Tetraamides Derived from Dialdehydes

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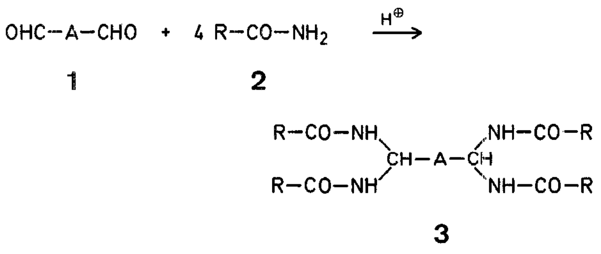
Although bis-amides derived from monoaldehydes are well known[1,2], the analogous derivatives of dialdehydes have apparently not been made. A brief study of their preparation was accordingly undertaken, since such compounds were required as part of a program on acid-catalyzed aldehyde-amide reactions[3].

It was found that dialdehydes (**1**) react easily with carboxamides (**2**) upon heating with an acid catalyst, forming the desired tetraamide derivatives (**3**).

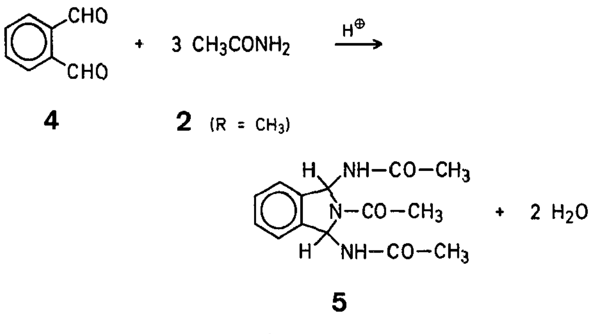


$$OHC{-}A{-}CHO + 4\ R{-}CO{-}NH_2 \xrightarrow{H^{\oplus}} (R{-}CO{-}NH)_2CH{-}A{-}CH(NH{-}CO{-}R)_2$$

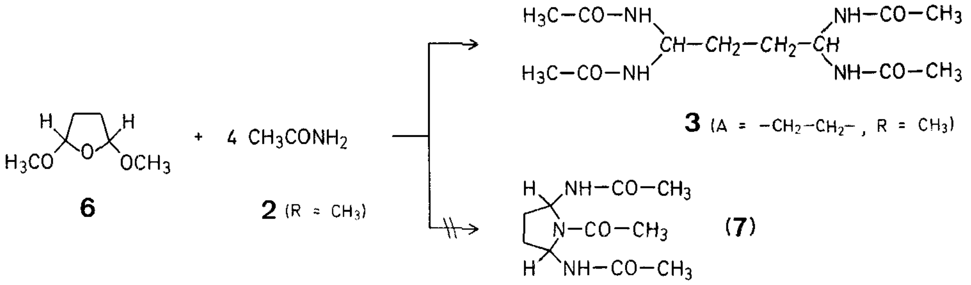
1 **2** **3**

The procedure involves boiling toluene as the reaction medium with a sulfonic acid catalyst, a method developed recently in this laboratory[2] as an improved approach to the preparation of monoaldehyde bis-amides. The tetraamides are insoluble in cold toluene and are isolated, generally in good yield, by simple filtration of the reaction mixture. The compounds so prepared are listed in Table 1. They are all high-melting solids, with the aliphatic derivatives dissolving easily in water or acetic acid, but with poor solubility in organic solvents. The aromatic analogues are easily soluble only in hexafluoroisopropanol.

Although dialdehydes (**1**) were employed in most cases, the corresponding tetramethyl acetal was used to prepare the malonaldehyde derivatives (**3a**, **3g**, **3h**). Three of the aromatic dialdehydes gave the expected tetraamide derivatives (**3d**, **3e**, **3f**). *o*-Phthalaldehyde (**4**), on the other hand, formed 2-acetyl-1,3-bis-[acetamido]-isoindoline (**5**).



Reynolds and coworkers[4] recently also noted the facile formation of this ring system, as in N-acetyl-1,3-dihydroxyisoindoline, from the same reagents under alkaline conditions. It is interesting that similar cyclization to give **7** was not noted from the reaction of acetamide with 2,5-dimethoxytetrahydrofuran (**6**).



Attempts to prepare a tetraamide from glyoxal, or from its tetraallyl acetal, were unsuccessful.

As shown in Table 1, acetamide was used in most cases. Attempts to react 1,1,3,3-tetramethoxypropane with formamide or with N-methylacetamide were unsuccessful, as was noted previously using the same procedure with paraformaldehyde[2]. Although stearamide combines easily with paraformaldehyde[2], attempts to react it either with terephthalaldehyde or with 1,1,3,3-tetramethoxypropane were fruitless, even at higher temperatures and catalyst concentrations.

Melting points were taken in a Mel-Temp apparatus and are uncorrected. I.R. spectra (KBr) were determined with a Perkin-Elmer Model 21 spectrophotometer. N.M.R. spectra were determined on a Varian T-60 spectrometer using tetramethylsilane as internal reference unless otherwise indicated. Microanalyses were run by Schwarzkopf Microanalytical Laboratory.

1,1,3,3-Tetrakis-[acetamido]-propane (3a):

A mixture of 1,1,3,3-tetramethoxypropane (8 g, 50 mmol), acetamide (6 g, 100 mmol), *p*-toluenesulfonic acid monohydrate (0.5 g), and toluene (200 ml) was heated rapidly to distillation temperature with magnetic stirring. About 30 ml of toluene-methanol mixture was distilled over a period of 15 min. The solid product began to separate after $\sim$5 min, and the mixture became quite thick as reaction proceeded. The reaction mixture was cooled, filtered, and dried; yield: 6 g (88%). I.R. and N.M.R. spectra are discussed below.

Attempted use of other solvents for preparing **3a** (benzene, acetic acid, or sulfolane) gave inferior results in the first case, and no product with the other two materials. No improvement resulted from changing the stoichiometry of the reagents or from doubling the volume of toluene. Use of the stated quantity of sulfonic acid is fairly critical, since no reaction occured with half the given amount, and darkening resulted with double the quantity. Equivalent methanesulfonic acid or sulfuric acid gave similar results.

The other compounds listed in Table 1 were prepared similarly with minor variations. In the case of **3b**, a 4:1 molar ratio of acetamide: 2,5-dimethoxytetrahydrofuran was used with 25 mmol methanesulfonic acid per mol amide; no product was formed with half the quantity of catalyst. In the preparation of **3c**, 25% aqueous glutaraldehyde was employed; toluene (100 ml) plus water was distilled over a 30 min period. Compound **3h** was prepared in refluxing benzene (without distillation) for 20 min. Concentrated hydrochloric acid (15 mmol per mol amide) was employed as catalyst, since earlier work[2] had shown that sulfonic acids induce polymerization.

The I.R. spectra of all compounds agreed with the assigned structures, with secondary amide absorption being noted in the ranges 1515–1570, 1640–1670, and 3220–3300 cm^{-1}. In addition, compounds **3d**, **3e**, **3f**, and **5** gave characteristic bands at 698, 803, 833, 855, 850, and 758 cm^{-1}, corresponding to the respective disubstituted aromatic rings. Compound **3g** showed monosubstituted aromatic absorption at 695 and 715 cm^{-1}, and compound **3h** at 808 cm^{-1} corresponding to a conjugated double bond.

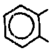
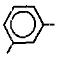
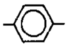
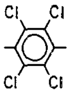
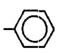
Proton N.M.R. spectra were determined on compounds with sufficient solubility.

3a: (D_2O/DSS), $\delta = 5.62$ (t, 2H, $J = 8$ Hz, CH), 2.13 (t, 2H, $J = 8$ Hz, CH_2), 2.00 (s, 12H, CH_3).

3c: (D_2O/DSS), $\delta = 5.38$ (broad m, 2H, CH), 2.00 (s, 12H, CH_3), 1.58 (broad m, 6H, CH_2).

5: (DMSO-d_6), $\delta = 8.33$ (broad s, 2H, NH), 7.40 (broad s, 4H, aromatic), 6.70 (broad s, 2H, $C\underline{H}$—N—$C\underline{H}$), 2.10 (s, 3H, N—CO—CH_3), 1.92 (s, 6H, NH—CO—$C\underline{H}_3$).

Table 1. Products Obtained from the Reaction of Dialdehydes (**1**) with Carboxamides (**2**)

A	R	Catalyst[a]	Product	Crude yield %	Recrystallization solvent	m. p.	Analyses
$-CH_2-$ [b]	CH_3	T	**3a**	88	DMF	285–287° (dec.)	calc. C 48.6 H 7.4 N 20.6 found 48.3 7.4 20.6
$-CH_2-CH_2-$ [c]	CH_3	M	**3b**	70	water	315–320° (dec.)	calc. C 50.3 H 7.7 N 19.6 found 50.3 7.9 19.5
$-CH_2-CH_2-CH_2-$ [d]	CH_3	T	**3c**	5	DMF	244–246°	calc. C 52.0 H 8.0 N 18.7 found 51.7 7.8 18.6
	CH_3	M	**5**	95	butanol	232–235° [e] (dec.)	calc. C 61.1 H 6.2 N 15.3 found 60.9 6.2 15.1
	CH_3	M	**3d**	75	water/hexafluoroisopropanol	315–317° (dec.)	calc. C 57.5 H 6.6 N 16.8 found 57.8 6.6 16.5
	CH_3	T	**3e**	97	DMF	400°	calc. C 57.5 H 6.6 N 16.8 found 57.4 6.7 16.5
	CH_3	M	**3f**	6	water/hexafluoroisopropanol	380°	calc. C 40.7 H 3.8 N 11.9 found 40.8 3.8 11.6
$-CH_2-$ [b]		S	**3g**	68	DMF	270–273°	calc. C 71.4 H 5.4 N 10.8 found 71.7 5.6 11.1
$-CH_2-$ [b]	$-CH=CH_2$	H	**3h**	58	DMF	305–310° (dec.)	calc. C 56.3 H 6.3 N 17.5 found 56.3 6.5 17.7

[a] T = *p*-toluenesulfonic acid; M = methanesulfonic acid;
S = *p*-toluenesulfonic acid made *in situ* from sulfuric acid;
H = conc. hydrochloric acid.

[b] 1,1,3,3-Tetramethoxypropane was used.

[c] 2,5-Dimethoxytetrahydrofuran was used.

[d] 25% aqueous glutaraldehyde was used.

[e] This compound decomposed without melting.

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[1] H. E. Zaugg, W. B. Martin, *α-Amidoalkylations at Carbon*, Org. Reactions **14**, 52 (1965).

[2] E. E. Gilbert, Synthesis **1972**, 30.

[3] Previous papers: E. E. Gilbert, J. Heterocyclic Chem. **8**, 327 (1971); and Ref. 2.

[4] R. D. Reynolds, D. L. Arendsen, D. F. Guanci, R. F. Wickham, J. Org. Chem. **35**, 3940 (1970).