an ethereal diazomethane solution yielded the corresponding methyl ester. Thus the IR spectrum of the

TABLE: PMR[a], IR and UV data of IIIa-f and V

Compounds	R_1 (for R_1=X: $H_{\alpha'}$ / $H_{\beta'}$ / $H_{\delta'}$)	R_2	R_3	H_α	H_β	H_δ	ν_{max}, cm^{-1}	λ_{max}^{EtOH} nm (lg ε)
IIIa	3.72 s	2.30 s	2.38 s	6.06 dd $J_{\alpha-\delta}$	7.56 d $<1; J_{\alpha-\beta}$	5.88 br s =5.30	3130, 3102, 1820, 1790, 1770, 1658, 1120, 1070, 940, 890, 875	231 (4.29), 346 (4.57)
IIIb	7.45 s	2.40 s	2.43 s	6.15 dd $J_{\alpha-\delta}$	7.52 d $<1; J_{\alpha-\beta}$	5.98 br s =5.32	3120, 3102, 3080, 3058, 1790, 1755, 1665, 1600, 1110, 1078, 860	225 (4.10), 345 (4.37)
$IIIc_1$	7.35 s	2.35 s	2.05 s[b] 8.08 brs[c]	6.12 dd $J_{\alpha-\delta}$	7.50 d $<1; J_{\alpha-\beta}$	5.92 br s =5.30	3200, 1795, 1760, 1740, 1675, 1665, 1600, 1120, 1070, 940, 895	226 (3.87), 345 (4.25)
$IIIc_2$	7.40 s	2.39 s	2.25 s	6.13 dd $J_{\alpha-\delta}$	7.50 d $<1; J_{\alpha-\beta}$	5.86 br s =5.40	3090, 1770, 1742, 1710, 1668, 1600, 1110, 1070, 930, 890	222 (3.87), 338 (4.18)
IIId	7.20-7.80 m	2.35 s	8.45 s	6.09 dd $J_{\alpha-\delta}$	7.50 d $<1; J_{\alpha-\beta}$	5.90 br s =5.30	3150, 3120, 1793, 1750, 1655, 1600, 1110, 1068, 935, 895	
IIIe[d]	6.33 dd 8.60 d 7.27 br s $J_{\alpha'-\delta'}$=1.5; $J_{\alpha'-\beta'}$=5.70	2.36 s	2.46 s	6.18 dd $J_{\alpha-\delta}$	7.50 d $<1; J_{\alpha-\beta}$	5.85 br s =5.20	3120, 3110, 3060, 1810, 1795, 1760, 1668, 1140, 1120, 1072, 940, 885	229 (3.90), 386 (4.70)
IIIf[d]	6.45 dd 8.05 d 7.33 br s $J_{\alpha'-\delta'}<1; J_{\alpha'-\beta'}$=5.30	2.32 s	8.58 br s	6.45 dd $J_{\alpha-\delta}$	7.94 d $<1; J_{\alpha-\beta}$	6.35 br s =5.30	3090, 1785, 1770, 1755, 1685, 1110, 1060, 940, 930, 898, 887	317 (4.39), 399 (4.47)
V	6.10 dd 7.54 d 6.83 br s $J_{\alpha'-\delta'}<1; J_{\alpha'-\beta'}$=5.40	2.30 s	8.28 d J=2.70		[e]		3165, 3140, 3120, 3095, 1780, 1745, 1685, 1125, 1075, 935, 890	227 (3.80), 349 (4.35)

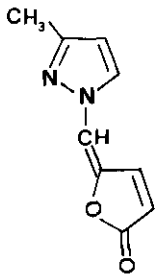
[a] $CDCl_3$, δ (ppm), TMS = 0, J (Hz); [b] CH_3 of the acetylamino group; [c] NH of the acetylamino group;

[d] DMSO-d_6 used as solvent in PMR spectrum; [e] signal attributed to the H-4 of the pyrazole ring: δ6.30 (1H, d, J_{4-5} = 2.70 Hz)

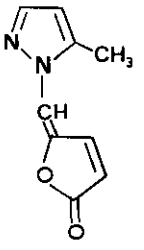
latter compound showed carbonyl bands for the carbomethoxy (1715 cm^{-1}) and the acetylamino (1685 cm^{-1}) groups which in the PMR spectrum gave signals at δ3.90 (3H, s, CH_3O) and at δ2.50 (3H, s, CH_3CO) and δ8.2 (1H, br s, NH) respectively.

Particularly interesting results were finally obtained from the reaction of I with 1-unsubstituted pyrazoles (IIe-f).In these cases the reactive site of the pyrazole ring was not only the 'normal' C_4-position but, surprisingly, even the N_1-position. This led to the formation of compounds with the butenolide system linked to both the sites,i.e. IIIe from 3,5-dimethylpyrazole (IIe) and IIIf from 3-methylpyrazole (IIf). From the latter reaction the 1-N-monosubstituted pyrazole (V) could also be isolated in fair yield.

In accordance with these structures the PMR and IR spectra of IIIe-f and V were devoid of amino signals, thus excluding the presence of free pyrazole NH. Moreover, due to the electron-withdrawing effect of the heteroatom, the N-CH= signal was readily identifiable as it was shifted downfield apart (δ6.8-7.3), farther than the corresponding C-CH= doublet (δ5.8-6.3).



V



VI

In principle two isomeric structures either V or VI could be attributed to the 1-N-monosubstituted pyrazole obtained from IIf, but VI was promptly discarded considering the PMR spectrum, particularly the chemical shift of the methyl group (δ2.30) and the pyrazole protons (δ6.30 and δ8.28 respectively, J_{vic} = 2.7 Hz). These data were in good agreement with those reported in the literature[5] for 3-methyl-1-substituted pyrazoles like V, whereas in 5-methylpyrazoles like VI the CH_3 signal should occur at δ2.4-2.7 and the H_3 doublet at δ7.3-7.5 (J_{3-4} = 1.5-1.8 Hz).

As far as the stereochemistry of the exocyclic double bond in the butenolide system is concerned all the compounds we could isolate showed a Z configuration (see IR and PMR data).[6]

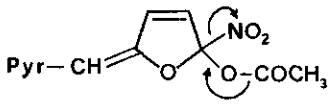
However at least in one case (i.e. from IIe) an isomeric product with the opposite stereochemistry was formed in traces, but was not completely characterized.

At this stage of our studies the mechanism of this reaction of I with pyrazoles has not been yet clarified.However we believe that the reaction involves an ionic process since the presence of the acid (not only in a catalytic amount) seems to be essential for yielding the products(III, V), as was shown by running the reaction in different conditions.Probably the acetic acid is involved by enhancing the electrophylicity of the aldehyde group and therefore promoting the attack of I to the pyrazole ring.Finally the displacement of the nitro group (abundant red fumes of nitrous oxides were always observed during the reflux of the reactants) allows to transform the fu-

ran ring into a γ-lactone.

We suggest that the acetic acid can add across the conjugated diene system of the furan ring forming an intermediate like VII which eventually rearranges to the butenolide ring.

Studies aimed to the application of the reaction of I towards other substrates are actively pursued in our laboratory and will be reported in due time.



VII

EXPERIMENTAL

Melting points were determined on a hot plate Fisher-Johns apparatus and are uncorrected.

IR spectra were recorded as nujol mulls on a Perkin Elmer 257 spectrophotometer and UV spectra on a Perkin Elmer 137 UV spectrophotometer. PMR spectra were recorded on a Perkin Elmer R-12 A-60 MHz spectrometer. Mass spectra were obtained on a Du Pont 21-492/B instrument at 75 eV. Microanalysis were performed for all new compounds and were in agreement with the proposed structures.TLC was carried out on Silica Gel GF_{254} plates, 0.2 mm layer thickness. Spots were visualized by exposure to iodine vapours. Merck 0.063-0.2 mm Kieselgel 60 and dry column Woelm Silica Gel were used for column chromatography.

5-Nitro-2-furancarbaldehyde (I) has been prepared[7] from commercial 5-nitrofurfuryliden acetate (Merck-Schuchardt). 5-Amino-3-methyl-1-phenylpyrazole has been purchased from Pfaltz and Bauer (Stamford CT,U.S.A.), 3 (or 5)-methylpyrazole from J.T. Baker Chemical CO. and 3-methyl-1-phenyl pyrazole from P.C.R. Inc. (Gainesville FLA, U.S.A.).

1,3,5-Trimethylpyrazole[8], *3,5-dimethyl-1-phenylpyrazole*[9] *and 3,5-dimethylpyrazole*[10] were synthetized by reaction of acetylacetone with methylhydrazine, phenylhydrazine and hydrazine hydrate respectively.

General procedures for the reaction of I with II (a-f).

A solution of 0.072 moles of I in 20 ml of acetic acid was added to a solution of 0.072 moles of pyrazole in 20 ml of acetic anhydride and the mixture was refluxed for 24 h. The reaction mixture was then poured onto ice and extracted exhaustively with chloroform.The organic layer was washed with 5% sodium bicarbonate solution, dried ($MgSO_4$) and evaporated under vacuum yielding a black residue. Pure compounds were obtained by column chromatography (eluent: mixtures of $CHCl_3$-$CH_3COOC_2H_5$ or $CHCl_3$-CH_3OH).

5-(1',3',5'-Trimethyl-4'-pyrazolylmethylene)-2(5H)-furanone(IIIa).

It was obtained in 20% yield as yellow needles, m.p. 89-90°C, after crystallization from isopropyl ether. EIMS (m/z, %): 204(100), 189(26), 176(25), 175(24), 161(15), 150(27), 148(37),147(75), 146(17), 134(15), 133(40), 132(16), 123(13), 122(45), 121(11), 107(13), 106(19), 105(10),102(12), 92(14), 81(19), 80(14), 79(13), 77(17), 75(13), 67(10), 66(44), 65(13), 63(11), 56(36), 55(14), 54(24), 53(21), 52(16), 51(21), 50(11), 43(11), 42(20).

5-(3',5'-Dimethyl-1'-phenyl-4'-pyrazolylmethylene)-2(5H)-furanone (IIIb).

It was obtained in 59% yield and crystallized as orange-yellow needles from isopropyl ether: m.p. 125°C. EIMS (m/z, %): 266(100), 251(5), 238(5), 237(5), 212(3), 209(32), 195(12), 184(6), 183(7), 172(4), 128(10), 118(10), 77(29).

5-(5'-Acetylamino-3'-methyl-1'-phenyl-4'-pyrazolylmethylene)-2(5H)-furanone ($IIIc_1$).

It was obtained in 10% yield and crystallized from benzene as yellow needles: m.p. 205°C. EIMS (m/z, %): 309(37), 308(60), 267(65, $m^*_{309-267}$=230.7), 266(44), 265(20), 237(11), 226(20), 211(18), 210(30), 193(13), 185(32), 184(27), 169(15), 154(17), 143(15), 119(12), 118(12), 117(12),104(11), 93(31), 92(30), 91(22), 78(36), 77(51), 65(33), 64(20), 54(22), 51(31), 50(21), 43(100), 42(17).

5-(5'-Diacetylamino-3'-methyl-1'-phenyl-4'-pyrazolylmethylene)-2(5H)-furanone ($IIIc_2$).

It was obtained in 9% yield and crystallized as yellow needles from benzene: m.p. 160-162°C. EIMS (m/z, %): 351(28), 310(13), 309(60, $m^*_{351-309}$=272.0), 268(12), 267(61, $m^*_{309-267}$=230.7), 210 (12), 92(12), 77(35), 51(18), 43(100).

5-(3'-methyl-1'-phenyl-4'-pyrazolylmethylene)-2(5H)-furanone (IIId).

m.p. 165°C (CH_3CN). EIMS (m/z, %): 252(100), 196(10), 195(31), 169(14), 154(17), 129(16), 128 (11), 77(41), 51(24).

3,5-Dimethyl-1,4-di(α,β-butenolide-γ-ylidenyl)pyrazole (IIIe).

m.p. 265°C (CH_3CN). EIMS (m/z, %): 284(100), 257(10), 203(11), 82(15), 78(10), 54(17), 52(25), 51(13).

3-Methyl-1,4-di(α,β-butenolide-γ-ylidenyl)pyrazole (IIIf).

Yellow needles from CH_3CN, m.p. 252-253°C. EIMS (m/z, %): 270(100), 189(12), 133(10), 92(11), 82(26), 65(18), 64(18), 63(11), 54(18).

5-(3'-Methyl-1'-pyrazolylmethylene)-2(5H)-furanone (V).

Yellow needles from C_2H_5OH, m.p. 125-126°C. Yield 20%. EIMS (m/z, %):176(100), 120(17),119(72), 95(19), 94(58), 82(15), 80(74), 79(13), 67(23), 66(11), 54(27), 53(21), 52(24).

Hydrogenation of IIIa: IVa.

A solution of 0.6 g of IIIa in C_2H_5OH was hydrogenated over 5% Pd-C at room temperature and atmospheric pressure. After the theoretical amount of hydrogen had been absorbed, the catalyst was filtered off and the product purified by column chromatography (eluent: $CHCl_3$ with increasing percentages of AcOEt). IR: 1780, 1190 cm^{-1} (saturated γ-lactone CO).

PMR ($CDCl_3$, TMS=0,δ): 2.15 (6H, s, 2 CH_3), 1.8-2.5 (4H, m, CH_2-CH_2), 2.68 (2H,d,J=6.0 Hz,Ar-$\underline{CH_2}$--CHO-), 3,64 (3H, s, N-CH_3), 4.66 (1H, m, CH-O).

Hydrogenation of IIIb: IVb.

0.5 g of IIIb was hydrogenated to IVb as described for IIIa. IR: 3070 (aromatic CH), 1770 (saturated γ-lactone CO), 1185, 1600, 1510, 765, 698 (monosubstituted phenyl) cm^{-1}. PMR ($CDCl_3$,TMS=0,δ): 2.23 (3H, s, CH_3),2.26 (3H, s, CH_3), 1.7-2.6 (4H, m, CH_2-CH_2), 2.78 (2H, d,J= 6.0 Hz, -$\underline{CH_2}$-CHO-), 4.62 (1H, m, CH-O), 7.4 (5H, s, phenyl protons).EIMS (m/z, %): 270(10), 186(17), 185(100),77(18).

Oxidation of $IIIc_1$ with $KMnO_4$: 5-acetylamino-3-methyl-1-phenylpyrazol-4-carboxylic acid.

0.5 g of $IIIc_1$ dissolved in acetone (15 ml) was oxidized with $KMnO_4$ (1.1 g) at r.t.. After the usual work-up,83.5 mg of 5-acetylamino-3-methyl-1-phenylpyrazol-4-carboxylic acid,m.p. 234-236°C,

was obtained. IR: 3238 and 3190 (NH), 2700-2400 (chelated OH), 1675 (COOH and CONH), 1600, 768, 695 (monosubstituted phenyl), 930 (O-H out of plane bending) cm^{-1}.

PMR (CD_3OD, TMS=0,δ): 1.98 (3H, s, CH_3), 2.47 (3H, s, CH_3CO), 7.45 (5H, s, C_6H_5), 8.15(1H,br s NH). On treatment with an ethereal diazomethane solution the corresponding methyl ester was obtained. IR: 3270 (NH), 1715, 1250, 1095 (ester), 1685 (CONH), 1600, 763, 693 (monosubstituted phenyl) cm^{-1}.

PMR ($CDCl_3$, TMS=0,δ): 2.05 (3H, s, CH_3), 2.50 (3H, s, CH_3CO), 3.90 (3H, s, CH_3O), 7.50 (5H, s, C_6H_5), 8.2 (1H, br s, NH).

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Received, 23rd June, 1982