Tetrahedron Vol. 48, No. 42, pp. 9355-9362, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

SYNTHESIS AND STEREOSTRUCTURE OF SOME 5,5'-DISUBSTITUTED 3-ACETYL-2,2'-BI-2*H*-1,3,4-OXA(THIA)DIAZOLINES

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(*Received in UK* 20 *July* 1992)

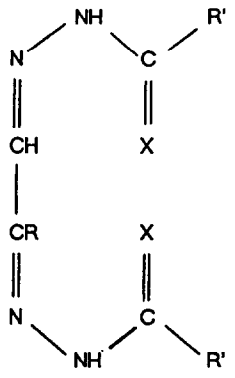
ABSTRACT- The synthesis of some (methyl)glyoxal 1,2-bis(acylhydrazones) (**1**, **3-6**) *and their cyclization into the title compounds* (**7-10**) *under acetylating conditions are described. The stereostructures of the new bi-heterocyclic diastereomers were studied by* ^{1}H- *and* ^{13}C-*NMR measurements as well as by X-ray analysis.*

INTRODUCTION

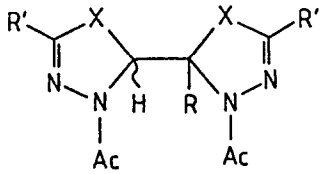
Acylhydrazines prove to be suitable trapping agents for the isolation of mono- and 1,2-dioxo compounds formed *via* chemical or biochemical transformations of carbohydrates as their presence does not disturb the formation of the latters.[1] Mono- and 1,2-bis[(acyl)hydrazones] have also complex forming properties with metal ions, and this can be utilized for their detection and separation. Moreover, such compounds due to their biological activities,[2-9] can be regarded as potential pharmacons. The bis(acylhydrazones) of methylglyoxal (methylglyoxal appears as a secondary product[10,11] in the alkaline degradation or alcoholic fermentation of carbohydrates) are prosperous in this respect as analogues to those of 3-deoxyosones formed by the Amadori rearrangement of aldoses.[1] Both types of 1,2-bis(acylhydrazones) have also comparable biological activities: *e.g.* methylglyoxal bis(guanylhydrazone) (Mitoguazone[12,13]) and the copper chelate of 3-deoxy-D-*erythro*-hexos-2-ulose bis(thiosemicarbazone)[1] show antineoplastic properties.

Under acylating conditions both aldehyde- and ketone acylhydrazones can be cyclized into 3-acyl-1,2-dihydro-1,3,4-oxa(thia)diazoles.[14-17] As a result of the intramolecular addition to the RR'C=N double bond the C-2 atom of the heterocycle formed may become asymmetric[18-23] its chirality being controlled[22] by that of the α-carbon of the R (or R') substituent.

The cyclization of non-chiral 1,2-bis(acylhydrazones) into 2,2'-bi-2*H*-1,3,4-oxa(thia)diazolines with two chirality-centers enables the simultaneous formation of 2(*R*),2'(*R*) and 2(*R*),2'(*S*) isomers as well as that of the corresponding enantiomers.[22] For this reason, a chiroptical study of the stereochemistry of products would be ineffective, on the other hand, capability for rotation around the 2,2'-bond restricts strongly the efficiency of stereochemical investigations by NMR measurements. A differentiation between the 2(*R*),2'(*R*) and 2(*R*),2'(*S*) structures of 3,3'-diacetyl-2'-methyl-5,5'-diphenyl-2,2'-bi-2*H*-1,3,4-oxadiazolines (**8**) obtained by the cyclization of methylglyoxal bis(benzoyl-hydrazone) (**2**) was suggested recently[22] considering the number of *o,o'* hydrogens with different chemical shifts.



	X	R	R'
1	O	H	Ph
2	O	Me	Ph
3	O	Me	C_5H_4N-*p*
4	S	Me	NH_2
5	O	Me	OPh
6	O	Me	HOC_6H_4-*o*



	X	R	R'
7	O	H	Ph
8	O	Me	Ph
9	O	Me	C_5H_4N-*p*
10	S	Me	NHAc

In the present work we report on the synthesis of some novel (methyl)glyoxal bis(acylhydrazones) (**1**, **3-6**) and on the stereostructures of isomeric cyclization products (**7-10**) proved by X-ray analysis and more detailed NMR studies.

SYNTHESIS

As starting materials for the synthesis of the title heterocycles (**8-10**) methylglyoxal bis(acylhydrazones) (**3-6**) have been prepared according to the method published recently[22] for the synthesis of **2** by treatment of pyruvic aldehyde dimethyl acetal with the appropriate acid hydrazide. For synthesis of compound **7** the glyoxal derivative **1** has also been prepared. The melting point of methylglyoxal bis(thiosemicarbazone) (**4**) obtained according to the above method is considerably higher (>360° C) than that claimed in the literature (m.p. 257° C) for the product obtained starting from aqueous methylglyoxal solution. Bis(thiosemicarbazone) **4** prepared in both ways by us proved to be identical (see Experimental).

Treatment of bis(benzoylhydrazone) **1** with hot acetic anhydride in pyridine afforded two isomeric bi-oxadiazolines **7**, one of which (**7b**) could be isolated in pure form. When methylglyoxal bis(thiosemicarbazone) **4** was treated with hot acetic anhydride the product (bi-thiadiazoline **10**, yield 75 %) proved to be homogeneous.

Acetylation of bis(isonicotinoylhydrazone) **3** with hot acetic anhydride in pyridine gave two isomeric 5,5'-(4-pyridylsubstituted) bi-oxadiazolines (**9**) with very similar R_f values (see Experimental), the less soluble one (**9a**) of which have been isolated in a crystalline form suitable for X-ray analysis.

SPECTROSCOPIC STUDIES

The IR-, ^{1}H- and ^{13}C-NMR data of compounds **7a,b**, **8a,b**, **9a,b** and **10a** are given in Tables 1 and 2. The most characteristic differences between diastereomers **a** and **b** are as follows:

1. The hydrogens of 2-methyl group are more shielded by ca. 0.15 ppm in **8a** and **9a** as compared to their pairs **8b** and **9b**;
2. Similarly, the multiplets of the aromatic hydrogens are partly upfield shifted in **7a**, **8a** and **9a** relative to their isomers **7b**, **8b** and **9b**;

TABLE 1. The amide-I IR bands (in KBr, cm^{-1}) and ^{1}H-NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds **7-10** in $CDCl_3$ or $(CD_3)_2SO$ solution[a] at 250 MHz.

Compound	Amide-I bands	CH_3(2') *s*(3H)	H-2 *s*(1H)[b]	CH_3(Ac) 2*s*(2x3H)[c]	ArH (phenyl or pyridyl) 2-4 m (2x5H or 2x4H)
7a	1672	-	6.67	2.31	7.3 - 7.5[d] 7.60[e]
7b	1670	-	6.70	2.14	7.55[d] 7.74[e]
8a	1677 1638	1.98	7.12	2.40 2.42	7.15 - 7.4[d] 7.55 - 7.70[e]
8b	1695 1677	2.13	6.96	2.17 2.31	7.35 - 7.6[d] 7.68 7.88[e]
9a	1686 1668	1.99	7.11	2.41 2.43	7.46[f,g] 7.51[f,h] 8.56[e,g] 8.58[e,h]
9b	1691	2.15	7.00	2.20 2.33	7.50[h,j] 7.72[f,h] 8.70[e,g] 8.80[e,h]
10a[i]	1701 1647	1.85	6.94	2.02[g,j] 2.14[g] 2.06[h,j] 2.16[h]	-

[a] Solvent $(CD_3)_2SO$ for compounds **7a,b** and **10a**; [b] Intensity 2H for **7a,b**; [c] *s*(6H) for **7a,b**; [d] ArH-3-5, *m*(6H); [e] ArH-2,6, *d*(*J*: 8.5 Hz, 4H), two separated *d* for **8b** and **9a,b**, coalesced for **8a**; [f] ArH-3,5, 2*d*(2x2H); [g,h] Signals belonging to the same half of the molecule as proved by DNOE experiments; [i] NH: 11.6[g] and 11.75[h], 2*s*, br(2x1H); [j] NHAc group.

3. Opposite small differences in the shifts are observable for the H-2 and CH_3(3,3'-Ac) signals;
4. Steric compression (upfield) shift[24] of both the C-2 and C-2' lines in the ^{13}C-NMR spectra of **8b** and **9b** in comparison with their diastereomers **8a** and **9a** suggests a more crowded steric structure for **8b** and **9b**.

TABLE 2. ^{13}C-NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds **7-10**[a] in $CDCl_3$ solution[b] at 63 MHz.

Compound	C-2 C-2'	CH_3(2')	C-5 C-5'	CH_3 NAc group	C=O	C-1	C-2,6	C-3,5	C-4
						phenyl or pyridyl group			
7a	89.9	-		22.2		124.8	130.1	127.8	133.1
7b	89.8	-	157.0	22.1	169.3	125.1	130.3	127.9	133.3
8a[c]	88.5 101.4	19.3	156.5[d] 154.0[e]	21.4 22.1	169.6[d] 167.4[e]	123.4 123.7	126.3 127.6	128.1 128.2	131.1 131.4
8b[c]	88.0 99.7	19.1	156.2[d] 154.0[e]	21.4 22.1	169.7[d] 168.4[e]	124.1 124.2	126.6 126.9	128.5 128.7	131.2 131.7
9a	89.4 102.4	19.3	154.5 152.0	21.5 22.1	169.9 167.9	- -	150.2 150.3	119.7 119.9	130.9 131.1
9b	88.6 100.6	19.1	154.6 152.0	21.4 22.1	170.0 168.7	- -	150.4 150.6	120.0 120.3	131.3 131.5
10a	70.4 86.4	27.8	149.8 144.7	23.9 24.46 25.4 24.52	170.8 171.4[f] 172.5	-	-	-	-

[a] Data for **7a** and **9b** were determined from the spectra of 10:7 and 11:9 mixtures of diastereomers **7a:7b** and **9b:9a**, respectively, comparing the spectra of these mixtures to the ones of pure diastereomers **7b** and **9a**. [b] Solvent: $(CD_3)_2SO$ for **7a,b** and **10**. [c] Assignments were supported by signal multiplicities in the H-coupled ^{13}C-NMR spectra [*t* for C-5(Ph'), *qa* for C-5 (Ph), *dqa* for C=O (3-Ac), *qa* for C=O (3'-Ac)]. [d/e] Line arising from the half-molecule including the CH(2) or CMe(2') group. [f] Two overlapping lines.

This is in accordance with the synthetic results, showing that isomer **a** is the main or in case of **10a** the only product in the ring closing reaction.

Molecule model studies on rotamers (around the C-2,C-2' axis) I-III of the 2*R*,2'*S* and 2*R*,2'*R* isomers [supposing the plausible[25] *E* configuration for the amide moieties, that is *trans* position of N-4(4') and the amide carbonyl oxygen] lead to the following conclusions:

1. The most symmetric rotamers I can be excluded for both the *R*,*S*' and *R*,*R*' isomers due to strong steric and electrostatic interactions between the sp^3 and sp^2 oxygens (*R*,*S*') or the carbonyl oxygen atoms (*R*,*R*'). The doubling of most of the ^{1}H- and ^{13}C-NMR signals corresponding to the two halfs of molecules **8-10** refers also to asymmetric structures;
2. The stronger shielding of the aromatic hydrogens in the isomers **a** suggests parallel and close arrangement of the two aromatic rings. Such an arrangement is feasible for rotamer III(*R*,*R*'), while it isn't possible for rotamer II(*R*,*R*'). In structures II(*R*,*S*') and III(*R*,*S*') a weaker interaction of the phenyl rings is also possible. Consequently, the *R*,*R*' configuration III is most probable for the isomers **a**;
3. To select the more probable one of conformers II(*R*,*S*') and III(*R*,*S*') of the isomers **b** we can set out from the fact, that the ^{1}H-NMR singlet of the 2'-methyl group is upfield shifted in **8a** and **9a**. This can be interpreted by the neighbouring anisotropic effect of the acetyl carbonyl getting near to the 2'-methyl substituent in structure III(*R*,*S*'). Since this upfield shift is not observable for the **b** isomers the II(*R*,*S*') conformation is more probable for compound **b**.
4. In the diastereomers **a** of *R*,*R*' configuration steric hindrance is diminished by the parallel arrangement of the phenyl rings. Consequently, the more crowded structure of compounds **b** suggests also *R*,*S*' configuration.

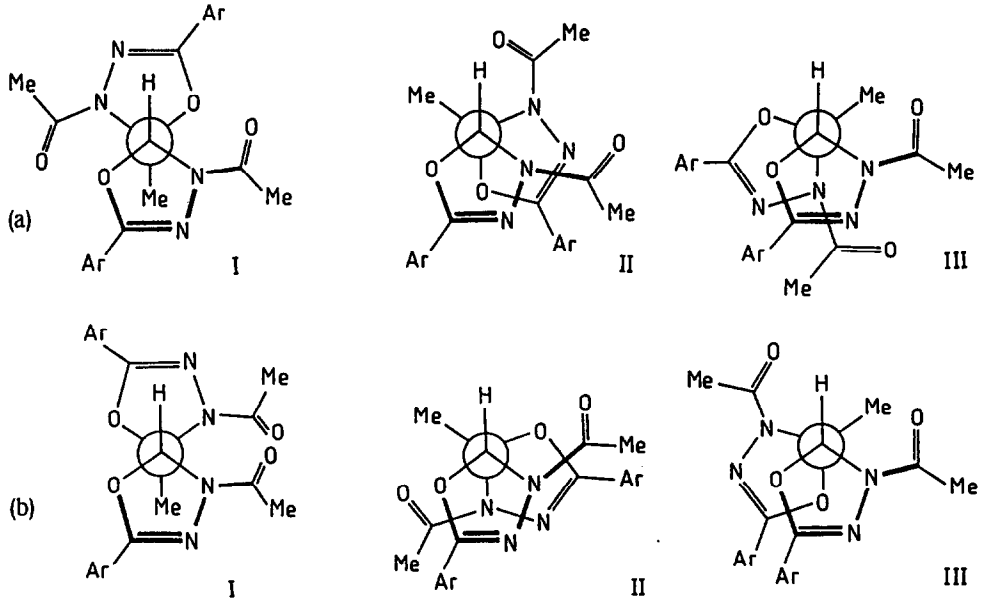


Fig. 1. Newman projections for 2,2'-rotamers of 3,3'-diacetyl-5,5'-diaryl-2'-methyl-2,2'-bi-2*H*-1,3,4-oxadiazoline diastereomers (a) 2(*R*),2'(*S*) and (b) 2(*R*),2'(*R*)

It should be emphasized, that all the conclusions above do not represent unambiguous evidences for the proposed stereostructures. The results of NOE measurements have been found to be not convincing, too, because of free rotation around the C_2-$C_{2'}$ axis. Thus, to decide the configurations of the compounds investigated, X-ray diffraction measurements were performed. Single crystal structure determination of **9a** reveals (Figure 2) that the 2 and 2' chiral centers' configurations are alike i.e. *R,R'* (or *S,S'*).

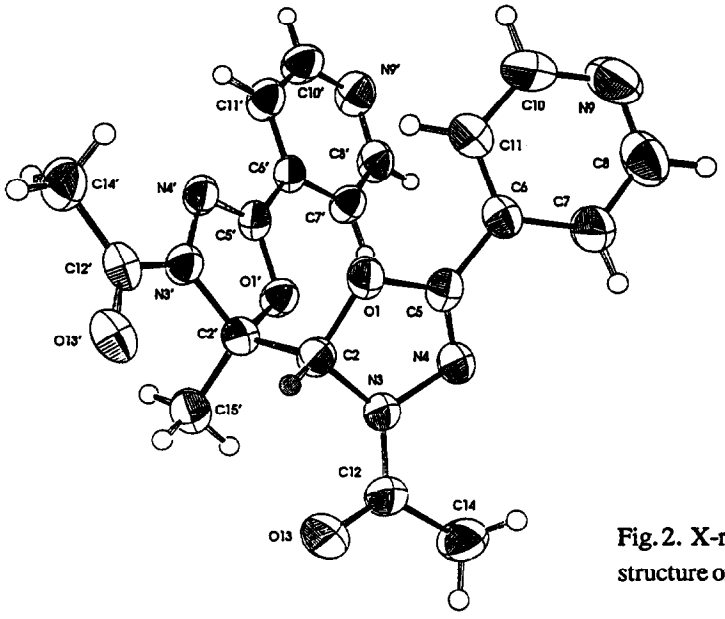


Fig. 2. X-ray crystal structure of compound **9a**

The above NMR and X-ray studies substantiate the hypothetic configurations for the diastereomers **8a** and **8b** suggested[22] on the basis of ^{1}H-NMR chemical shifts.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler block. Solutions were concentrated under reduced pressure by using a rotatory evaporator. TLC was performed on Alurolle-Kieselgel $60F_{254}$ (Merck).

IR spectra (KBr pellets) were measured on a Perkin-Elmer 283B and an Aspect 2000 computer controlled Bruker IFS-113v vacuum optic FT-spectrometer.

^{1}H- and ^{13}C-NMR spectra for solutions in $CDCl_3$ or $(CD_3)_2SO$ in 5 or 10 mm tubes were recorded at room temperature on a Bruker WM-250 FT-spectrometer at 250.13 (^{1}H) and 62.89 MHz (^{13}C), respectively, using the ^{2}H signal of the solvent as the lock and $SiMe_4$ as internal standard. NOE difference (DNOE) measurements were carried out using the standard software written for the Aspect 2000 computer of the Bruker spectrometers.

Single crystal X-ray structure determination of **9a**

Preliminary examination and data collection were performed with M_oK_α radiation (λ = 0.71073 Å) on an Enraf-Nonius CAD4 computer controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator.

X-ray diffraction experiment was made on a colorless prism crystal of $C_{19}H_{18}N_6O_4$ measuring 0.25 x 0.35 x 0.40 mm, mounted on a glass fiber in a random orientation. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range $11 < \Theta < 15^o$, measured by the computer controlled diagonal slit method of centering. The orthorhombic cell parameters and calculated volume are a = 11.430(2), b = 13.558(2), c = 12.428(2) Å, V = 1926(1)Å^3.

For Z = 4 and F.W. = 394.40 the calculated density is 1.36 g/cm^3 . From the systematic absences and from subsequent least-squares refinement, the space group was determined to be $Pna2_1$ (# 33). The data were collected at 296(2)K, using the ω - 2Θ scan technique. The scan rate varied from 1 to 20°/min (in ω). Data were collected to $2\Theta_{max}$ of 54.0° ($2\Theta_{min}$ = 3.0°). The scan range was varied as a function of Θ to correct for the separation of the K_α doublet. The scan width was calculated as Θ_{width} = 0.50+0.30*tanΘ. Moving-crystal moving-counter background counts were made by scanning an additional 25% above and below this range. Thus the ratio of peak counting time to background counting time was 2:1. For intense reflections an attenuator was automatically inserted in front of the detector (factor = 18.0). A total of 4783 reflections were collected (h = 0 -> 14, k = -17 -> +17, l = 0 -> 15) of which 2199 were unique, non-zero and not systematically absent. Lorentz and polarization corrections were applied to the data. Due to the virtual time independence of three monitor reflexions decay correction was deemed unnecessary. The linear absorption coefficient is 0.87 cm^{-1} for M_oK_α radiation therefore no absorption correction was made. Intensities of equivalent reflections were averaged. 134 reflections were rejected from the averaging process because their intensities differed significantly from the average. The agreement factors for the averaging of the 2816 observed and accepted reflections was 5.2% based on intensity and 3.6% based on F_o. The initial structure model was derived by direct methods. Using 238 reflections (E_{min} of 1.54) and 2836 relationships, a total of 30 phase sets were produced. 23 atoms were located from an E-map prepared from the phase set with probability statistics ABS. FOM = 0.94, Ψ_o = 1.28, and RESID = 17.4. The remaining atoms were located in succeeding difference/weighted Fourier syntheses. Hydrogen atoms were positioned and added to the structure factor calculations but their positions were not refined. The structure was refined in full-matrix least-squares using 1454 reflections having $I > 3.0^* \sigma(I)$. The final cycle of refinement included 262 variable parameters and converged (largest Δ/σ was 0.182) with unweighted and weighted agreement factors of R_1 = 0.046 and R_2 = 0.059. The standard deviation of an observation of unit weight was 2.14. The final difference Fourier map showed no significant residual electron density. All calculations were performed on a PDP-11/34 128Kw minicomputer using SDP-PLUS and local programs.[26]

Glyoxal bis(benzoylhydrazone) (1):

A mixture of trimeric glyoxal dihydrate (7.85 g, 109.8 mmol glyoxal, 98 % pure) and benzoylhydrazine (29.95 g, 220 mmol) in 96 % AcOH (66 ml) was heated on a steam bath for 2 h. The material separeted was filtered off, washed with 80 % EtOH and then with water to give crude (30.45 g, 94 %) or recrystallized 1 (25.56 g, 79 %), m.p. >360° C [from DMSO with addition of water; lit.[27] m.p. ~380° C (dec.), lit.[28] m.p. >300° C]; IR (KBr, cm^{-1}) bands: 3210, 3040, 1654, 1600 and 1580, 1535.

Methylglyoxal bis(isonicotinoylhydrazone) (3):

A mixture of isonicotinic hydrazide (16.623 g, Janssen, 99 % pure, 120 mmol), methylglyoxal dimethyl acetal (7.159 g, 99 %, 60 mmol) and 96 % AcOH (5 ml) was heated on a steam bath for 100 min then cooled and diluted gradually with water (~100 ml) to give 3 (15.926 g, 85.5 %, lit.[29] yield 55 %), m.p. 287-289° C (for a reprecipitated product lit.[29] m.p. >300° C).

Methylglyoxal bis(thiosemicarbazone) (4):

a) Methylglyoxal dimethyl acetal (5.907 g, 49.5 mmol, 99 % purity) was added to a suspension of finely powdered thiosemicarbazide (9.114 g, 100 mmol) in warm 96 % AcOH (30 ml). The mixture was warmed on a steam bath for 2 h then cooled. The product was filtered off, washed successively with AcOH, 50 % AcOH, and water to give 4 (9.863 g, 91.3 %), m.p. >360° C. The crude product was purified for elemental analysis and IR spectroscopy:

i) A solution of 4 (0.2 g) in warm DMF (4 ml) or DMSO (1 ml) was diluted with water (0.7 ml and 0.4 ml, respectively).

ii) Aqueous ~2N NaOH (6 ml, ~12 mmol) was added to a suspension of 4 (1.092 g, 5 mmol) in 96 % EtOH (10 ml). The solution was filtered and acidified with AcOH (2 ml). The product precipitated was filtered off, washed with water, EtOH and hexane to give pure 4 (1.033 g); IR (KBr, cm^{-1}) bands: 3390, 3262, 3228, 3150, 2990, 1599, 1528, 1496. The crude and the recrystallized or reprecipitated 4 had identical IR spectra.

Anal. Calc. for $C_5H_{10}N_6S_2$ (218.3): C, 27.51; H, 4.62; N, 38.50; S, 29.38. Found: C, 27.86; H, 4.63; N, 38.44; S, 29.40.

b) Aqueous methylglyoxal (1.44 ml, ~5 mmol, 25 %, Fluka) was added to a solution of thiosemicarbazide (1.003 g, 11 mmol) in warm water (60 ml). The mixture was kept for 3 h at room temp. The crude product (4, 0.915 g, ~84 %) isolated as above had m.p. >360° C (lit.[30] m.p. 257° C), and was identical (IR spectrum) with that obtained in *a*).

Methylglyoxal bis(phenoxycarbonylhydrazone) (**5**):

A mixture of methylglyoxal dimethyl acetal (5.905 g, 49.5 mmol, 99 % purity), 96 % AcOH (20 ml), and phenyl carbazate (15.215 g, 100 mmol) was heated on a steam bath for 1.5 h, then cooled. The solid precipitated was filtered off, washed with 96 % and 50 % AcOH, and finally with hexane to give crude **5** (11.925 g, 70.8 %), m.p. 207-208° C (dec.). Concentration of the mother liquor afforded a second crop of **5** (3.288 g, 19 %). A solution of the crude product (2.60 g) in hot $CHCl_3$ (450 ml) was treated with fuller's earth and charcoal and then concentrated. The residue was boiled in EtOAc (50 ml) to give pure **5** (2.07 g), m.p. 208-209° C (dec.); IR (KBr, cm^{-1}) bands: 3250, 1747, 1600, 1523, 1493, 1380, 1205.

Anal. Calc. for $C_{17}H_{16}N_4O_4$ (340.3): C, 59.99; H, 4.74; N: 16.46. Found: C, 60.29; H, 4.94; N, 16.68.

Methylglyoxal bis(salicyloylhydrazone) (**6**):

A mixture of methylglyoxal dimethyl acetal (1.181 g, 9.9 mmol, 99 % purity), 96 % AcOH (7 ml), and salicyloylhydrazine (3.100 g, 20.37 mmol) was boiled for 1 h. To the crude product (3.410 g, 100 %, m.p. >365° C) suspended in a mixture of 96 % EtOH (20 ml) and water (5 ml) was added aqueous 2N NaOH (12 ml, 24 mmol). The filtered solution was acidified with 96 % AcOH (2 ml) to give pure **6** (3.224 g, 95.7 %); IR (KBr, cm^{-1}) bands: 3250, 3065, 2930, 2850, 2730, 2580, 1655(sh), 1636, 1604, 1528, 1490, 1452, 749.

Anal. Calc. for $C_{17}H_{16}N_4O_4$ (340.3): C, 59.99; H, 4.74; N, 16.46. Found: C, 60.31; H, 5.10; N, 16.14.

3,3'-Diacetyl-5,5'-diphenyl-2,2'-bi-2H-1,3,4-oxadiazolines (**7a** *and* **7b**).

A mixture of **1** (25.3 g, 85.97 mmol), anhydrous pyridine (140 ml), and Ac_2O (250 ml) was boiled until dissolution was complete (~6 h) and for an additional 1.5 h, and then kept overnight at room temp. The crystalline material separated was filtered off, washed with Ac_2O and hexane, and dried in a vacuum desiccator over P_4O_{10} and KOH to give inhomogeneous crude product (15.140 g, 46.6 %), m.p. 232° C; TLC (PhH/EtOAc 2:1): R_f 0.37 and 0.44.

The mother liquor of the crude product was concentrated (<48° C). The residue was cooled, triturated with anhydrous EtOH (20 ml) and when kept for 1 h at room temp. it was diluted gradually with hexane (25 ml). The solid was filtered off, washed with EtOH/hexane 1:2, and then with hexane. This second crop of crude product (10.790 g, 33.2 %, m.p. 212° C and 230-231° C) was stirred in $CHCl_3$ (100 ml) for 15-20 min at room temperature, the undissolved material collected by filtration was dissolved in hot $CHCl_3$ (100 ml), treated with fuller's earth and activated carbon, and the filtrate was concentrated. The residue was crystallized by boiling in EtOH (40 ml) to give homogeneous (R_f 0.37) product **7b** (2.990 g, 9.19 %), m.p. 209-210° C.

Anal. Calc. for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81. Found: C, 63.51; H, 4.92; N, 14.85.

Recrystallization of the first crop of the crude product from hot Me_2SO with addition of water (or that of the material dissolved in the $CHCl_3$ mother liquors from EtOH) afforded mixtures consisting of the isomeric components **7a** and **7b** (with R_f values 0.44 and 0.37, respectively) in various ratios.

Anal. Found: C, 63.41; H, 4.88; N, 14.79.

3,3'-Diacetyl-2'-methyl-5,5'-(4-pyridyl)-2,2'-bi-2H-1,3,4-oxadiazolines (**9a** *and* **9b**):

A mixture of **3** (15.50 g, 49.95 mmol), Ac_2O (150 ml) and anhydrous pyridine (75 ml) was heated on a steam bath until dissolution was complete (~1 h) and then for an additional 3 h, and finally concentrated (<50° C, bath). The syrupy residue was triturated with ice and water and the solid formed was, after standing overnight in the refrigerator, filtered off by suction, washed with water and then with hexane. A solution of the crude product (17.94 g, 91.06 %) in $CHCl_3$ (50 ml) was treated with fuller's earth and charcoal, then concentrated. The residue was crystallized from hot anhydrous EtOH (15 ml) with addition of heptane (40 ml) to give a mixture of isomers (^{1}H-NMR) **9a**,**b** (14.36 g, 72.9 %), m.p. 158-160° C (total melting at 184° C). When investigated by TLC the product seemed to be homogeneous in solvent mixtures 9:1 $CHCl_3$/MeOH or 95:5 $CHCl_3$/MeOH applying 3-fold and in 9:1 $CHCl_3$-Me_2CO 4-fold sequential runs.

Anal. Calc. for $C_{19}H_{18}N_6O_4$ (394.4): C, 57.86; H, 4.60; N, 21.31. Found: C, 58.23; H, 4.80; N, 21.31.

Systematic recrystallization of the above mixture (with correct analysis) from EtOH afforded pure **9a** (7.04 g, 35.7 %), m.p. 194-195° C. On TLC using solvent-system 9:1 $CHCl_3$/Me_2CO after a 4-fold sequential run this substance showed a scarcely greater migration then the above material **9a**,**b**.

5,5'-Diacetamido-3,3'-diacetyl-2'-methyl-2,2'-bi-2H-1,3,4-thiadiazoline (**10**).

A mixture of **4** (4.500 g, 20.613 mmol) in Ac_2O (45 ml) was boiled for 4.5 h, and then concentrated. The solid was filtered off, washed successively with cold Ac_2O, water, and hexane to give crude [5.984 g, 75.1 %, m.p. 280-281° C (dec.)] or recrystallized **10** (1.646 g, 20.66 %), m.p. 281-282° C (dec., from pyridine).

The pyridine mother liquor was concentrated and the residue was crystallized from hot toluene (~15 ml) to give a second crop of **10** (1.02 g, 12.8 %), m.p. 278-279° C (dec.).

Anal. Calc. for $C_{13}H_{18}N_6O_4S_2$ (386.5): C, 40.40; H, 4.70; N, 21.75; S, 16.60. Found: C, 40.37; H, 4.93; N, 21.52; S, 16.42.

ACKNOWLEDGEMENTS

Our thanks are due to Ms. M. Mörtl and M. Halász for preparing of the manuscript and to Mr. A. Fürjes for skilled technical assistance. One of us (L. S.) is indebted to the Universitas Fund of the Hungarian Trade and Credit Bank Co. for financial support of this work.

REFERENCES AND NOTES

1. D. Horton, R. G. Nickol, and O. Varela, *Carbohydr. Res.*, **1987**, *168*, 295-300.
2. J. Zemek, K. Linek, B. Kadlecikova, S. Kucar, and L. Somogyi, *Folia Microbiol. (Prague)*, **1985**, *30*, 396-399, and references cited therein.
3. H.-W. Stock and A. Hetzheim, *Pharmazie*, **1987**, *42*, 157-159, and references cited therein.
4. P. Tomasik and J. Chociej, *Pol. PL 142.796* (31 Dec 1987); *Chem. Abstr.*, **1990**, *112*, 77855w.
5. E. R. Dilanyan, T. R. Ovsepyan, F. G. Arsenyan, G. M. Stepanyan, B. T. Garibdzhanyan, G. M. Paronikyan, and L. G. Akopyan, *Khim.-Farm. Zh.*, **1989**, *23*, 602-605; *Chem. Abstr.*, **1989**, *111*, 146281z.
6. T. R. Ovsepyan, D. M. Terdzhanyan, F. G. Arsenyan, G. M. Stepanyan, B. T. Garibdzhanyan, G. M. Paronikyan, L. G. Akopyan, E. V. Kazaryan, and Yu. Z. Ter-Zakharyan, *Khim.Farm. Zh.*, **1989**, *23*, 678-682; *Chem. Abstr.*, **1990**, *112*, 611f.
7. E. K. John and M. A. Green, *J. Med. Chem.*, **1990**, *33*, 1764-1770.
8. B. G. Patil, B. R. Havinale, J. M. Shallom, and M. P. Chitnis, *J. Inorg. Biochem.*, **1989**, *36*, 107-113; *Chem. Abstr.*, **1989**, *111*, 70433c.
9. A. M. M. E. Omar, I. C. Ahmed, A. M. Hassan, O. M. Aboulwafa, H. Aboushleib, and K. A. Ismail, *Alexandria J. Pharm. Sci.*, **1990**, *4*, 182-186; *Chem. Abstr.*, **1991**, *114*, 143216h.
10. F. Klages, *Lehrbuch der Organischen Chemie*, Vol. I/1, Walter de Gruyter and Co., Berlin, **1952**, 442.
11. L. Hough and A. C. Richardson in S. Coffey (Ed.), *Rodd's Chemistry of Carbon Compounds*, 2nd edn., Elsevier Publ. Co., Amsterdam **1967**, *I/F*, 253-255.
12. *The Merck Index*, 10th edn., Merck and Co., Inc., Rahway, N. J. USA, **1983**.
13. V. S. Alekseev and N. V. Alekseeva, *Ukr. Biokhim. Zh.*, **1990**, *62*, 13-22, and references cited therein; *Chem. Abstr.*, **1990**, *113*, 3856w.
14. V. N. Yandovskii, *Zh. Org. Khim.*, **1976**, *12*, 1093-1096, and references cited therein.
15. S. Kubota, K. Fujikane, M. Uda, and T. Yoshioka, *Heterocycles*, **1976**, *4*, 1909-1912.
16. S. Kubota, Y. Ueda, K. Fujikane, K. Toyooka, and M. Shibuya, *J. Org. Chem.*, **1980**, *45*, 1473-1481, and references cited therein.
17. S. Andreae, E. Schmitz, and H. Seeboth, *J. Prakt. Chem.*, **1986**, *328*, 205-214.
18. L. Somogyi, *Carbohydr. Res.*, **1977**, *54*, C14-C16.
19. L. Somogyi, *Carbohydr. Res.*, **1987**, *165*, 318-324.
20. L. Somogyi, *Symp. Pap. - IUPAC Int. Symp. Chem. Nat. Prod. 11th*, **1978**, *3*, 178-180 (N. Marekov and A. Orahovats, Eds.) - Izd. BAN, Sofia.
21. L. Somogyi, *Carbohydr. Res.*, **1979**, *75*, 325-330.
22. L. Somogyi, *Carbohydr. Res.*, **1988**, *182*, 19-29, and references cited therein.
23. K. Toyooka, Y. Takeuchi, Z. Taira, and S. Kubota, *Heterocycles*, **1989**, *29*, 1233-1236.
24. D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **1967**, *89*, 5315-5318.
25. R. Benassi, U. Folli, L. Schenetti, and F. Taddei, *Adv. Heterocycl. Chem.*, **1987**, *41*, 75-186.
26. B. A. Frenz, *The Enraf-Nonius CAD 4 SDP - A Real-Time System for Concurrent X-Ray Data Collection and Crystal Structure Determination*, in Computing in Crystallography, H. Schenk, R. Olthof-Hazekamp, H. van Koningsveld, and G. C. Bassi, Eds. Delft University Press. Deft, Holland, **1978**, 64-71. Supplementary material available. Tables of atomic coordinates, bond distances and angles and torsion angles for non-hydrogen atoms, all with their estimated standard deviations.
27. G. Pinkus, *Ber.*, **1898**, *31*, 31-37.
28. H. v. Pechmann and W. Bauer, *Ber.*, **1909**, *42*, 659-674.
29. H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, and J. Bernstein, *J. Am. Chem. Soc.*, **1953**, *75*, 1933-1942.
30. C. Neuberg and M. Kobel, *Biochem. Z.*, **1927**, *188*, 211-216; *Beilst.*, *3 II*, 135.