Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Ahmed H. M. Elwahy [a] & Ashraf A. Abbas [a]
[a] Department of Chemistry, Faculty of Science , Cairo University , Giza, A.R., Egypt E-mail:
Published online: 04 Dec 2007.

To cite this article: Ahmed H. M. Elwahy & Ashraf A. Abbas (2000) Bis(β-Difunctional) Compounds: Versatile Starting Materials for Novel Bis(Heterocycles), Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:16, 2903-2921, DOI: 10.1080/00397910008087441

To link to this article: http://dx.doi.org/10.1080/00397910008087441

SYNTHETIC COMMUNICATIONS, 30(16), 2903–2921 (2000)

BIS(β-DIFUNCTIONAL) COMPOUNDS: VERSATILE STARTING MATERIALS FOR NOVEL BIS(HETEROCYCLES)

Ahmed H. M. Elwahy* and Ashraf A. Abbas

Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt
e-mail: aelwahy@hrzPUB.tu-darmstadt.de

ABSTRACT. New bis(β-difunctional) compounds could be prepared in good yields. Their utility as intermediates in the synthesis of novel bis(heterocycles) were also investigated .

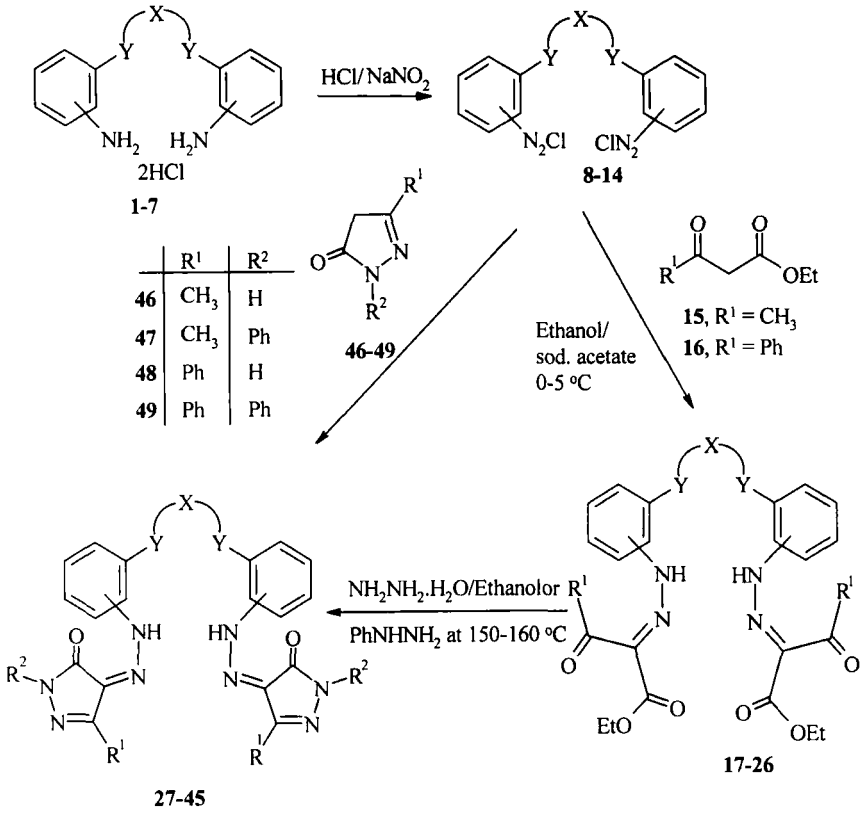
The chemistry and wide applicability of β-difunctional compounds in organic synthesis have been intensively studied.[1-5] Most of them are key intermediates in the synthesis of different reported biologically active heterocycles. For example, the use of hydrazine and β-dicarbonyl compounds continue to be the method of choise for the synthesis of pyrazole derivatives.[6-8] The latters were reported in many publications as analgesic, antipyretic, antiinflammatory and hyperglycenic agents.[9-13] Moreover,the classical synthetic route to isooxazoles involve the reaction of 1,3-diketones or their derivatives with hydroxylamine hydrochloride.[14] The isooxazole derivatives found diverse applications in the areas of medicine and agriculture.[15,16] On the other hand, little

* To whom correspondence should be addressed.

attention has been paid to the synthesis of bis(β-difunctional) compounds. The latter represent a class of compounds which are ideally suited for the purpose of serving as multifunctional building units for new promising twin compounds in one or two easily reaction steps. During the last decades these compounds obtained great attention for being model compounds for main chain polymers.[17-22] It was also reported that many biologically active natural and synthetic products have molecular symmetry.[23]

In connection with these findings, this project is directed towards the synthesis of some new bis difunctional building units and studying their utilization as intermediates in the synthesis of novel bis(5-membered heterocycles) having in most cases arylazo substitutents. The presence of these substitutents was reported to enhance the biological activity of some 5-membered heterocycles.[24] In search of an expedient pathway to the new bis(β-difunctional) compounds **17-26** and **50-53**, our attention focused on the coupling of the bis diazonium salts **8-14** with the appropriate active methylene compounds. The bis amines **1-7** were chosen as the starting materials. The synthetic strategy is outlined in Schemes 1 and 2.

Thus, the diamine dihydrochlorides **1-7**[25,26] were diazotized with sodium nitrite in hydrochloric acid to give the corresponding bis diazonium salts **8-14**. Coupling of **8-14** with the appropriate β-ketoesters **15** and **16** in ethanol containing sodium acetate at 0-5 °C afforded the corresponding bis(hydrazones) **17-26** respectively in 60-82% yields. The reactivity of the latters towards a series of amino nucleophiles are now investigated. Thus, condensation of **17-26** with hydrazine hydrate in ethanol under reflux gave the corresponding bis(pyrazolones) **27-33**, **41** and **42** respectively in 60-80% yields. Compounds **27-32** and **41** were alternatively obtained in 65-82% yields by coupling of the bis diazonium salts **8-13** with each of 3-methyl-1H-pyrazol-5-one (**46**)[27] and 3-phenyl-1H-pyrazol-5-one (**48**)[27] in ethanol containing sodium acetate. Similarly, the bis(pyrazolones) **34-40**, **43-45** were prepared in 60-75% yields by coupling of the bis diazonium salts **1-7** with each of **15** and **16** followed by heating with phenylhydrazine in an oil bath at 150-160 °C. The bis(pyrazolones) **34-37**, **39**, **43** and **45** could also obtained in



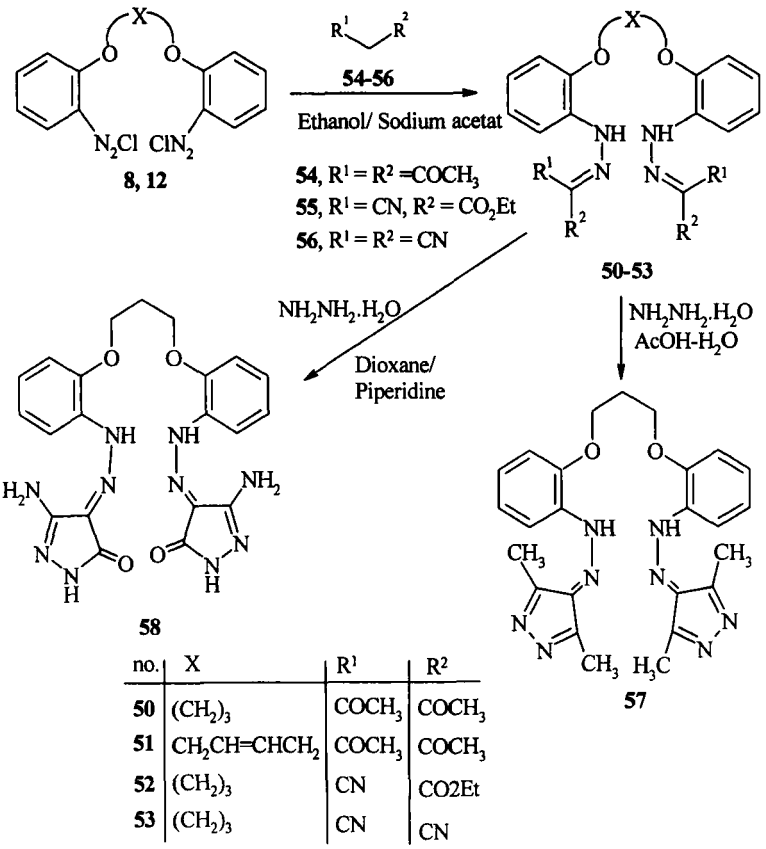
	R^1	R^2
46	CH_3	H
47	CH_3	Ph
48	Ph	H
49	Ph	Ph

Compounds no.	X	Y
1,8,17,24,27,34,41,43	$(CH_2)_3$	O
2,9,18,25,28,35,42,44	$(CH_2)_4$	O
3,10,19,29,36	$(CH_2CH_2)_2O$	O
4,11,20,30,37	$CH_2CH(OH)CH_2$	O
5,12,21,31,38	$CH_2CH{=}CHCH_2$	O
***6,13,22,32,39**	*$(CH_2)_3$	O
7,14,23,26,33,40,45	$(CH_2)_3$	S

Compds **17-23**, $R^1 = CH_3$
Compds **24-26**, $R^1 = CH_3$
Compds **27-33**, $R^1 = CH_3$, $R^2 = H$
Compds **34-40**, $R^1 = CH_3$, $R^2 = Ph$
Compds **41,42**, $R^1 = Ph$, $R^2 = H$
Compds **43-45**, $R^1 = R^2 = Ph$

* Position of the substituents (amino, hydrazono) is "para" to the phenoxy group.
In all other compounds the position of these substituents is "ortho" to the phenoxy group.

Scheme 1

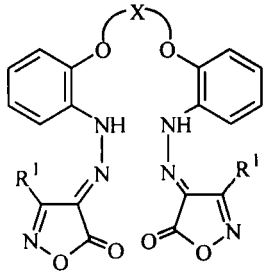


no.	X	R^1	R^2
50	$(CH_2)_3$	$COCH_3$	$COCH_3$
51	$CH_2CH{=}CHCH_2$	$COCH_3$	$COCH_3$
52	$(CH_2)_3$	CN	CO2Et
53	$(CH_2)_3$	CN	CN

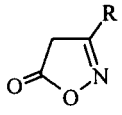
Scheme 2

72-82% yields by coupling of the bis diazonium salts **1-3** and **7** with the appropriate pyrazolone derivatives **47**[28] and **49**[28] respectively in ethanol containing sodium acetate. The synthesis of the new bis(3,5-dimethylpyrazole) **57** and the bis(3-aminopyrazole) **58** were also described (Scheme 2). Thus, condensation of the bis(hydrazone) **50** with hydrazine hydrate in aqueous acetic acid afforded **57** in 60% yield. On the other hand **58** was obtained in 60% yield by cyclocondensation of **52** with hydrazine hydrate in refluxing dioxane containing few drops of piperidine. The latter is considered to be the most useful synthon for building fused pyrazoles.[30,31] The bis hydrazones **50-53** were obtained in 70-80% yields by

coupling of the bis diazonium salts **8, 12** with each of acetylacetone (**54**), ethyl cyanoacetate (**55**) and malononitrile (**56**) respectively in ethanol containing sodium acetate. We have also described the synthesis of the new bis(isooxazolone) derivatives **59**, **60** in 60 and 66% yields by cyclocondensation of the bis(hydrazones) **17** and **19** with hydroxylamine hydrochloride in refluxing acetic acid. Compounds **59, 60** were alternatively obtained in 75-80% yields by coupling of each of the bis(diazonium) compounds **8** and **10** respectively with 3-methylisoxazol-5-one (**63**).[32] Similarly the bis(isoxazolones) **61, 62** were prepared in 60-72% yields by coupling each of the diazonium compounds **8** and **10** respectively with 3-phenylisooxazole-5-one (**64**).[32]



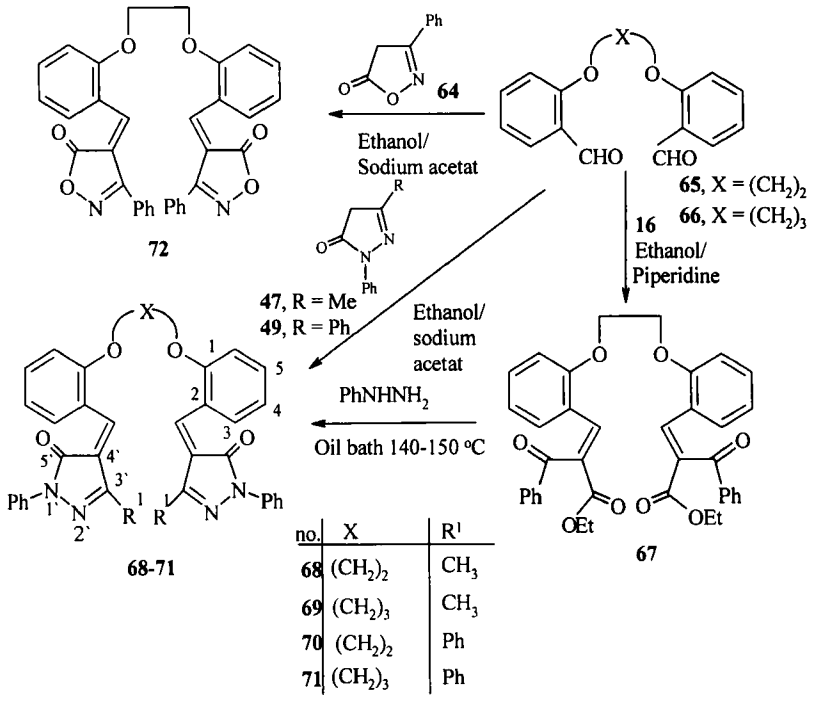
no.	X	R^1
59	$(CH_2)_3$	CH_3
60	$(CH_2CH_2)_2O$	CH_3
61	$(CH_2)_3$	Ph
62	$(CH_2CH_2)_2O$	Ph



63, R = CH_3
64, R = Ph

59-62

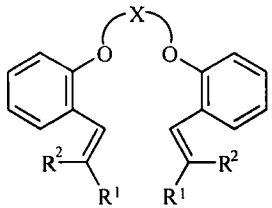
Our study is now extended to include the synthesis of the new bis(pyrazolone) derivatives **68-71** as outlined in Scheme 3. Thus, condensation of 1,2-bis(2-formylphenoxy)ethane[33] **65** with ethyl benzoylacetate (**16**) in refluxing ethanol containing few drops of piperidine afforded the corresponding bis(ethyl 3-oxo-3-phenylpropionate) 2,2`(2,2`-ethylenedioxydibenzylidene) (**67**) in 50% yield. Heating of the latter with phenylhydrazine in an oil bath at 150-160 °C afforded the corresponding bis(pyrazolone) derivative **70** in 50% yield. Compound **70** was alternatively obtained in 60% yield by the condensation of **65** with 1,3-diphenylpyrazol-5-one (**49**) in refluxing ethanol containing sodium acetate. Similarly were prepared the bis (pyrazolone) derivatives **68**, **69**, **71** and the bis(isoxazolone) derivatives **72** in 50-60 % yields by the condensation of the corresponding bis(aldehydes) **65** and **66**[33] with each of 3-methyl-1-phenylpyrazol-5-one (**47**), 1,3-diphenylpyrazol-5-one (**49**) and 3-phenylisoxazol-5-one (**64**) respectively.



no.	X	R^1
68	$(CH_2)_2$	CH_3
69	$(CH_2)_3$	CH_3
70	$(CH_2)_2$	Ph
71	$(CH_2)_3$	Ph

Scheme 3

We have also described the synthesis of the new bis(benzylidineethylcyanoacetates) **73**, **74** and the bis(benzylidinemalononitriles) **75**, **76** in 55-65% yields respectively by the condensation of the corresponding bis(aldehydes) **65** and **66** with each of ethyl cyanoacetate (**55**) and malononitrile (**56**) respectively.



no.	X	R^1	R^2
73	$(CH_2)_2$	CN	CO_2Et
74	$(CH_2)_3$	CN	CO_2Et
75	$(CH_2)_2$	CN	CN
76	$(CH_2)_3$	CN	CN

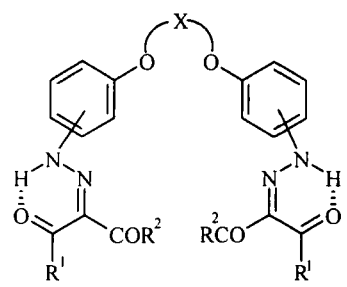
73-76

These compounds are considered to be useful synthons for building new bis(heterocycles).

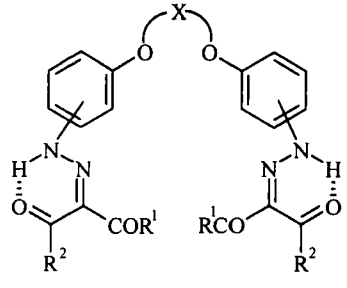
Further studies utilizing these systems are now under investigation.

From the IR and ^{1}H NMR spectra of compounds **17-26, 27-45, 50, 51, 59-62, 68-71, 76**, the following conclusions were derived:-

1- The existence of compounds **17-26** as equilibrium mixture of the intermolecular H-bonding arylhydrazone tautomers I and II ($R^1 = CH_3$, Ph; R^2 = OEt) whereas the ester group seems to be more or less exclusively involved in the H-bonded system (both of the possible tautomers I, II have been detected but not isolated). This was inferred from the following facts:-



I



II

a- The ^{1}H NMR spectra of these compounds showed a very low down field signals at $\delta \cong 13$ ppm and at $\delta \cong 15$ ppm characteristic for the intermolecular H-bonded protons.

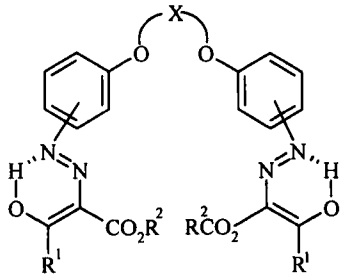
b- Compounds **17-23** showed also two singlet signals at $\delta \cong 2.5$ ppm and $\delta \cong 2.6$ ppm characteristic for the methyl protons of the acetyl groups.

The predominant form in the equilibrium mixture (in most cases) was I in which the acyl rather than the ester was involved in the H-bonded system.[34] Nonhebel et-al[34,35] reported a detailed spectroscopic study on 2-arylhydrazone of a number of 1,2,3-tricarbonyl compounds with particular references to the factors which enhance the stability of one or other tautomeric form. They revealed that the electronic effect of the substituents in the aryl group influence not only the composition of the tautomeric mixture but also the chemical shift of the H-bonded protons.

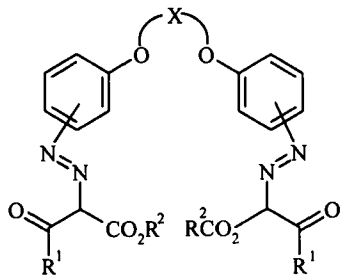
The other alternative tautomers III, IV were excluded depending on the following facts:-

a- The absence of the methine protons in the ^{1}H NMR spectra of the hydrazones **17-26**.

b- Previous studies which revealed the preference of an NH...OH rather than OH...NH bond.[36-39]



III



IV

2- Compounds **50**, **51** are assigned the structure I ($R^1 = R^2 = CH_3$) depending on the following facts:-

a- The presence of a very low field signal at $\delta \cong 14.8$ ppm diagnostic of an intermolecular H-bonded proton

b- the presence of two singlet signals characteristic for the non-equivalent methyl groups. The chemical shift of the methyl of the acetyl group involved in the H-bonded system ($\delta \cong 2.6$ ppm) is slightly further downfield than the free acetyl group ($\delta \cong 2.5$ ppm).[34]

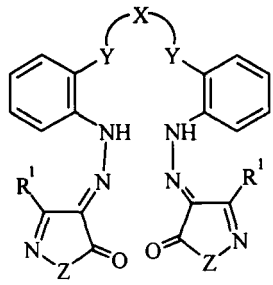
3- Compounds **27-45** and **59-62** exist in the keto form V rather than any other alternative tautomeric forms, depending on the following facts:-

a- The presence of C=O absorption at $\nu \cong 1660$ cm^{-1} in their IR spectra.

b- The absence of signal characteristic for methine proton in their ^{1}H NMR spectra.

c- The fact that the hydrazone is the most stable form whenever condensation occur at a methylene carbon.[40,41]

4- Evidence from ^{13}C-NMR data for compounds **67** and **72** indicate that they exist as one stable isomer. The trans orientation of the vinyl protons to the carbonyl group (cf. Scheme 3) was assigned for compounds **68-72** depending on



V, Z = O, N-R^2, R^2 = H, Ph

previous ^{13}C-NMR studies.[42] This study examine the long-range coupling constants between the vinylic protons and the carbon atoms of the carbonyl and azomethine groups, respectively, of the pyrazolinone ring in some 4-arylidinepyrazolin-5-one derivatives. It showed that the vinylic hydrogen atom is coupling to the carbon atom of the carbonyl group with the larger of the two coupling constants. This observation is consistent with a trans-orientation of the hydrogen atom to the carbonyl group.

5- Compounds **68-72** showed one of the aromatic protons (H-3) unexpectedly downfield at $\delta \cong 9.00$ ppm. (J = 8 Hz). This may be attributed to the anisotropic effect of $C^{5'}$=O group of each of the pyrazole and the isooxazole rings. The position of the carbonyl group in the suggested isomer is close enough to cause such effect.

In conclusion we could prepare a series of new bis difunctional compounds which are considered promising class of building blocks combining broad synthetic versatility. These new classes of symmetrical bis(heterocycles) should possess useful theoretical and biological applications

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. NMR spectra were measured with a Varian GEMINI 200 spectrometer (200 MHz) and Brucker WM-300 instrument and chemical shift are given in parts per million downfield from Me_3Si. Mass spectra

were recorded on a Varian 311 A and GCMS-QP 1000 EX. Elemental analyses were carried out at the Microanalytical Center, at Cairo University; their results were in satisfactory agreement with the calculated data.

Synthesis of compounds 17-45, 50-53, 57-62 (Table 1).

General procedure A: (for compounds **17-32, 34-37, 39, 41, 43, 45, 50-53, 59-62**). A stirred solution of the appropriate diamine dihydrochloride **1-7** (1 mmol) in water (5 ml) and concentrated hydrochloric acid (3 ml) was diazotized at -5 °C with a solution of sodium nitrite (0.23 g in 5 ml of water) during 1/2 h. Stirring was continued for 0.5 h at -5 °C. The solution was then added dropwise with stirring to a solution containing the appropriate active methylene compounds **15, 16, 54-56**, the appropriate pyrazolone compounds **46-49**, or the appropriate isooxazolone derivatives **63, 64** (2 mmol) in ethanol (10 ml) containing sodium acetate (2.5 mmol) over 0.5 h. The reaction mixture was then allowed to stand at 0 °C for 2 h. The solid obtained was collected and crystallized from the proper solvent for each derivative.

General procedure B: (for compounds **27-33, 41, 42**).

A solution of the appropriate hydrazones **17-21** (10 mmol) and hydrazine hydrate (3 ml) in ethanol (20 ml) was heated under reflux for 2 h. The solid obtained was collected and crystallized from the proper solvent to give the corresponding bis(pyrazolone) derivatives **27-33, 41, 42**.

General procedure C: (for compounds **34-40, 43-45**).

A solution of the appropriate hydrazone **17-26** (10 mmol) and phenyl hydrazine (20 mmol) was heated in an oil bath at 150-160 °C for 2 h. The reaction mixture was triturated with ethanol, filtered and crystallized from the proper solvent to give compounds **34-40** and **43-45** respectively.

Procedure D: (for compound **57**).

A solution of **50** (10 mmol) and hydrazine hydrate (3 ml) in aqueous acetic acid (50%) (25ml) was heated under reflux for 2 h. The solid obtained upon cooling was collected and crystallized from the proper solvent to give yellow crystals of **57**.

Table 1: Physical and analytical data of compounds **17-45, 50-53, 57-62**.

No.	MP.°C*	Method/ Yield (%)	IR ν (cm^{-1})	^{1}H NMR δ (ppm)**
17	160	A/ 75	-	1.37 (m, 6H, $OCH_2\underline{CH_3}$), 2.26 (quintet, 2H, $OCH_2\underline{CH_2}$), 2.49, 2.58 (2s, 6H, CH_3CO), 4.30 (m, 4H, $O\underline{CH_2}CH_3$), 4.45 (m, 4H, $O\underline{CH_2}CH_2$), 6.9-7.8 (m, 8H, ArH`s), 13.07,14.96 (2 br s, 2H, NH).
18	195	A/ 80	3250 (NH), 1708 (C=O).	1.38 (m, 6H, OCH_2CH_3), 2.20, (m, 4H, $OCH_2\underline{CH_2}$), 2.49, 2.56 (2s, 6H, CH_3CO), 4.23-4.35 (m, 8H, $O\underline{CH_2}CH_3$, $O\underline{CH_2}CH_2$), 6.9-7.8 (m, 8H, ArH`s), 13.0, 14.9 (2 br s, 2H, NH).
19	158	A/ 72	3320 (NH), 1701 (C=O).	1.2, 1.3 (2 t, 6H, $OCH_2\underline{CH_3}$), 2.2, 2.4 (2s, 6H, CH_3CO), 4.02 (m, 4H, $O\underline{CH_2}CH_3$), 4.24 (m, 8H, $O\underline{CH_2}CH_2$), 6.8-7.8 (m, 8H, ArH`s), 12.88,14.80 (2 br s, 2H, NH).
20	155-7	A/ 60	-	1.39 (m, 6H, $OCH_2\underline{CH_3}$), 2.49, 2.57 (2s, 6H, CH_3CO), 4.27-4.48 (m, 9H, $O\underline{CH_2}CH_3$, OCH_2, $\underline{CH}OH$), 4.62 (br s, 1H, OH), 7.05-7.76 (m, 8H, ArH`s), 13.22, 15.15 (2 br s, 2H, NH).
21	194-5	A/ 75	3200 (NH), 1700 (C=O).	1.38 (m, 6H, $OCH_2\underline{CH_3}$), 2.50, 2.58 (2 s, 6H, CH_3CO), 4.30 (m, 4H, $O\underline{CH_2}CH_3$), 4.7 (brs, 4H, $O\underline{CH_2}CH$=), 6.3 (m, 2H, CH=CH), 6.9-7.8 (m, 8H, ArH`s), 13.0, 14.90 (2 brs, 2H, NH)
22	113-5	A/ 65	3250 (NH), 1707 (C=O).	1.39 (t, 6H, $OCH_2\underline{CH_3}$), 2.28 (quintet, 2H, $OCH_2\underline{CH_2}$), 2.48, 2.58 (2 s, 6H, CH_3CO), 4.17 (t, 4H, $O\underline{CH_2}CH_2$), 4.33 (q, 4H, $O\underline{CH_2}CH_3$), 6.91, 7.39 (2 d, 8H, ArH`s), 12.93, 15.06 (2 br s, 2H, NH).
23	90-2	A/ 75	-	1.39 (m, 6H, $OCH_2\underline{CH_3}$), 1.78 (quintet, 2H, $SCH_2\underline{CH_2}$), 2.51, 2.58 (2s, 6H, CH_3CO), 2.92 (t, 4H, $S\underline{CH_2}CH_2$), 4.35 (m, 4H, $O\underline{CH_2}CH_3$), 7.02-7.83 (m, 8H, ArH`s), 13.23, 15.07 (2 br s, 2H, NH).
24	132-4	A/ 80	-	1.1, 1.3 (2 t, 6H, $OCH_2\underline{CH_3}$), 2.4 (m, 2H, $OCH_2\underline{CH_2}$), 4.0, 4.30 (2 q, 4H,

(continued)

Table 1 (continued)

				$O\underline{CH_2}CH_3$), 4.40 (m, 4H, $O\underline{CH_2}CH_2$), 6.4-8.5 (m, 18H, ArH`s), 13.05,14.05 (2 br s, 2H, NH).
25	176-8	A/ 70	3300 (NH), 1660 (C=O).	1.1, 1.31 (2 t, 6H, $OCH_2\underline{CH_3}$), 2.2 (br s ,4H, $OCH_2\underline{CH_2}$), 4.25-4.37 (m, 8H, $O\underline{CH_2}CH_2$, $O\underline{CH_2}CH_3$), 6.85-7.94 (m, 18H, ArH`s), 12.97, 14.05 (2 br s, 2H, NH).
26	oil***	A/ 82	-	1.11, 1.38 (2 t, 6H; $OCH_2\underline{CH_3}$), 1.82 (quintet, 2H, $SCH_2\underline{CH_2}$), 2.95 (t, 2H, $S\underline{CH_2}$), 4.17, 4.35 (2 q, 4H, $O\underline{CH_2}CH_3$), 6.93-7.97 (m, 18H, ArH`s), 13.23, 13.91 (2 br s, 2H, NH).
27	292-4	A/ 72	-	(Insoluble in DMSO).
28	320-2	A/ 82	-	(Insoluble in DMSO).
29	274-6	A/ 75 B/ 65	-	2.15 (s, 6H, CH_3), 3.95 (t, 4H, $\underline{CH_2}O\underline{CH_2}$), 4.29 (t, 4H, $\underline{CH_2}OAr$), 7.01-7.62 (m, 8H, ArH`s), 11.51 (s, 2H, NH-CO), 13.48 (s, 2H, NH).
30	296-8	A/ 70 B/ 60	-	2.16 (s, 6H, CH_3), 4.28-4.45 (m, 5H, $O\underline{CH_2}$, $\underline{CH}OH$), 5.45 (d, 1H, OH), 7.0-7.65 (m, 18H, ArH`s), 11.60 (s, 2H, NH-CO), 13.59 (s, 2H, NH).
31	318-20	A/ 62 B/ 66	3184 (NH), 1660 (C=O).	(Insoluble in DMSO).
32	246-8	A/ 75 B/ 70	3180 (NH), 1666 (C=O).	2.15 (s, 8H, CH_3, $OCH_2\underline{CH_2}$), 4.16 (t, 4H, OCH_2), 7.04, 7.48 (2 d, 8H, ArH`s), 7.95 (s, 2H, NH-CO), 11.49 (s, 2H, NH)
33	234-6	B/ 75	3310 (NH), 1655 (C=O).	1.64 (quintet, 2H, $SCH_2\underline{CH_2}$), 2.17 (s, 6H, CH_3), 2.95 (t, 4H, SCH_2), 7.12-7.69 (2 d, 8H, ArH`s), 11.5 (s, 2H, NH-CO), 13.15 (s, 2H, NH).
34	186-8	A/ 81 C/ 62	3320 (NH), 1658 (C=O).	2.27 (s, 6H, CH_3), 2.40 (quintet, 2H, $OCH_2\underline{CH_2}$), 4.56 (t, 4H, OCH_2), 6.99-7.86 (m, 18H, ArH`s), 13.63 (s, 2H, NH).
35	214-16	A/ 75 C/ 60	3225 (NH), 1658 (C=O).	2.12-2.16 (m, 10H, CH_3, $OCH_2\underline{CH_2}$), 4.30 (br s, 4H, OCH_2), 7.02-7.83 (m, 18H, ArH`s), 13.52 (s, 2H, NH).
36	175-7	A/ 72 C/ 60	3200 (NH), 1658 (C=O).	2.18 (s, 6H, CH_3) 4.01 (t, 4H, CH_2OCH_2), 4.34 (t, 4H, $\underline{CH_2}OAr$), 6.91-7.82 (m, 18H, ArH`s), 13.38 (s,

Table 1 (continued)

				2H, NH).
37	220-2	A/ 75 C/ 65	3150 (NH) 1649 (C=O).	2.28 (s, 6H, CH_3), 4.37 (t, 1H, CHOH), 4.5 (d, 4H, OCH_2), 5.58 (d, 1H, OH), 7.01-7.85 (m, 18H, ArH`s), 13.52 (s, 2H, NH).
38	242-4	C/ 65	-	2.09 (s, 6H, CH_3), 4.87 (s, 4H, OCH_2), 6.46 (s, 2H, CH=CH), 7.16-7.86 (m, 18H, ArH`s), 13.64 (s, 2H, NH).
39	202-4	A/ 71 C/ 62	3350 (NH), 1655 (C=O).	2.25 (m, 8H, CH_3,$OCH_2\underline{CH_2}$), 4.19 (t, 4H, OCH_2), 7.06-7.97 (m, 18H, ArH`s), 13.35 (s, 2H, NH).
40	238-40	C/ 65	-	1.75 (br s, 2H, $SCH_2\underline{CH_2}$), 2.18 (s, 6H, CH_3), 3.15 (brs, 1H, SCH_2), 7.02-7.83 (m, 18H, ArH`s), 13.77 (s, 2H, NH).
41	292-4	A/ 65 B/ 65	-	2.28 (br s, 2H, $OCH_2\underline{CH_2}$), 4.54 (t, 4H, OCH_2), 7.09-8.12 (m, 18H, ArH`s), 12.15 (s, 2H, NHCO), 14.15 (s, 2H, NH).
42	310-12	B/ 65	3201 (NH), 1662 (C=O).	2.17 (br s, 4H, $OCH_2\underline{CH_2}$), 4.32 (br s, 4H ,OCH_2), 7.02-8.14 (m, 18H, ArH`s), 12.13 (s, 2H, NHCO), 14.0 (s, 2H, NH).
43	242-4	A/ 82 C/ 75	3310 (NH), 1651 (C=O).	(Insoluble in DMSO).
44	264-6	C/ 70	3350 (NH), 1653 (C=O).	(Insoluble in DMSO).
45	198-99	A/ 81 C/ 63	3165 (NH), 1688 (C=O).	1.81 (br s, 2H, $SCH_2\underline{CH_2}$) 3.10 (t. 4H, SCH_2), 7.07-8.00 (m, 28H, ArH`s), 14.17 (s, 2H, NH).
50	213-5	A/ 75	3400 (NH), 1668 (C=O).	2.54 (m, 14H, CH_3, $OCH_2\underline{CH_2}$) 4.49 (t, 4H, OCH_2), 7.02-7.73 (m. 8H, ArH`s), 14.89 (s, 2H, NH).
51	242-5	A/ 70	3350 (NH), 1680 (C=O).	2.5, 2.59 (2 s, 6H, CH_3CO), 4.8 (br s, 4H, OCH_2) 6.3 (br s, 2H, CH=CH), 7.0-7.8 (m, 8H, ArH`s). 14.87 (br s, 2H, NH)
52	178-9	A/ 80	3182 (NH), 2221 (CN), 1650 (C=O).	1.37 (t, 6H, CH_3), 2.45 (quintet, 2H, $OCH_2\underline{CH_2}$) 4.29 (q, 4H, $\underline{CH_2}CH_3$), 4.41 (t, 4H, OCH_2), 6.99-7.66 (m. 8H, ArH`s), 13.43 (s, 2H, NH).
53	160-2	A/ 61	3267 (NH), 2227 (CN).	2.30 (quintet, 2H, $OCH_2\underline{CH_2}$) 4.37 (t, 4H, OCH_2), 6.99-7.44 (m. 8H, ArH`s), 14.49 (s, 2H, NH).

(continued)

Table 1 (continued)

57	240-2	D/60	3186 (NH).	2.43 (m, 14H, CH_3, $OCH_2\underline{CH_2}$) 4.36 (t, 4H, OCH_2), 6.97-7.52 (m, 8H, ArH`s), 12.79 (s, 2H, NH).
58	290-2	E/60	3182, 3460 (NH), 1670 (C=O).	2.31 (quintet, 2H, $OCH_2\underline{CH_2}$) 4.4 (t, 4H, OCH_2), 5.86 (s, 4H, NH_2), 7.03-7.74 (m, 8H, ArH`s), 10.6 (s, 2H, NHCO), 13.37 (s, 2H, NH).
59	200-2	A/ 80 F/60	3399 (NH), 1711 (C=O).	2.30 (m, 8H, CH_3, $OCH_2\underline{CH_2}$), 4.47 (t, 4H, OCH_2), 7.0-7.65 (m, 4H, ArH`s), 12.79 (s, 2H, NH).
60	180-2	A/ 70 F/60	-	δ 2.21 (s, 6H, CH_3), 3.91 (t, 4H, $\underline{CH_2}O\underline{CH_2}$), 4.30 (t, 4H, $CH_2\underline{CH_2}OAr$), 6.89-7.54 (m, 8H, ArH`s), 12.59 (s, 2H, NH).
61	248-50	A/ 72	-	(Insoluble in DMSO).
62	205-6	A/ 60	-	3.94 (t, 4H, $\underline{CH_2}O\underline{CH_2}$), 4.36 (t, 4H, $CH_2\underline{CH_2}OAr$). 6.85-7.99 (m, 18H, ArH`s), 13.01 (s, 2H, NH).

*Compounds **17-20** and **22-25** were crystallized from ethanol, **21, 25, 50-53** and **57-60** from acetic acid, **27, 29, 30, 32-41, 43-45, 61** and **62** from DMF, **28, 31** and **42** from DMSO.

Compounds **17-26 and **50-52** are measured in $CDCl_3$. the others are measured in DMSO.

***Compound **26** was purified over a short silica column using $CHCl_3$ as an eluent.

Compound **27** Ms: m/z 476 (M^+, 50.2%), 220 (29.7%), 152 (52.6%), 148 (100%), 77 (23.5%), 67 (30.6%), 56 (15.5%); compound **28** Ms: m/z 491 (M^++1, 9.6%), 274 (11.2%), 218 (41.6%), 163 (15.2%), 146 (26.9%), 119 (9.5%), 106 (15.7%), 108 (100%), 77 (19.7), 65 (42%); compound **29** Ms: m/z 506 (M^+, 42.8%), 400 (4.3%), 262 (11.1%), 218 (22.3%), 167 (14.4%), 134 (54.8%), 125 (33.1%), 120 (100%), 77 (32.7), 51 (32.2%); compound **30** Ms: m/z 493 (M^++1, 46.3%), 218 (46.9%), 164 (12.6%), 146 (22%), 133 (14.5%), 108 (100%), 80 (65.5%), 77 (20.3%); compound **31** Ms: m/z 488 (M^+, 8.4%), 271 (27.7%), 218 (49%), 160 (49%), 120 (100%); compound **35** Ms: m/z 642 (M^+, 21.6%), 350 (30.1%), 294 (12.6%), 248 (8.1%), 200 (3.4%), 163 (44.2%), 120 (50.3%), 77 (100%); compound **36** Ms: m/z 659 (M^++1, 33.2%), 365 (13.7%), 295 (12.1%), 212 (10.2%), 187 (15.4%), 135 (18.8%), 120 (50%), 91 (35.6%), 77 (100%), 65 (31.7%); compound **43** Ms: m/z 753 (M^++1, 5.3%), 697 (5.3%), 490 (15.3%), 356 (23.3%), 328 (18%). 230 (95.3%), 199 (28.6%), 77 (100%); compound **44** Ms: m/z 766 (M^+, 7.7%). 412 (13.3%), 356 (12.3%), 237 (17.7%), 195 (14.5%). 163 (17.6%). 119 (23.4%). 102 (19.2%), 77 (100%); compound **50**: ^{13}C NMR ($CDCl_3$) δ 26.8, 31.7 (2 CH_3CO), 29.3 ($OCH_2\underline{CH_2}$), 64.8 (OCH_2). 112.5,115.1,121.8, 126.2 (ArCH`s), 130.9, 133.8, 147.8 (C=N, ArC`s), 197.2, 197.4 (C=O) ppm; compound **51**: ^{13}C NMR ($CDCl_3$) δ 26.8, 31.8 (2 CH_3CO), 68.5 (OCH_2), 112.7, 115.5, 121.9, 126.2, 127.6 (ArCH`s, CH=CH), 130.8, 133.7, 147.6 (C=N, ArC`s), 197.30, 197.35 (C=O) ppm; compound **61** Ms: m/z 603 (M^++1, 7.3%), 456 (2%), 430 (12.6%), 322 (3.3%), 263 (4.6%), 103 (100%), 76 (30%).

Table 2: Physical and analytical data of compounds **67, 73-76**.

No.	MP.°C*	Yield (%)	IR ν (cm^{-1})	^{1}H NMR δ (ppm)**
67	146-8	50	3300 (NH), 1708, 1670 (C=O)	1.26 (t, 6H, CH_3), 4.35 (q, 4H, OCH_2CH_3), 4.49 (s, 4H, OCH_2), 6.85-8.00 (m, 18H, ArH`s), 8.48 (s, 2H, CH=C)
73	167-8	65	-	1.33 (t, 6H, CH_3), 4.32 (q, 4H, OCH_2CH_3), 4.49 (s, 4H, OCH_2), 7.03-8.32 (m, 8H, ArH`s), 8.72 (s, 2H, CH=C).
74	215-7	60	2216 (CN), 1726 (C=O).	1.38 (t, 6H, CH_3), 2.41 (quintet, 2H, OCH_2CH_2), 4.27-4.42 (m, 8H, OCH_2CH_3, OCH_2), 6.99-8.3 (m, 8H, ArH`s), 8.75 (s, 2H, CH=C).
75	244-6	50	2225 (CN).	4.6 (s, 4H, OCH_2), 7.16-8.05 (m, 8H, ArH`s), 8.43 (s, 2H, CH=C)
76	140-1	55	2223 (CN).	2.35 (quintet, 2H, OCH_2CH_2), 4.36 (t, 4H, OCH_2), 7.13-8.03 (m, 8H, ArH`s), 8.52 (s, 2H, CH=C)

*Compounds **67, 73, 74** were crystallized from ethanol, **75** and **76** from DMF.

Compounds **67, **73** and **74** are measured in $CDCl_3$, the others are measured in DMSO.

Compound **67**: ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 61.45 (CH_3CH_2O), 66.97 (OCH_2CH_2O), 112, 121.23, 128.75, 129.19, 130.48, 131.97, 132.7, 138.37 (ArCH`s, CH=C), 127.71, 131.33, 136.53, 157.07 (ArC`s, C=CH), 165.64 (CO_2Et), 195.64 (COPh) ppm. Compound **73** ^{13}C NMR ($CDCl_3$) δ 14.22 (OCH_2CH_3), 62.63 (OCH_2CH_3), 67.25 ($CH_2OC_6H_4$), 102.93 (CN-C=C), 115.9 (CN), 112.6, 121.3, 121.8, 129.7, 135.1, 149.5, 158.2 (CH=C, ArC`s and ArCH`s), 162.7 (C=O) ppm.

Procedure E: (for compound **58**).

A solution of **52** (10 mmol) and hydrazine hydrate (3 ml) in dioxane (25 ml) containing few drops of piperidine was heated under reflux for 2 h. The solid obtained upon cooling was collected and crystallized from the proper solvent to give brown crystals of **58**.

General procedure F: (for compound **59** and **60**).

A solution of each of **17** and **19** (10 mmol) and hydroxylamine hydrochloride (20 mmol) in acetic acid (20 ml) was heated under reflux for 3 h. The solid obtained

Table 3: Physical and analytical data of compounds **68-72**.

No.	MP.°C*	Yield (%)	IR ν (cm^{-1})	^{1}H NMR δ (ppm)**
68	234-6	60	1682 (C=O)	1.9 (s, 6H, CH_3), 4.63 (s, 4H, OCH_2), 7.1-8.99 (m, 20H, ArH's, CH=C).
69	148-50	58	-	2.26, 2.29 (2 s, 6H, CH_3), 2.44 (quintet, 2H, $OCH_2\underline{CH_2}$), 4.34 (t. 4H, OCH_2), 6.95-9.07 (m, 20H, ArH's, CH=C).
70	258-9	60	-	4.41 (s, 4H, OCH_2), 6.97-9.22 (m, 30H, ArH's, CH=C).
71	208	60	1681 (C=O)	2.15 (quintet, 2H, $OCH_2\underline{CH_2}$), 3.99 (t, 4H, OCH_2), 6.69-9.20 (m, 30H, ArH's, CH=C).
72	207-9	50	-	4.37 (s, 4H, OCH_2), 6.99-8.93 (m, 20H, ArH's, CH=C).

*Compounds **68-71** were crystallized from DMF and **72** from acetic acid

Compounds **69, **71** are measured in $CDCl_3$, the others are measured in DMSO.

Compound **71** Ms: m/z 720 (M^+, 16.8%), 379 (14.1%), 340 (35.2%), 325 (19.4%), 323 (66.6%), 279 (11.5%), 236 (30.6%), 178 (11.0%), 77 (100%).

Compound **72** ^{13}C NMR (DMSO) δ 60.17 (CH_2O), 112.37, 120.70, 127.88, 128.40, 130.37, 132.58, 137.19, 145.57,(ArCH's, CH=C), 116.09, 120.94, 126.44, 159.10, 163.77 (ArC's, C=CH, C=N), 168.04 (CO-O) ppm.

upon cooling was collected and crystallized from the crystallized from the proper solvent to give yellow crystals of **59** and **60** respectively.

Synthesis of compounds 67, 73-76 (Table 2).

General procedure: A solution of each of the appropriate bis(aldehydes) **65, 66** (10 mmol) and the appropriate active methylene compounds **55, 65** (20 mmol) in ethanol (20 ml) containing few drops of piperidine was heated under reflux for 3 h. The solid obtained upon cooling was collected and crystallized from the proper solvent to give the corresponding bis(benzylidene) derivatives **67, 73-76**.

Synthesis of compounds 68-72 (Table 3).

General procedure: A solution of each of the appropriate bis(aldehydes) **65, 66** (10 mmol) and the appropriate pyrazolones **47, 49** or the isooxazolone **64** (20 mmol) in ethanol (20 ml) containing sodium acetat (25 mmol) was heated under reflux

for 3 h. The solid obtained upon cooling was collected and crystallized from the proper solvent to give compounds **68-72** respectively.

Acknowledgement: *The authors thank Prof. K. Hafner, Institut fur Organische Chemie, Universitat Darmstadt for his continuous support. Dr. Ahmed H. M. Elwahy is also indebted to the Alexander von Humboldt foundation for a research fellowship.*

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Received in the UK 8/6/99