J. Chem. Research (S), 2003, 117-120
J. Chem. Research (M), 2003, 0362–0380

Addition reactions of acetylenic esters to 6,7-dihydrobenzo[*b*]furan-4(5*H*)-one, 6,7-dihydroindol-4(5*H*)-one, 5,6-dihydrobenzo[*b*]furan-7(6*H*)-one and 5,6-dihydroindol-7(6*H*)-one ketoximes. Formation of reduced furo[*g*]- and pyrrolo[*g*]-indoles

Gérard Aimè Pinna*, Mario Sechi, Giuseppe Paglietti and Maria Antonietta Pirisi

Dipartimento Farmacochimico Tossicologico, University of Sassari, Via Muroni 23/A, 07100 Sassari, Italy

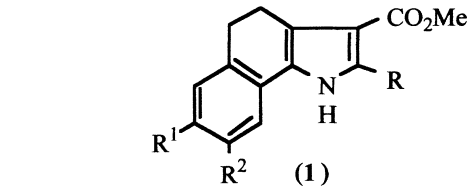
Thermal rearrangement of 6,7-dihydrobenzo[*b*]furan-4(5*H*)-one and 4,5,6,7-tetrahydroindol-4-one 4(7)-*O*-(*E*)-(1,2-dimethoxycarbonylvinyl)ketoximes gave 4,5-dihydrofuro[2,3*g*]- and 4,5-dihydropyrrolo[2,3*g*]- and [3,2-*g*] indoles, three novel tricyclic systems

Keywords: Michael reactions, acetylenic esters, thermal aza-Cope rearrangement

Our previous work on the thermal rearrangement of *O*-vinyl-oximes of α-tetralones and tetrahydrobenzo[*b*]thiophen-4(7)-ones has provided a novel route to the synthesis of 4,5,6,7-tetrahydrobenzo[*g*]indoles (**1**),[1] 2-[thien-2(3)-yl]pyrroles (**2**) and 4,5-dihydrothieno[*g*]indoles (**3**).[2]

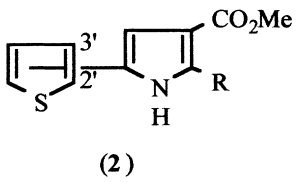
The tricyclic system of type **1** has been used to form a series of carbamate derivatives (**4, 5** and **6**), which proved to be endowed with interesting anticancer *in vitro* activity.[3-5] Now, in connection with a medicinal chemistry project, it seemed very important to us to replace both benzene and thiophene rings in the structures of **4**–**6** with those of furan and pyrrole for evaluation of the effect of their isosterism upon the biological activity of the corresponding carbamates which may be prepared from the structures **7–10**, the main objectives of the present work.

Thus, we have reacted the oximes **12** and **13a–j** with dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate (MP) according to Scheme 1, and the adducts so formed were submitted to thermal rearrangement at 120–140 °C in the absence of solvent.



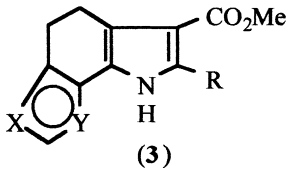
(**1**)

R^1 = H, Cl, OMe; R^2 = H;
R^1 = R^2 = Cl;



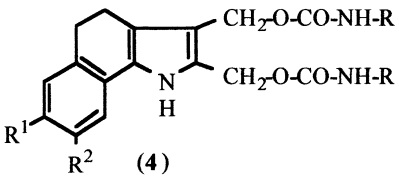
(**2**)

R = CO_2Me; H throughout



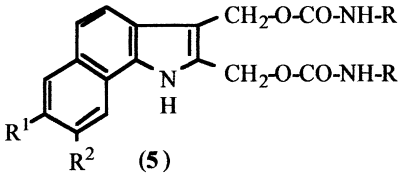
(**3**)

X = S; Y = H
X = H; Y = S



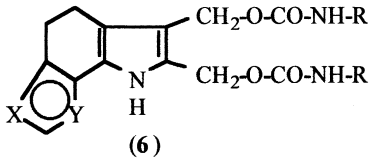
(**4**)

R^1 = H, Cl, OMe; R^2 = H;
R^1 = R^2 = Cl;
R = isopropyl



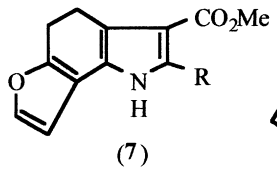
(**5**)

R^1 = H, Cl, OMe; R^2 = H;
R^1 = R^2 = Cl;
R = isopropyl; Ph; cyclohexyl

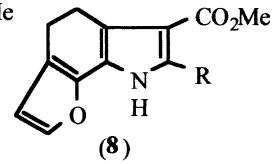


(**6**)

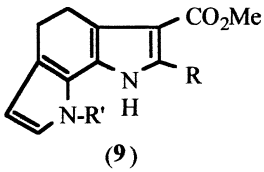
X = S; Y = H
X = H; Y = S
R = isopropyl



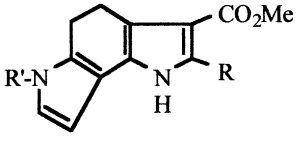
(**7**)



(**8**)



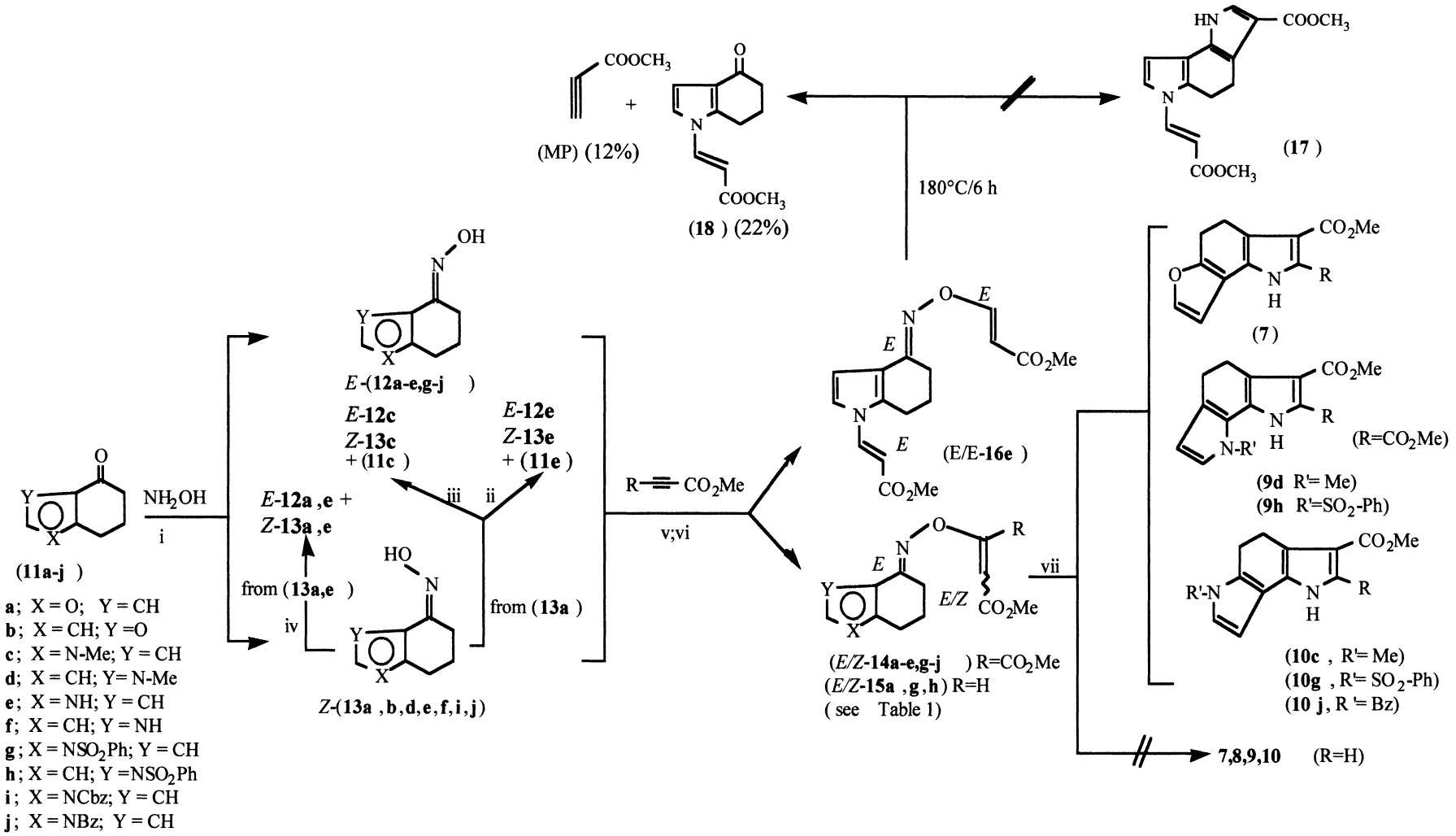
(**9**)



(**10**)

R= CO_2Me; H throughout
R' according to scheme 1

* To receive any correspondence. E-mail: pinger@uniss.it



Scheme 1 Reagents and conditions: i, in refluxing EtOH-H_2O; ii, 29% NH_3 in EtOH at 150 °C for 12h; isolated pure after chromatography; iii, 33% $MeNH_2$ in EtOH as in ii and isolated pure after chromatography; iv, in refluxing HCl-MeOH; v, dry DMSO, 55 °C for 24-36h; vi, Ph_3P in CH_2Cl_2 at 10 °C; vii, 120-140 °C for 24 h.

Table 1 Yields, M.p's, R_f and ratios of compounds (*E/Z*)-**14a,b,c,d,e,g,h,i,j**, **15a,g,h** and **16e**

Compd	Method	Overall yield (%)	M.p./°C (from)	δ_{Hx} (*E*)-isomer	R_f	δ_{Hx} (*Z*)-isomer	R_f	% of *E*-isomer	% of *Z*-isomer
				singlet		singlet			
(E/Z)-**14a**	A	53	oil	5.90	0.55[a]	6.00	0.45[a]	77.8	22.2
(E/Z)-**14b**	A	45	oil	5.98	0.53[b]	6.10	0.47[b]	63.2	36.8
(E/E)-**14c**	A	38	105–106 (ethanol)	5.88	0.69[b]	-		100	-
(E/Z)-**14d**	A	38	oil	5.74	0.75[b]	5.94	0.68[b]	61.4	38.6
(E/E)-**14e**	A	35	92–94 (ethanol)	5.89	0.53[c]	-		100	-
(E/Z)-**14e**	A	31	oil	-		5.92	0.43[d]	-	100
(E/E)-**14e**	B	59	92–94 (ethanol)			-		100	
(E/Z)-**14g**	A	83	115–117 (chrom.[d])	5.86	0.50[d]	5.94	0.43[d]	63.3	36.7
(E/E)-**14h**	A	39	oil	5.95	0.40[b]	-		100	-
(E/Z)-**14i**	A	37	oil	5.90	0.51[b]	5.92	0.37[b]	61.9	38.1
(E/Z)-**14j**	A	30	oil	5.90	0.62[b]	5.92	0.58[b]	64.9	35.0
(E/Z)-**14j**	B	65	oil	5.90	0.62[b]	5.92	0.58[b]	64.9	35.0
				δ_{Ha} δ_{Hx} doublets *J*		δ_{Ha} δ_{Hx} doublets *J*			
(E/Z)-**15a**	A	46	oil	8.01 5.63 12.2	0.64[a]	7.41 4.90 7.4	0.52[a]	65	35
(E/Z)-**15g**	A	53	137–139 (ethanol)	7.97 5.40 13.2	0.45[b]	7.10 4.90 7.4	0.40[b]	65	35
(E/Z)-**15h**	A	76	95–98 (ethanol)	7.90 5.60 12.6	0.50[b]	7.40 4.92 8.0	0.45[b]	82	18
(E/E)-**16e**	A	42	156–158 (ethanol)	8.02 5.63 12.6	0.79[c]	-	-	100	-

[a] Petrol ether 40-60 °C (P.E) / ethyl acetate (E.A) in ratio of 8 : 2; [b]P.E / E.A = 7 : 3; [c]P.E / E.A = 1 : 1; [d]P.E / E.A = 6 : 4

Ketoximes

The oximes, for the most part [(*E*)-**12d**, **e**, **g**, **h**, **i**, **j** and (*Z*)-**13a**, **f**, **j**] new compounds or characterised now for the first time, were obtained from the parent ketones **11a–j** by standard methods and their configuration was assigned according to $^1H/^{13}C$ –HETCOR NMR spectra whose data matched very well those reported by us, [2] by Cho *et al.*[10], and by Hawkes *et al.*[11], for ^{13}C-NMR of α-methylene resonances. Of the ketones **11**, only the **11i** was unknown; this was prepared from **11e** and dibenzyl carbonate in dichloromethane. Interestingly, we have discovered that the known ketoxime (*Z*)-**13a**,[6,7] by treatment with an appropriate base adapting a known reaction,[8] may be directly converted into a mixture of both known ketoximes of (*E*)-**12c** (34%) and (*Z*)-**13c** (66%) as well as of (*E*)-**12e** (15.5%) and (*Z*)-**13e** (49%) which, after separation by column chromatography, were better characterised than those previously incompletely described.[9] In the case of (*Z*)-**13a**,**e**, where a single isomer was mainly formed, we operated its interconversion into a mixture of *Z/E* isomers by refluxing the oxime with methanolic hydrogen chloride as reported in the literature.[8] Hence, separation of the mixture was accomplished by repeated flash chromatography to give the required pure isomers (*E*)-**12a** and (*E*)-**12e**, now unambiguously identified.

Addition reactions

Whenever possible a single ketoxime isomer was used for the addition reactions with DMAD. With few exceptions all ketoximes add to the triple bond of this ester in dry DMSO in the presence of catalytic amounts of triethylamine (TEA) to give modest to fair yields of single (*Z*)- or (*E*)-*O*-vinylketoximes **14a–e**, **g–j**. Under identical conditions, similar adducts were observed with MP to give **15a**, **g**, **h** and **16e** according to a general Michael addition mechanism (Scheme 1 and Table 1). Compounds (*E*)-**14e**,**j** were alternatively obtained in better yields carrying out the reaction in dichloromethane using triphenylphosphine as catalyst according to a described procedure.[12] The formation of the isomers seems very conditional upon the configuration of the starting oxime and in some cases proved to be highly stereospecific [(*E*,*E*)-**14e**, (*E*,*Z*)-**15e**, (*E*,*E*,*E*)-**16e**, (*E*,*E*)-**14h**].

Our experiments show that the (*E*) adduct prevails and is the fastest moving on TLC. The sterochemistry of the addition was based upon both the chemical shift and coupling constant of the vinyl proton according to previous reports for similar cases,[1] and this also enabled us to determine the proportions of the isomers in the mixtures. Addition of (*Z*)-**13e** to MP gave exclusively the adduct (*E*,*E*,*E*)-**16e** in 42% yield. This result is noteworthy since both pyrrole and indole are reported to undergo electrophilic Michael addition to the acetylenic esters only with difficulty[15] and once more confirms that during the addition an interconversion of *Z* into *E* oxime configuration was taking place. Only in the case of (*Z*)-**13f** was no addition observed with either DMAD or MP. This fact can be explained by the poor reactivity of the oxime group engaged in intramolecular hydrogen bonding.

Aza-Cope rearrangement of O-alkenoates (**14**, **15**)

Thermal rearrangement of the *O*-vinyl ketoximes **14a–e**, **g–j**, **15a**, **g**, **h** and **16e**, according to an aza-Cope mechanism ([3,3] sigmatropic shift) previously reported,[1-4] was successful in a few cases to give the 4,5-dihydro-1*H*-furo[2,3-*g*]indole (**7**), the 8-substituted 4,5-dihydro-1*H*-pyrrolo[3,2-*g*]indoles (**9d**, **h**) and the 6-substituted 4,5-dihydro-1*H*-pyrrolo[2,3-*g*]indoles (**10c**, **g**, **j**) (Scheme 1) in low yields. The failure of the *O*-vinyl ketoximes **14b**, **e**, **f**, **g**, **i**, **j**, **15a**, **g**, **h**, **j** and **16e** to

form rearrangement products was due to an observed competitive retro-Michael addition. In particular, from compound (*E*,*E*,*E*)-**16e** the retro-Michael reaction concerned only the *O*-alkenoate portion, giving rise to the ketone **18** (22%) and methyl propiolate (12%). The assignments of the proposed structures were made on the basis of the analytical, physical and spectroscopic data.

The UV spectra of compounds **7**, **9d**, **h**, and **10c**, **g**, **j** show that the chromophore of the dihydro-1*H*-furo[2,3-*g*]indole (**7**) system displayed two maxima at 336 and 331nm whereas that associated with 8-substituted 4,5-dihydro-1*H*-pyrrolo [2,3-*g*]indoles (**9d**,**h**) exhibited an intense peak at 350-345nm. A certain difference was observed in the cases of **10c**, **j** in comparison with **10g** where in the latter the electron-withdrawing group on the nitrogen causes a collapse of the maximum around 320-350nm.

Techniques used: UV, IR, ^{1}H- and ^{13}C-NMR, column chromatography.

References: 18

Schemes: 1

Table 1: Spectroscopic data of *O*-alkenoates **14a-j**, **15a,g,h**, and **16e**

Received 15 April 2002; accepted 1 March 2003
Paper 02/1335

References cited in this synopsis

1 G.A. Pinna, M.A. Pirisi, and G. Paglietti, *J. Chem. Res.*, 1990, *(S)*, 360, *(M)*, 2777.
2 G.A. Pinna, M.A. Pirisi, and G. Paglietti, *J. Chem. Res.*, 1993, *(S)*, 210, *(M)*, 1279.
3 G.A. Pinna, M.A. Pirisi, and G. Paglietti, *Il Farmaco*, 1994, **49**, 121.
4 G.A. Pinna, M.A. Pirisi, M. Sechi, and G. Paglietti, *Il Farmaco*, 1998, **53**, 161.
5 G.A. Pinna, M.A. Pirisi, L. Gherardini, and G. Paglietti, *Abstract of XIV National Meeting on Medicinal Chemistry* of the Società Chimica Italiana, Salsomaggiore Terme-Parma, 21-25 September 1998, p. 198.
6 R. Royer, G. Lamotte, J.P. Bachelet, P. Demerseman, R. Cavier, and J. Lemoine, *Eur. J. Med. Chem.*,1976, **11**, 221.
7 A.N. Kost and L.G.Tret'yacova, Russian Pat. 210.182 (1968); *Chem. Abs*. ,1968, .**69**, 59088n.
8 A.P.Stoll and F. Troxler, *Helv. Chim. Acta*, 1968, **51**, 1864.
9 M. Matsumoto and N. Watanabe, *Heterocycles*, 1984, **22**, 2313.
10 H. Cho, K. Murakami, H. Nakanishi, H. Isoshima, K. Hayakawa, and I. Uchida, *Heterocycles*, 1998, **48**, 919.
11 G.E. Hawkes, K. Herwig, and J.D. Roberts, *J. Org. Chem.*, 1974, **39**, 1017.
12 I. Yavari and A. Ramazani, *Synth. Commun.*, 1977, **27**, 1449.
15 R. M. Acheson and N. F. Gilmore, *Adv. Heterocyclic Chem.*, 1978, **23**, 263 and references cited therein.