Tetramido Derivatives of Glyoxal

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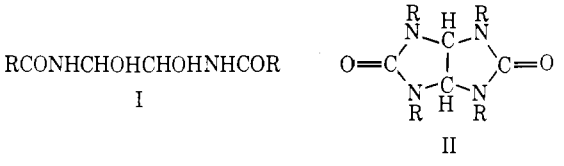
Nine glyoxal tetramides (III) were prepared by acid-catalyzed condensation of glyoxal with aliphatic, aromatic, and heterocyclic amides. Methylglyoxal (pyruvic aldehyde) and phenylglyoxal formed bisamides.

Although glyoxal is known to react with amides to form adducts of structure **I** (*7*) and with ureas to give glycolurils (**II**) (*5, 6*), glyoxal tetramides (**III**) have not been reported, except for a recent reference (noted after completion of the present study) to the benzamido derivative (**IIIe**) (*4*).



I II

Since the tetramides were required as part of a study (*2, 3*) of the acid-catalyzed reactions of aldehydes with amides, we first attempted to prepare them by the published procedures (*5, 6*) found suitable for making glycolurils. When these attempts proved fruitless, attention was turned to the procedure recently developed at this laboratory (*3*) for converting dialdehydes other than glyoxal to the tetramido derivatives by acid-catalyzed condensation with amides in boiling toluene. This approach was also unsuccessful, until it was found that glyoxal, unlike the other dialdehydes, requires the use of excess amide to obtain appreciable yields of the tetramides from aliphatic amides:

$$4\ RCONH_2 + CHOCHO \xrightarrow{H^+} (RCONH)_2CHCH(NHCOR)_2 + 2\ H_2O$$

III

Stoichiometry appeared less crucial in the reaction of glyoxal with aromatic amides, however.

The compounds, obtained in 20–83% yields (Table I), are all high-melting solids with low solubility in most organic solvents. The amides used include aliphatic, aromatic, and heterocyclic; efforts to react 3,5-dinitrobenzamide, *N*-methylbenzamide, or ethyl oxamate were unsuccessful. Pyruvic aldehyde (methylglyoxal) and phenylglyoxal yielded bisamides [$R'COCH(NHCOR)_2$, R′ = CH_3 (**IVa**) and C_6H_5 (**IVb**), respectively], apparently by reaction with the aldehyde, but not with the ketone group. This structure is similar to that recently reported for the reaction product of phenylglyoxal with methylurethane (*1*) and is consistent with our failure to obtain a reaction between cyclohexanone and acetamide, as reported previously (*2*). Concentrated sulfuric acid is a satisfactory substitute for methanesulfonic; trifluoromethanesulfonic acid or boron fluoride–acetic acid complex proved unsuitable. Glyoxal was applied as the 80% solid; use of the 40% aqueous solution in the case of benzamide gave a much lower yield of tetramide **IIIe**, as was also noted recently by others (*4*).

Experimental

Melting points were taken in a Mel-Temp apparatus and are uncorrected. Ir spectra (KBr) were determined with a Perkin-Elmer Model 457 A spectrophotometer. Nmr spectra were determined on a Varian T-60 spectrometer by using tetramethylsilane as internal reference, unless otherwise indicated. Microanalyses were run by Schwarzkopf Microanalytical Laboratory. Glyoxal (80% solid) was obtained from Centerchem Products Inc., 350 Fifth Ave., New York, N.Y. 10001.

The following typical procedure incorporates minor changes over that used for reacting amides with other dialdehydes (*3*): 1,1,2,2-tetrakis(acetamido)ethane (**IIIa**).

A mixture of acetamide (12 grams, 200 mmol), methanesulfonic acid (6 drops), and toluene (200 ml) was heated to about 50° with magnetic stirring, and 80% glyoxal (1.8 grams, 25 mmol) was added. The flask was then equipped for distillation, and the mixture was heated, with stirring, rapidly to distillation temperature. About 80 ml of toluene–water mixture was distilled over a period of 10 min. The solid product began to separate after about 5 min. The reaction mixture was cooled, filtered,

Table I. Glyoxal Amides[a]

	R	Mol amide/mol glyoxal	Yield[b]	Mp, °C[c]	Formula
IIIa	CH_3	8	19[d]	370 dec[e]	$C_{10}H_{18}N_4O_4$ (258.3)
b	C_2H_5	8	38	366	$C_{14}H_{26}N_4O_4$ (314.4)
c	*n*-C_3H_7	8	54[f]	348	$C_{18}H_{34}N_4O_4$ (370.5)
d	2-Furyl	4	21	328	$C_{22}H_{18}N_4O_8$ (466.4)
e	C_6H_5	4	67[g]	332[h]	$C_{30}H_{26}N_4O_4$ (506.5)
f	2-$CH_3C_6H_4$	4	40[i]	356	$C_{34}H_{34}N_4O_4$ (562.6)
g	4-$CH_3C_6H_4$	4	20	337	$C_{34}H_{34}N_4O_4$ (562.6)
h	4-ClC_6H_4	4	20	353	$C_{30}H_{22}Cl_4N_4O_4$ (644.3)
i	4-$CH_3OC_6H_4$	4	45	323	$C_{34}H_{34}N_4O_8$ (626.6)
IVa	C_6H_5[j]	2	3	212[k]	$C_{17}H_{16}N_2O_3$ (296.3)
b	C_6H_5[l]	2.5	79	243[m]	$C_{22}H_{18}N_2O_3$ (358.4)

[a] Elemental analyses (C, H, N) in agreement with theoretical values have been obtained and were submitted for review. [b] Mol % acetone-washed crude based on glyoxal. [c] After recrystallization from *N,N*-dimethylformamide, except as indicated. [d] Four moles of amide gave 0.8–7.7% yields. [e] Recrystallized from dimethyl sulfoxide. [f] Four moles of amide gave a 2.7% yield. [g] Two moles of amide gave an 83% yield. [h] Ref. 4 reports 323–4°. [i] Two moles of amide gave a 33% yield. [j] Formed a bisamide with pyruvic aldehyde (methylglyoxal). [k] Recrystallized from *n*-butanol. [l] Formed a bisamide with phenylglyoxal. [m] Recrystallized from isopropanol.

and sucked dry. The filter cake was removed, triturated with 50 ml acetone, and filtered. Yield and other data are given in Table I.

For the preparation of compounds **IVa** and **b**, respectively, pyruvic aldehyde (methylglyoxal) was used as the 40% aqueous solution and phenylglyoxal as the monohydrate. These aldehydes required a reaction time of 30–45 min.

The ir spectra of all compounds agreed with the assigned structures, with secondary amide absorption being noted in the ranges 1530–1580, 1630–1660, and 3280 cm^{-1}. In addition, compounds **IIIe–i** and **IVa** and **b** gave bands characteristic of the respective aromatic substitution. Compound **IVa** showed absorption at 1725 and 1370 cm^{-1}, characteristic of the carbonyl and acetyl groups, respectively. *IVb* gave carbonyl absorption at 1690 cm^{-1}.

Confirmatory proton nmr spectra were obtained as follows: **IVa:** (DMSO-d_6), δ 2.25 (s, CH_3CO), 6.17–5.92 (t, —CH, J = 7 Hz), 8.03–7.40 (m, 10H, C_6H_5), 9.17–9.03 (d, 2H, —NH, J = 7 Hz). **IVb:** (DMSO-d_6), δ 7.15–7.04 (t, —CH, J = 7 Hz), 8.12–7.42 (m, 15H, C_6H_5), 9.30–9.18 (d, 2H, —NH, J = 7 Hz).

Attempts to obtain mass spectral data were unsuccessful because of the instability of the compounds at the required temperature.

Acknowledgment

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Synthesis of *N*-Aryl-*N'*-2-naphthiazolylguanidines

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The experimental conditions for the synthesis of naphthiazolylguanidines are given.

Because guanidine derivatives possess a high degree of biological activity (*1*, *2*), it was thought worthwhile to synthesize some naphthiazolylguanidines.

Experimental

***N*-Phenyl-*N'*-2-naphthiazolylthiocarbamide.** Phenylisothiocyanate (3 ml) and 2-aminonaphthiazole (5 grams) were refluxed for 2 hr. The excess phenylisothiocyanate and 2-aminonaphthiazole were removed by washing several times with petroleum ether and ether. The thiocarbamide thus obtained was crystallized from EtOH, mp 161°, yield 75%. Similarly, various substituted *N*-aryl-*N'*-2-naphthiazolylthiocarbamides were prepared (Table I).

***N*-Phenyl-*N'*-2-naphthiazolylguanidine.** *N*-phenyl-*N'*-2-naphthiazolylthiocarbamide quantitatively formed the corresponding guanidine when heated with yellow lead oxide and ethanolic NH_3 in a sealed tube at 110°C. The product was crystallized from 50% EtOH, mp 185°. Similarly, various aryl-substituted *N*-aryl-*N'*-2-naphthiazolylguanidines and their hydrochlorides were prepared (Table II).

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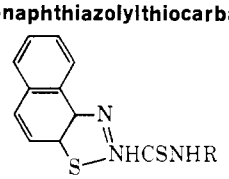
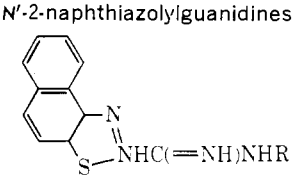
Table I. *N*-Aryl-*N'*-2-naphthiazolylthiocarbamides



S No.	Nature of R	Mp, °C	Molecular formula[a]
1	o-MeC_6H_4	135	$C_{19}H_{15}N_3S_2$
2	m-MeC_6H_4	132	$C_{19}H_{15}N_3S_2$
3	p-MeC_6H_4	158	$C_{19}H_{15}N_3S_2$
4	o-$OMeC_6H_4$	141	$C_{19}H_{15}N_3OS_2$
5	m-$OMeC_6H_4$	135	$C_{19}H_{15}N_3OS_2$
6	p-$OMeC_6H_4$	120	$C_{19}H_{15}N_3OS_2$
7	p-$OEtC_6H_4$	159	$C_{20}H_{17}N_3OS_2$
8	p-ClC_6H_4	164	$C_{16}H_{12}ClN_3S_2$

[a] All compounds analyzed satisfactorily for N,S.

Table II. *N*-Aryl-*N'*-2-naphthiazolylguanidines



S No.	Nature of R	Mp, °C	Molecular formula[a]	Mp, °C, hydrochloride	Molecular formula, hydrochloride
1	o-MeC_6H_4	141	$C_{19}H_{16}N_4S$	253–54	$C_{19}H_{17}ClN_4S$
2	m-MeC_6H_4	177	$C_{19}H_{16}N_4S$	185	$C_{19}H_{17}ClN_4S$
3	p-MeC_6H_4	175	$C_{19}H_{16}N_4S$	204–205	$C_{19}H_{17}ClN_4S$
4	o-$OMeC_6H_4$	175	$C_{19}H_{16}N_4OS$	195	$C_{19}H_{17}ClN_4OS$
5	m-$OMeC_6H_4$	169	$C_{19}H_{16}N_4OS$	180	$C_{19}H_{17}ClN_4OS$
6	p-$OMeC_6H_4$	171	$C_{19}H_{16}N_4OS$	190	$C_{19}H_{17}ClN_4OS$
7	p-$OEtC_6H_4$	165	$C_{20}H_{18}N_4OS$	185	$C_{20}H_{19}ClN_4OS$
8	p-ClC_6H_4	175	$C_{18}H_{13}ClN_4S$	181–82	$C_{18}H_{14}Cl_2N_4S$

[a] All compounds analyzed satisfactorily for N,S.