Bicyclic Amide Acetals. Synthesis and Reactions

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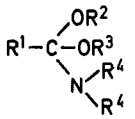
The synthesis and properties of bicyclic amide acetals, a new class of very reactive compounds, are reviewed. The reactions of the bicyclic amide acetals described have a wealth of possibilities for the preparation of new classes of substances.

Es wird eine Übersicht über Synthese und Eigenschaften von bicyclischen Amidacetalen, einer neuen Klasse sehr reaktionsfähiger Verbindungen, gegeben. Die beschriebenen Reaktionen der bicyclischen Amidacetale zeigen eine Fülle präparativer Möglichkeiten zur Herstellung neuer Substanzklassen.

Carboxylic acid amide acetals (**1**) were first prepared in 1956 by Meerwein et al.[1]:

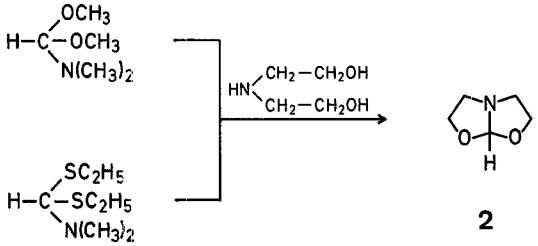


1

1a $R^1 = H$

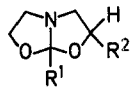
In the years that followed, methods of preparation and reaction possibilities, chiefly of the formamide acetals (**1a**), were investigated by the groups of Meerwein, Bredereck, and Eilingsfeld[2]. In this connection, reference should be made to the recent review article on the preparation and use of open-chain amide acetals by Gloede, Haase, and Gross[3].

The bicyclic amide acetal **2**, 4,6-dioxa-1-azabicyclo-[3.3.0]octane, was prepared in 1964 by Arnold and Kornilov[4] by transacetalization of dimethylformamide dimethyl acetal and in 1965 by Ivanova et al.[5] from dimethylformamide diethyl mercaptal and diethanolamine in 90 and 50% yields, respectively:



2

The present review deals with the synthesis and the properties of a new class of bicyclic amide acetals having the structure **3**, which have been investigated in the author's laboratory in recent years:



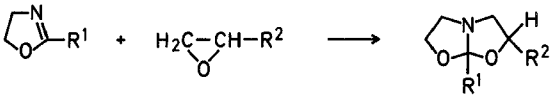
3

The synthesis of bicyclic amide acetals ring-homologous to **3**, bicyclic O,N amide acetals as well as bicyclic thioamide acetals, is likewise dealt with, although there have so far been no investigations of the reactions of these compounds.

1. Preparation of Bicyclic Amide Acetals

1.1. Addition of Epoxides to Δ^2-1,3-oxazolines

The bicyclic amide acetals **3**, 4,6-dioxa-1-azabicyclo-[3.3.0]octanes, are obtained in good yields by addition of epoxides (**5**) to Δ^2-1,3-oxazolines (**4**) at 120–200°[6,7]:



4 **5** **3**

Addition of a catalyst such as lithium chloride is favourable, but is not necessary in all cases. Instead of epoxides there can also be employed, for example, cyclic carbonates of 1,2-diols.

The formation of the 4,6-dioxa-1-azabicyclo[3.3.0]-octanes (**3**) is a further example of a cycloaddition of epoxides to unsaturated systems. Thus, additions of epoxides to aldehydes and ketones[8], lactones[9], nitriles[10], isocyanates[11,12,13], isothiocyanates[14,15], carbodiimides[16], and aldimines[17] are known[18], while the previously known reactions of Δ^2-1,3-oxazolines predominantly proceed with ring opening[7,19,20,21]. Only very recently has a further 2,3-addition to Δ^2-1,3-oxazolines, with maleic anhydride, been observed[22].

The 4,6-dioxa-1-azabicyclo[3.3.0]octanes prepared from epoxides and Δ^2-1,3-oxazolines are summarized in Table 1.

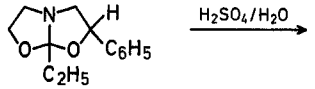
3,5-Dimethyl-4,6-dioxa-1-azabicyclo[3.3.0]octane (**3**, $R^1 = R^2 = CH_3$) : A mixture of 2-methyl-Δ^2-1,3-oxazoline (2125 g, 25 mol), 1,2-epoxypropane (1450 g, 25 mol), and lithium chloride (10.5 g, 1 mol %, on oxazoline) is heated at 120° for 10 hr under nitrogen in a 10-l autoclave. After cooling and venting the autoclave, the reaction mixture is distilled at a vacuum of 9–12 mm via an 80-cm column (packed with Raschig rings) at a reflux ratio of ~1:5. As the main fraction there is obtained 2073 g (58%) of 3,5-dimethyl-4,6-dioxa-1-azabicyclo[3.3.0]octane; b.p. 67°/10 mm. The fore-run consists mainly of unreacted oxazoline (oxazoline conversion: 88%); a brown viscous distillation residue is also obtained.

Table 1. 4,6-Dioxa-1-azabicyclo[3.3.0]octanes (3) from Epoxides (5) and Δ^2-1,3-Oxazolines (4)

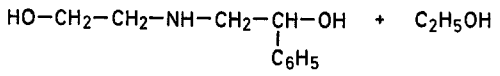
R^1	R^2	Yield %	b.p./mm	m.p.(n_D^{20})
CH_3	H	25	65°/11	(1.4560)
CH_3	CH_3	58	67°/10	(1.4471)
CH_3	C_6H_5	17	85–87°/0.05	(1.5321)
CH_3	$-CH_2-O-C_6H_5$	48	116–120°/0.1	74.5–75.5°
CH_3	$-CH_2-O-CH_2-CH=CH_2$	50–60	88°/0.1	(1.4671)
C_2H_5	H	30–40	72°/12	(1.4570)
C_2H_5	CH_3	40–50	77°/12	(1.4499)
C_2H_5	C_6H_5	62	90–92°/0.05	(1.5278)
C_2H_5	$-CH_2-O-C_6H_5$	69	121°/0.1	64.5°
C_2H_5	$-CH_2-O-CH_2-CH=CH_2$	36	65–67°/0.03	(1.4669)
n-C_3H_7	$-CH_2-O-C_6H_5$	57	145–147°/0.6	53–54°
i-C_3H_7	$-CH_2-O-C_6H_5$	60–70	132°/0.2	59–63°
C_6H_5	H	17	79–80°/0.03	(1.5379)
C_6H_5	C_6H_5	20–30	159°/0.05	(1.5828)
C_6H_5	$-CH_2-O-C_6H_5$	37	196°/0.6	82.5°
C_2H_5	$-CH_2-O-C_{12}H_{25}$	20	148°/0.05	(1.4586)

The structure of the bicyclic amide acetals **3** follows unequivocally from elemental analysis, I.R. and N.M.R. spectra, and degradation experiments. The I.R. spectra of the products **3** show that the bands typical of the Δ^2-1,3-oxazoline double bond have disappeared[7,23]. In the 900–1150 cm^{-1} range there appears a strongly structured maximum which is ascribed to the ring structure of the compounds **3**.

By hydrolytic degradation of **3a** there is obtained, besides propanoic acid, the diethanolamine derivative **6**, the structure of which is confirmed by synthesis from styrene oxide (**8**) and ethanolamine (**7**) by the method of Emerson[24]:



3a



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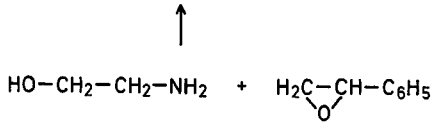
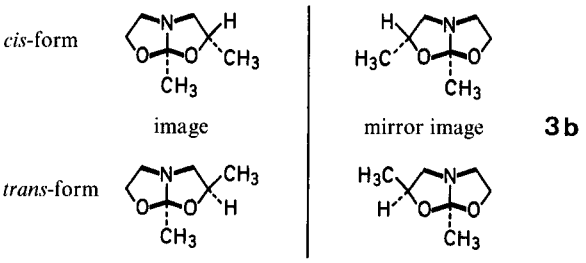


7 **8**

This reaction sequence proves that the cleavage of the epoxide ring in **5** takes place at the unsubstituted carbon atom, so that the substituent originating from the epoxide is located in the 3-position in **3**. Such a cleavage of the epoxide ring has been observed on numerous occasions in epoxide reactions[11,12,14].

The 3,5-disubstituted 4,6-dioxa-1-azabicyclo[3.3.0]-octanes exist as isomer mixtures. Thus, for example, for 3,5-dimethyl-4,6-dioxa-1-azabicyclo[3.3.0]octane (**3b**) one can consider a *cis* and *trans* form, each of which must be capable of resolution into optical antipodes:



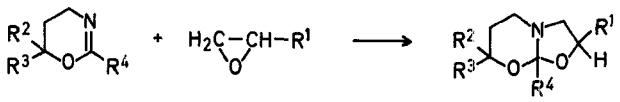
3b

Gas-chromatographic separation into the isomers has not been possible with **3b**, but the N.M.R. spectrum of **3b** indicates two isomers in a ratio of ~70:30. According to the N.M.R. data it is probable that the *trans* and *cis* forms are indicated in this case. Thus, the 3-methyl group of **3b** gives two doublets at 8.83 τ (*trans* form?) and 8.67 τ (*cis* form?) with coupling constants of 6 and 3.5 Hz, respectively (solvent CCl_4, apparatus Varian A 60 A).

[1] H. Meerwein et al., Chem. Ber. **89**, 2060 (1956).
[2] see the Literature cited in Ref.[3].
[3] J. Gloede, L. Haase, H. Gross, Z. Chem. **9**, 201 (1969); see also, R. H. De Wolfe, *Carboxylic Acid Derivatives*, in: *Organic Chemistry, A Series of Monographs*, Vol. 14, Academic Press, New York·London, 1970, p. 420.
[4] Z. Arnold, M. Kornilov, Collect. Czech. Chem. Commun. **29**, 654 (1964).
[5] I.A. Ivanova, B.P. Fedorov, F.W. Stoyanovich, Izv. Akad. Nauk SSSR, Ser. Khim. **1965**, 2179; C.A. **64**, 12538 (1966).
[6] R. Feinauer, W. Seeliger, Liebigs Ann. Chem. **698**, 174 (1966).
[7] W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, H. Hellmann, Angew. Chem. **78**, 913 (1966); Angew. Chem., Internat. Edit. **5**, 875 (1966).
[8] M.T. Bogert, R.O. Roblin, J. Amer. Chem. Soc. **55**, 3741 (1933).
[9] K. Bodenbenner, Liebigs Ann. Chem. **623**, 183 (1959).

1.2. Addition of Epoxides to 5,6-Dihydro-4*H*-1,3-oxazines

5,6-Dihydro-4*H*-1,3-oxazines (**9**) add epoxides (**5**) analogously to the Δ^2-1,3-oxazolines (**4**) to yield 5,7-dioxa-1-azabicyclo[4.3.0]nonanes (**10**)[6]:



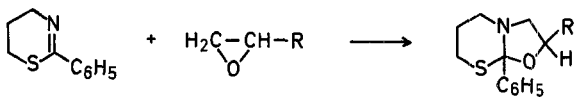
9 **5** **10**

The compounds **10** behave similarly to the bicyclic amide acetals **3** (for example, they are readily hydrolyzed with aqueous mineral acids). The structure of **10** follows unequivocally from elemental analysis and I.R. and N.M.R. spectra. The typical double bond bands of the starting materials **9** are absent from the I.R. spectra[7,23,25]; the spectra display the same characteristics as those of the compounds **3**.

1.3. Addition of Epoxides to Δ^2-1,3-Thiazolines and 5,6-Dihydro-4*H*-1,3-thiazines

One would expect to obtain thio analogs of the compounds **3** and **10** when epoxides are added to Δ^2-1,3-thiazolines (**13**) or 5,6-dihydro-4*H*-1,3-thiazines (**11**).

When the epoxides **5a** and **5b** were reacted with 2-phenyl-5,6-dihydro-4*H*-1,3-thiazine (**11**) the 7-oxa-5-thia-1-azabicyclo[4.3.0]nonanes (**12a, b**) were isolated in yields of 25 and 28%, respectively[26]:

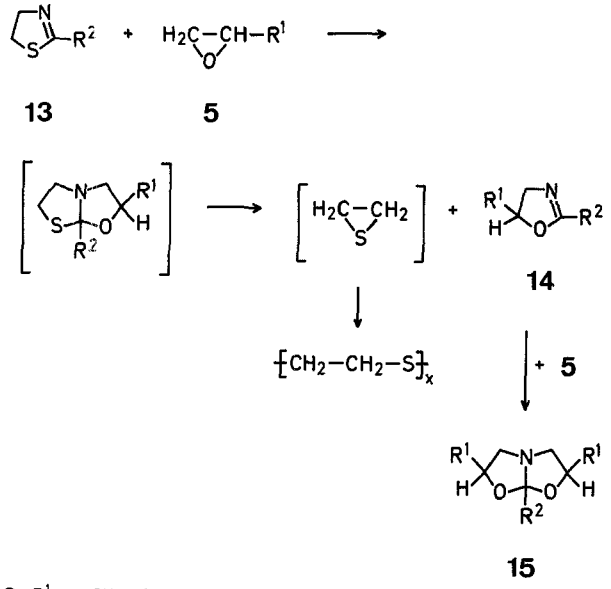


11 **5** **12**

a R = $-CH_2-O-C_6H_5$

b R = $-CH_2-O-CH_2-CH=CH_2$

On the other hand, the reaction of epoxides (**5**) with Δ^2-1,3-thiazolines (**13**) proceeds in a different manner and leads via the following probable mechanism to 2,5-disubstituted Δ^2-1,3-oxazolines (**14**)[26]:



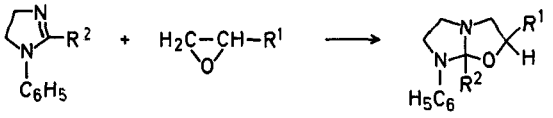
13 **5**

c R^1 = $-CH_2-O-CH_2-CH=CH_2$
R^2 = $-CH_3$

It is assumed that 1:1 addition products are intermediately formed and that, with loss of ethylene sulfide (which polymerizes under the reaction conditions), these are converted into the 2,5-disubstituted Δ^2-1,3-oxazolines (**14**), which can be isolated in yields of up to 30%. Since the Δ^2-1,3-oxazolines (**14**) can in turn add excess epoxide (**5**), there exists the possibility of further reaction to give the trisubstituted bicyclic amide acetals **15**. Thus, compound **15c** was prepared in 22% yield (on epoxide) by reaction of allyl glycidyl ether (**5c**) and 2-methyl-Δ^2-1,3-thiazoline (**13c**)[26].

1.4. Addition of Epoxides to Δ^2-Imidazolines

The addition of epoxides (**5**) to Δ^2-imidazolines (**16**) proceeds particularly smoothly and with good yields to give the bicyclic amide O,N acetals (aminal esters) **17**[27,28]:



16 **5** **17**

4-Oxa-1,6-diazabicyclo[3.3.0]octanes (17); General Procedure: The starting materials (**5** and **16**) are heated to 90–150° without solvent and the resulting products **17** are isolated by distillation in vacuo.

[10] R. Oda, M. Okano, S. Tokiura, F. Misumi, Bull. Chem. Soc. Japan **35**, 1219 (1962).
[11] K. Gulbins, G. Benzing, R. Maysenhölder, K. Hamann, Chem. Ber. **93**, 1975 (1960).
[12] G.P. Speranza, W. Peppel, J. Org. Chem. **23**, 1922 (1958).
[13] M.L. Weiner, J. Org. Chem. **26**, 951 (1961).
[14] R. Feinauer, M. Jacobi, K. Hamann, Chem. Ber. **98**, 1782 (1965).
[15] V.S. Étlis, A.P. Sineokov, G.A. Razuvaev, Zh. Obshch. Khim. **34**, 4018, 4090 (1964); Engl. Edit., p. 4076, 4149.
[16] K. Gulbins, K. Hamann, Chem. Ber. **94**, 3287 (1961).
[17] R. Oda, M. Okano, S. Tokiura, A. Miyasu, Bull. Chem. Soc. Japan **35**, 1216 (1962).
[18] L.N. Grobov, A.P. Sineokov, V.S. Étlis, Uspekhi Khimii **35**, 1574 (1966); Russian Chem. Rev. **35**, 671 (1966).
[19] R.H. Wiley, L.L. Bennett, Chem. Rev. **44**, 447 (1949).
[20] J.W. Cornforth, *Oxazole and its Derivatives*, in: R.C. Elderfield, *Heterocyclic Compounds*, J. Wiley & Sons, New York, 1957, Vol. 5, p. 298.
[21] N.H. Cromwell, *The Monocyclic Oxazines*, in: R.C. Elderfield, *Heterocyclic Compounds*, Vol. 5, John Wiley & Sons, New York, 1957, p. 534.

Table 2. 5,7-Dioxa-1-azabicyclo[4.3.0]nonanes (**10**) from Epoxides (**5**) and 5,6-Dihydro-4*H*-1,3-oxazines (**9**).

R^1	R^2	R^3	R^4	Yield %	b.p./0.05 mm	m.p.(n_D^{20})
$-CH_2-O-C_6H_5$	H	C_2H_5	C_6H_5	68	162–164°	(1.5560)
$-CH_2-O-C_6H_5$	CH_3	CH_3	C_6H_5	60	175°	106.5°
$-C_6H_5$	H	H	CH_3	27	107°	(1.5365)
$-CH_2-O-CH_2-CH=CH_2$	H	C_6H_5	n-$C_{11}H_{23}$	61	190–196°	(1.5030)

Table 3. 4-Oxa-1,6-diazabicyclo[3.3.0]octanes (**17**) from Epoxides (**5**) and Δ^2-Imidazolines (**16**).

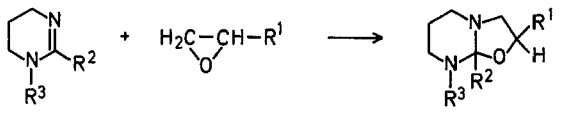
R^1	R^2	Yield %	b.p./mm	n_D^{20}
H	C_2H_5	18	107–108°/0.2	1.5615
CH_3	C_2H_5	79	114–115°/0.4	1.5519
C_6H_5	C_2H_5	92	171–172°/0.2	1.5920
$-CH_2-O-C_6H_5$	C_2H_5	86	174–176°/0.05	1.5800
$-CH_2-O-CH_2-CH=CH_2$	C_2H_5	85	135–136°/0.05	1.5428
$-CH_2-O-C_{12}H_{25}$	C_2H_5	66	212–213°/0.1	1.5071
$-CH_2-O-CH_2-CH=CH_2$	n-C_3H_7	71	126–127°/0.05	1.5395

Table 4. 7-Oxa-1,5-diazabicyclo[4.3.0]nonanes (**19**) from Epoxides (**5**) and 1,4,5,6-Tetrahydropyrimidines (**18**).

R^1	R^2	R^3	Yield %	b.p./mm	n_D^{20}
CH_3	CH_3	CH_3	83	78°/10	1.4697
CH_3	CH_3	C_2H_5	78	86°/10	1.4662
CH_3	CH_3	n-C_4H_9	92	107°/10	1.4666
$-CH_2-O-CH_2-CH=CH_2$	CH_3	n-C_4H_9	78	105°/0.1	1.4754
$-CH_2-O-CH_2-CH=CH_2$	CH_3	C_2H_5	85	95°/0.4	1.4785
C_6H_5	CH_3	C_2H_5	89	104°/0.1	1.5315
$-CH_2-O-C_6H_5$	CH_3	C_2H_5	80	123–124°/0.1	1.5279
CH_3	C_6H_5	C_2H_5	56	97–99°/0.1	1.5311
CH_3	n-$C_{11}H_{23}$	C_2H_5	79	136–137°/0.15	1.4695

1.5. Addition of Epoxides to 1,4,5,6-Tetrahydropyrimidines

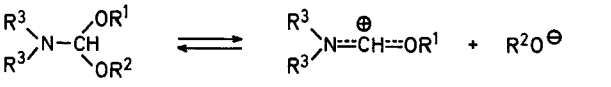
The 1,4,5,6-tetrahydropyrimidines (**18**) ring-homologous to the Δ^2-imidazolines (**16**) add epoxides (**5**) in the same way to yield 7-oxa-1,5-diazabicyclo-[4.3.0]nonanes (**19**)[28]:



18 **5** **19**

2. Reaction of Bicyclic Amide Acetals

Like the open-chain amide acetals[3], the bicyclic amide acetals **3** are very reactive compounds. Their reactions may be understood by considering the reactive amide acetal grouping. As compared with the open-chain amide acetals, the bicyclic amide acetals have yet other reaction possibilities on account of their ring strain. In the case of amide acetals of the structure **1a**, an ionization into an ambident cation is possible[3,29,30]:

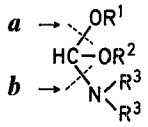


1a

[22] R. NEHRING, W. SEELIGER, Angew. Chem. **82**, 448 (1970).
[23] W. SEELIGER, W. THIER, Liebigs Ann. Chem. **698**, 158 (1966).
[24] W.S. EMERSON, J. Amer. Chem. Soc. **67**, 516 (1945).
[25] W. SEELIGER, W. DIEPERS, Liebigs Ann. Chem. **697**, 171 (1966).
[26] R. FEINAUER, Angew. Chem. **78**, 938 (1966); Angew. Chem., Internat. Edit. **5**, 894 (1966).
[27] R. FEINAUER, Angew. Chem. **78**, 938 (1966); Angew. Chem., Internat. Edit. **5**, 894 (1966).
[28] K.H. MAGOSCH, R. FEINAUER, Liebigs Ann. Chem., in press.
[29] H. MEERWEIN, W. FLORIAN, N. SCHÖN, G. STOPP, Liebigs Ann. Chem. **635**, 1 (1960).
[30] G. SIMCHEN, H. HOFFMANN, H. BREDERECK, Chem. Ber. **101**, 51 (1968).
[31] H. BREDERECK, G. SIMCHEN, S. REBSDAT, Chem. Ber. **101**, 1872 (1968).
[32] R. FEINAUER, E. HENCKEL, Liebigs Ann. Chem. **716**, 135 (1968).
[33] see, for example, G.R. PORTER, H.N. RYDON, J.A. SCHOFIELD, J. Chem. Soc. **1960**, 2686.
[34] R. GREENHALGH, R.M. HEGGIE, M.A. WEINBERGER, Canad. J. Chem. **41**, 1622 (1963).

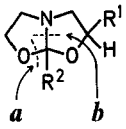
Since little is known about the primary step in reactions with amide acetals of the structure **1a**[3], Gloede et al.[3] divide the reactions of these compounds, depending on the end-product, into the following main types:

Reactions that proceed with C—O cleavage (*a*).
Reactions that proceed with C—N cleavage (*b*):



1a

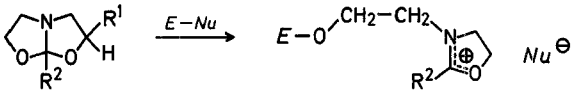
This division can also be used to describe the reactions of the bicyclic amide acetals of type **3**:



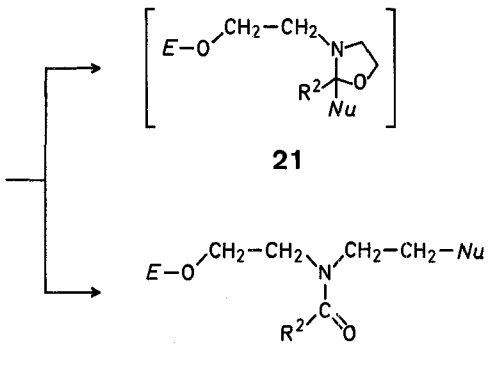
3

In the case of compounds **3** in which $R^1 \neq H$, the C—O cleavage occurs in the unsubstituted ring (steric effect).

a, Reactions that proceed with C—O cleavage:



3 (R^1 = H) **20**

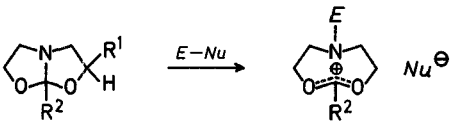


21 **22**

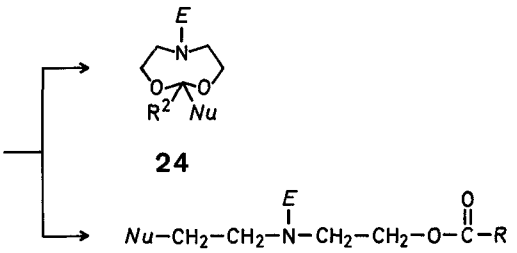
E = Electrophile
Nu = Nucleophile

The assumption of the oxazolinium salt form **20** as intermediate indicates two reaction possibilities for the reaction products with *E—Nu* (electrophile-nucleophile): the reaction to give the oxazolidine **21** and the ring opening to give the amide **22**. In no instance could reaction products of the type of **21** be isolated in reactions of bicyclic amide acetals. All reactions proceeding with C—O cleavage invariably led to the amide **22**.

b, Reactions that proceed with C—N cleavage:



3 (R^1 = H) **23**



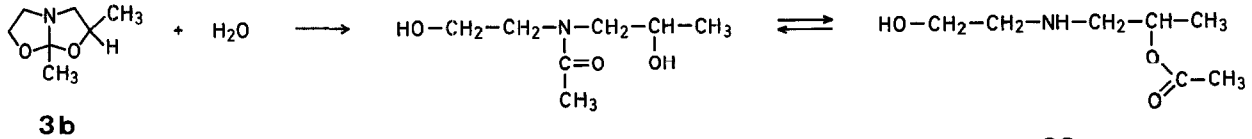
24 **25**

If an ionic intermediate (**23**) is assumed in the case of a C—N cleavage of the bicyclic amide acetals **3**, two possibilities are conceivable for the reaction with *E—Nu* (electrophile-nucleophile): ring-opening to give the ester **25** or direct conversion to the transannular ring-opened product **24**. Both reaction types are known.

2.1. Reactions that proceed with C—O Cleavage

2.1.1. Hydrolysis

According to Bredereck et al.[31], the hydrolysis of dimethylformamide acetals (**1a**) proceeds to the extent of 98.5% with cleavage of the C—O bond and to the extent of 1.5% with cleavage of the C—N bond[31]. The hydrolysis of **3b** under mild conditions (allowing to stand with water) yields the C—O cleavage product **28** to the extent of 90–95% and the C—N cleavage product **29** to the extent of 5–10%[32]. In this case, however, the possibility cannot be excluded that the hydrolysis initially proceeds uniformly and that the observed proportions of reaction products **28** and **29** are the result of equilibration after the formation of a uniform product. Such amino-ester/hydroxy-amide equilibria are known[33,34]:



3b **28** **29**

Hydrolysis of 3b[32]: A mixture of compound **3b** (50 g) and water (100 ml) was allowed to stand for 1 day. After azeotropic removal of the excess water with benzene, the residue was distilled in vacuo. There was obtained 38 g (67%) of an oil; b.p. 157–167°/0.1; n_D^{20}: 1.4830; elemental analysis and I.R. spectrum accorded the structure of the amide **28**, contaminated with 5–10% of the amino ester **29**.

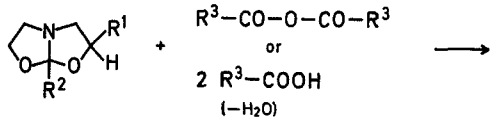
The hydrolysis of the bicyclic amide acetals **3** under more vigorous conditions, for example by boiling with dilute sulfuric acid, leads to carboxylic acid and bis-[2-hydroxyalkyl]-amine, as has already been shown in Section 1.1. by the example of the hydrolysis of 5-ethyl-3-phenyl-4,6-dioxa-1-azabicyclo[3.3.0]-octane (**3a**) to propanoic acid and the bis-[2-hydroxyalkyl]-amine **6**.

2.1.2. Reactions with Carboxylic Acids and Carboxylic Acid Anhydrides

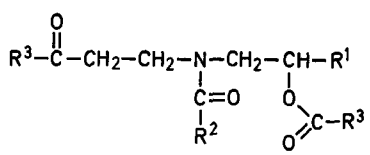
As with hydrolysis, reaction of the bicyclic amide acetals (**3**) with carboxylic acids and carboxylic acid anhydrides also leads, with C—O cleavage, to reaction products derived from the amide **22**.

Analogous reactions of dimethylformamide acetals (**1a**) with carboxylic acids and with dicarboxylic acid anhydrides have been described by Eschenmoser et al.[35,36,37] and by Gross et al.[3], respectively.

The 1:1 reaction products of bicyclic amide acetals (**3**) with carboxylic acids cannot be isolated in substance, since on working up (distillation) further reaction takes place (OH besides ester groups). The reaction of **3** with double the molar amount of carboxylic acid or with equimolar amounts of carboxylic acid anhydride, on the other hand, leads to the isolable O,O′,N-triacyl-diethanolamines (**30**)[38]:



3

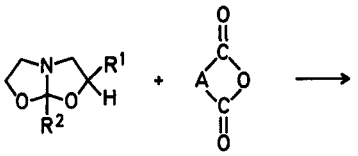


30

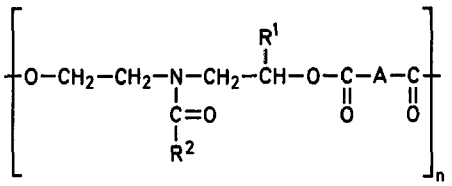
The products **30** obtained are summarized in Table 5.

O,O′,N-Triacyl-diethanolamines (30); General Procedure[38]: The components are heated at 120° for 2 hr without solvent using a 5-fold excess of carboxylic acid or anhydride; the carboxamides (**30**) are isolated by distillation. The structure follows from elemental analysis, molecular-weight determination, and I.R. spectrum.

If equimolar amounts of dicarboxylic acid anhydrides are reacted with bicyclic amide acetals (**3**) at 140° (2 hr), there are obtained linear polyamide esters of the structure **31** which for purification can be precipitated from chloroform/ether[38]:



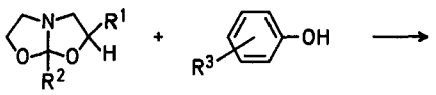
3



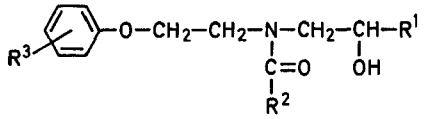
31

2.1.3. Reactions with Phenols

Phenols may be alkylated with dimethylformamide acetals (**1a**) with C—O cleavage[39]. Reaction of bicyclic amide acetals (**3**) with phenols leads, likewise with C—O cleavage, to open-chain products (**32**) which are derived from the amide **22**[40]:



3



R^3 = H, 2–, 3–, 4–CH_3 **32**

The analytical data of the reaction products **32** are indicative of the cleavage of bicyclic compound **3** in the unsubstituted ring.

Table 7 gives a summary of the compounds **32** obtained from **3** and phenols.

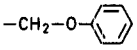
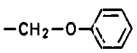
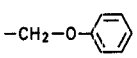
N-(2-Phenoxyethyl)-N-(2-hydroxyisopropyl)-acetamide[40]: A mixture of 3,5-dimethyl-4,6-dioxa-1-azabicyclo[3.3.0]octane (**3b**; 28.6 g, 0.2 mol) and phenol (18.8 g, 0.2 mol) is heated at 120° for 2 hr. The mixture is then distilled in vacuo to give an almost colorless oil; yield: 39.4 g (83%); b.p. 178°/0.1 mm; n_D^{20}: 1.5298.

In contrast to the dimethylformamide acetals (**1a**), which are reacetalized by alcohols[3], the bicyclic amide acetals (**3**) do not react with alcohols to give isolable products. When the bicyclic amide acetals (**3**) are heated with alkanols, distillation yields the unchanged starting materials.

Table 5. O,O',N-Triacyl-diethanolamines (**30**) from Bicyclic Amide Acetals (**3**) and Cyrboxylic Acids or Anhydrides

R^1	R^2	R^3	Yield %	b.p./mm	n_D^{20}
C_6H_5	C_2H_5	H	60	198°/0.4	1.5152
C_6H_5	C_2H_5	CH_3	95	177°/0.1	1.5052
C_6H_5	C_2H_5	C_2H_5	66	179°/0.1	1.5038
$-CH_2-O-C_6H_5$	C_2H_5	H	92	228–230°/1.7	1.5159
$-CH_2-O-C_6H_5$	C_2H_5	CH_3	92	205°/0.3	1.5052
$-CH_2-O-C_6H_5$	C_2H_5	C_2H_5	84	207°/0.1	1.5055
C_6H_5	C_6H_5	CH_3	82	245°/1	1.5450

Table 6. Polyamide Esters (**31**) from Bicyclic Amide Acetals (**3**) and Dicarboxylic Acid Anhydrides

R^1	R^2	A	Yield %	Softening point	$\overline{M}_n$ [a]
	C_2H_5	$-CH_2-CH_2-$	96	65–73°	9100
	C_2H_5	$-CH_2-CH_2-$	90	61–66°	10500
	C_2H_5		83	87–92°	3850
	C_2H_5		94	75–83°	5880
			71	134–138°	4250
	CH_3		93	85–92°	3640

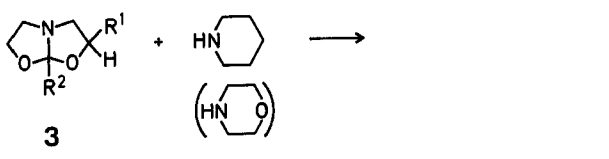
[a] Mean molecular weight from vapour pressure osmotic measurements.

2.1.4. Reactions with Amines

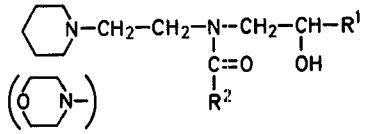
Dimethylformamide acetals (**1a**) react with higher-boiling secondary amines such as piperidine and morpholine; amine exchange occurs (C—N cleavage)[29]. With low-boiling secondary amines, other types of reactions are also observed[3,41].

The bicyclic amide acetals (**3**), on the other hand, behave differently on reaction with high-boiling secondary aliphatic amines.

Reaction of **3** with piperidine or morpholine leads, with C—O cleavage, to reaction products **33** which are derived from the amide **22**[40]:



3



33

From the analytical data of the reaction products from **3** and piperidine or morpholine it follows that the cleavage again takes place predominantly in the unsubstituted ring of the bicyclic compound, so that the secondary alcohols **33** are formed.

Table 8 gives a summary of the products **33** obtained from the bicyclic amide acetals **3** and piperidine or morpholine.

N-(2-Morpholinoethyl)-N-(2-hydroxypropyl)-acetamide[40]: A mixture of morpholine (8.7 g, 0.1 mol) and 3,5-dimethyl-4,6-dioxa-1-azabicyclo[3.3.0]octane (**3b**; 14.3 g, 0.1 mol) is heated at 150° for 2 hr. Distillation of the resultant mixture affords the amide as almost colorless oil; yield: 20.3 g (88%); b.p. 148–150°/0.4 mm; n_D^{20}: 1.4958.

2.2. Reactions that proceed with C—N Cleavage

2.2.1. Acylation

In addition to the amine-exchange already mentioned, in the case of dimethylformamide acetals (**1a**) reactions with strongly acidic compounds and acylations and alkylations proceed with C—N cleavage[3].

[35] H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber, A. Eschenmoser, Angew. Chem. **75**, 296 (1963).

[36] H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber, A. Eschenmoser, Helv. Chim. Acta **48**, 1746 (1965).

Table 7. Reaction Products **32** from Bicyclic Amide Acetals **3** and Phenols

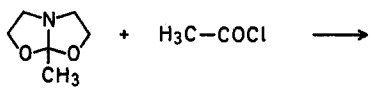
R^1	R^2	R^3	Yield %	b.p./mm	n_D^{20}
CH_3	CH_3	H	83	178°/0.1	1.5298
H	CH_3	H	82	174°/0.15	1.5319
CH_3	CH_3	2-CH_3	76	165°/0.1	1.5291
H	CH_3	2-CH_3	94	183°/0.1	1.5381
CH_3	CH_3	3-CH_3	82	175°/0.17	1.5259
H	CH_3	3-CH_3	83	180°/0.1	1.5349
CH_3	CH_3	4-CH_3	71	174°/0.1	1.5280
H	CH_3	4-CH_3	89	191°/0.15	1.5339
C_6H_5	C_2H_5	H	67	196°/0.2	1.5553
$-CH_2-O-CH_2-CH=CH_2$	CH_3	H	86	185°/0.05	1.5245
C_6H_5	CH_3	H	83	204°/0.15	1.5685
H	C_2H_5	H	84	173°/0.15	1.5269
$-CH_2-O-C_6H_5$	n-C_3H_7	H	75	227°/0.1	1.5446

Table 8. Reaction Products from Bicyclic Amide Acetals **3** and Piperidine (*P*) or Morpholine (*M*).

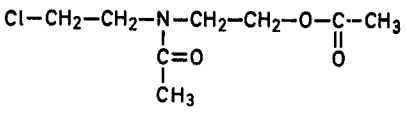
R^1	R^2	Piperidine or morpholine	Yield %	b.p./mm	n_D^{20}
CH_3	CH_3	*M*	88	148–150°/0.4	1.4958
CH_3	CH_3	*P*	74	131–135°/0.4	1.4942
H	CH_3	*M*	67	150°/0.4	1.5022
H	CH_3	*P*	43	137–140°/0.4	1.4980
$-CH_2-O-CH_2-CH=CH_2$	CH_3	*P*	78	152–156°/0.1	1.4956
$-CH_2-O-CH_2-CH=CH_2$	CH_3	*M*	84	170–173°/0.1	1.4975
C_6H_5	C_2H_5	*P*	50	183–187°/0.2	1.5354
C_6H_5	C_2H_5	*M*	80	190–193°/0.1	1.5342
C_6H_5	CH_3	*M*	52	185°/0.05	1.5466
$-CH_2-O-C_6H_5$	CH_3	*M*	74	214–217°/0.05	1.5419
$-CH_2-O-C_6H_5$	C_2H_5	*P*	80	208–212°/0.05	1.5313
C_6H_5	C_6H_5	*P*	54	225–230°/0.1	1.5762
CH_3	C_2H_5	*M*	80	145–146°/0.05	1.4920
H	C_2H_5	*P*	69	141–145°/0.1	1.4939

From bicyclic amide acetals (**3**) and strong acid (hydrogen chloride in ether) there are obtained salt-like reaction products of unclarified structure[40]. The acylation of compounds **3** with aliphatic and aromatic acid chlorides proceeds very vigorously. The work-up of the reaction mixture, however, presents difficulties because the reaction products readily decompose on distillation.

Only from bicyclic amide acetals with a low degree of substitution (e.g. **3c**) and acetyl chloride has it been possible by cautious distillation of the reaction mixture to isolate a product with the probable structure **34**[40]:



3c



34

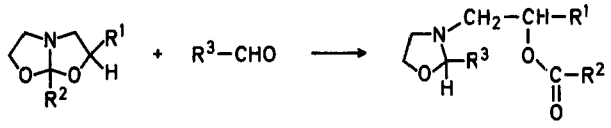
This reaction probably proceeds with C—N cleavage, but a C—O cleavage cannot be excluded since in this instance the reaction product derived from the amide **22** would be the same as the C—N cleavage product **34** derived from the ester **25**.

N-(2-Chloroethyl)-N-(2-acetoxyethyl)-acetamide (34)[40]: A solution of 5-methyl-4,6-dioxa-1-azabicyclo[3.3.0]octane (**3c**; 51.6 g, 0.4 mol) in chloroform (100 ml) is added dropwise while stirring and cooling with ice-water to a solution of acetyl chloride (31.4 g, 0.4 mol) in chloroform (100 ml) at such a rate that the internal temperature does not exceed 40°. After reaction is over, the solvent is evaporated in vacuo and the residue is distilled in vacuo; yield: 77.2 g (93%); colorless oil, b.p. 118–120°/0.15 mm; n_D^{20}: 1.4781.

2.2.2. Reactions with Aliphatic Aldehydes

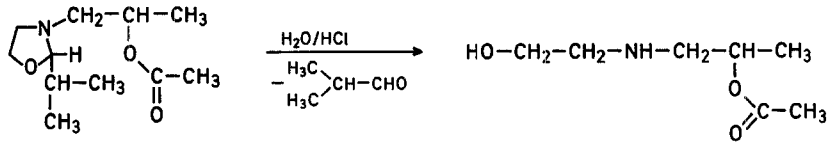
Little is known about the reaction of simple amide acetals (**1**) with carbonyl compounds. From 3-oxo-steroids and dimethylformamide ethylene acetal (2-dimethylamino-1,3-dioxolane), the corresponding 3-ethylene ketals were obtained[42] (C—O cleavage). While aromatic aldehydes and ketones do not react with bicyclic amide acetals (**3**), the reaction of ali-

phatic aldehydes with bicyclic amide acetals (**3**) proceeds with C—N cleavage and leads in good yields to reaction products **35** which are derived from the ester **25**[32] (*E—Nu* linked by ring):

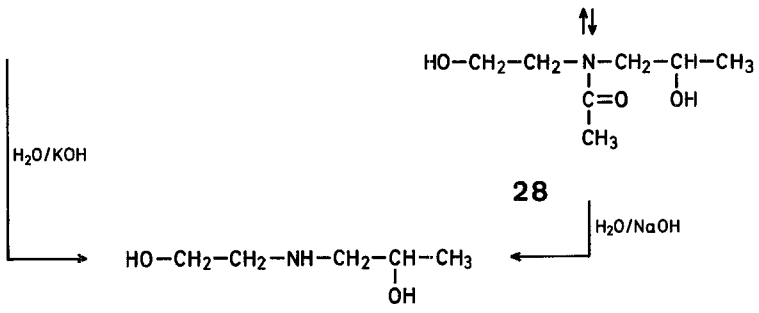


3 **35**

An accurate analysis of the N.M.R. spectra of the compounds **35**[32] showed unequivocally the attack by the aldehyde on the unsubstituted ring of the bicyclic compounds (**3**). Reaction products that could have resulted from attack by the aldehyde on the substituted ring **3** were not detected (steric effect). Hydrolysis experiments with the compound **35a** prepared from **3b** and isobutanal confirm the structure of the products **35**:



35a **29**



36

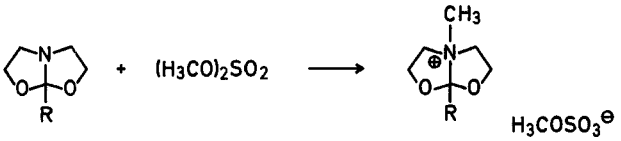
Mild hydrolysis of **35a** with water in the presence of a catalytic amount of hydrochloric acid leads, with loss of isobutanal, to the amide **28** which still contains 5–10% of the amino-ester **29**. The same product **28** (besides 5–10% **29**) results from hydrolysis of **3b** (see Section 2.2.1.). The hydrolysis of **35a** with aqueous potassium hydroxide under reflux leads, with loss of isobutanal and acetic acid, to (2-hydroxyethyl)-(2-hydroxypropyl)-amine (**36**), which is also obtained by hydrolysing **28** with aqueous sodium hydroxide under reflux.

Table 9 gives a summary of the 2-alkyl-3-acyloxyalkyl-1,3-oxazolidines (**35**) obtained from bicyclic amide acetals (**3**) and aldehydes.

2-Alkyl-3-(2-acyloxyalkyl)-1,3-oxazolidines (35); General Procedure: 4,6-Dioxa-1-azabicyclo[3.3.0]octane (**3**; 0.4 mol) and the aldehyde (0.4 mol) are heated in benzene (200 ml) at 60–80° for 1–4 hr. The solvent is evaporated and the residue distilled in vacuo. Compounds **35** are obtained as colorless liquids.

2.2.3. Alkylation and Transannular Ring Opening

According to Meerwein et al.[29], the alkylation of dimethylformamide acetals (**1a**) leads to C—N cleavage products. In this reaction with methyl iodide, a salt-like primary addition product could be detected. The reaction of bicyclic amide acetals (**3**) with dimethyl sulfate in dichloromethane at a temperature below 30° leads to very stable N-alkylation products (**37c,d**) which in the case of monosubstituted 4,6-dioxa-1-azabicyclo[3.3.0]octanes (**3c,d**) can be obtained in crystalline form[43]:



3c (R = CH_3)
3d (R = C_2H_5)

37c,d

A comparison of the N.M.R. spectra of **3c** and **37c** indicates the individual structures of the N-alkylation products **37**. The CH_3 group in the 5-position of **3c** gives a singlet at 8.62 τ (solvent CCl_4), while the corresponding CH_3 group in the 5-position of **37c** gives two singlets lying close together at 7.98 and 8.08 τ (solvent $CDCl_3$). This strong shift to lower τ-values points to the positivization of the bridge carbon atom in **37c**.

1-Methyl-5-alkyl-4,6-dioxa-1-azoniabicyclo[3.3.0]octane Methyl Sulfate (37)[43]: Dimethyl sulfate (0.4 mol) is added dropwise with stirring and cooling to a solution of **3c** or **3d** (0.4 mol) in dichloromethane (200 ml) in such a way that the internal temperature does not exceed 30°. The mixture is stirred for 30 min. and the reaction vessel then placed in ice. The N-alkylation products **37c** and **37d** are isolated by filtration (water pump), washed with dichloromethane, and dried in a desiccator; yield of **37c**: 79%, m.p. 100–101°; yield of **37d**: 82%, m.p. 112–113°.

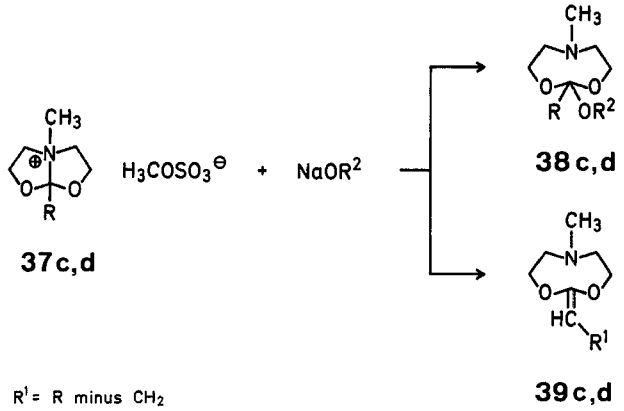
Transannular ring opening starting from the N-alkylation products **37** leads to products which are directly derived from the intermediates **23**. Reaction

[37] H. BÜCHI, K. STEEN, A. ESCHENMOSER, Angew. Chem. **75**, 1176 (1963).

Table 9. 2-Alkyl-3-(2-acyloxyalkyl)-1,3-oxazolidines (**35**) from Bicyclic Amide Acetals (**3**) and Aldehydes.

R^1	R^2	R^3	Yield %	b.p./mm	n_D^{20}
H	CH_3	i-C_3H_7	82	63–64°/0.15	1.4473
CH_3	CH_3	i-C_3H_7	89	67°/0.3	1.4438
H	C_2H_5	i-C_3H_7	77	77°/0.5	1.4481
CH_3	C_2H_5	i-C_3H_7	72	73°/0.3	1.4452
$-CH_2-O-C_6H_5$	CH_3	i-C_3H_7	84	157–161°/0.6	1.5041
$-CH_2-O-CH_2-CH=CH_2$	CH_3	i-C_3H_7	63	106–109°/0.2	1.4576
C_6H_5	C_2H_5	i-C_3H_7	81	134–139°/0.1	1.5016
$-CH_2-O-C_6H_5$	C_2H_5	i-C_3H_7	82	152–160°/0.3	1.5016
$-CH_2-O-C_6H_5$	n-C_3H_7	i-C_3H_7	87	154°/0.2	1.4980
$-CH_2-O-C_6H_5$	i-C_3H_7	i-C_3H_7	88	146–150°/0.3	1.4953
C_6H_5	C_6H_5	i-C_3H_7	57	180°/0.05	1.5623
H	CH_3	n-C_3H_7	69	72°/0.3	1.4496
CH_3	CH_3	n-C_3H_7	81	80–83°/0.3	1.4449
$-CH_2-O-C_6H_5$	CH_3	n-C_3H_7	59	170–174°/0.2	1.5020
C_6H_5	C_2H_5	n-C_3H_7	78	127–134°/0.05	1.5019
$-CH_2-O-C_6H_5$	C_2H_5	n-C_3H_7	77	166–170°/0.2	1.5021
H	CH_3	C_2H_5	70	44°/0.01	1.4564
CH_3	CH_3	C_2H_5	64	81–83°/0.2	1.4443
$-CH_2-O-C_6H_5$	CH_3	C_2H_5	77	156–160°/0.2	1.5100
$-CH_2-O-C_6H_5$	C_2H_5	C_2H_5	74	132–142°/0.05	1.5058
C_6H_5	C_2H_5	CH_3	62	132–136°/0.3	1.5203
$-CH_2-O-C_6H_5$	C_2H_5	H	33	149–160°/0.1–0.4	1.5272

of the N-alkylation products **37** with alkoxides in alcohols leads to a mixture of the 1,3-dioxa-6-aza-cyclooctanes **38** and **39**[43], which may be separated by distillation using a spinning-band column:



R^1 = R minus CH_2

Compound **38c** is formed predominantly from **37c** with methoxide and ethoxide; only traces of **39c** could be detected (spectroscopically), presumably because of its low stability. From **37d**, with sodium methoxide there results predominantly **38d**, and with sodium ethoxide mainly **39d**. It was not possible to thermally transform **38d** into **39d**. This indicates that the addition of the alkoxide anion and the elimination of a proton occur concurrently during the formation of **38** or **39** from **37** and alkoxide. The structure of the products **38** and **39** is confirmed by elemental analysis, molecular-weight determination, and I.R., N.M.R., and mass spectra.

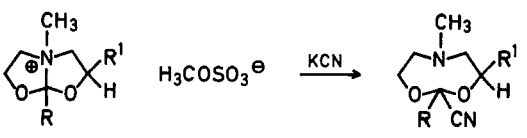
The tetrahydro-1,3,6-dioxazocines **38** and **39** obtained from **37c** and **37d** with alkali metal alkoxides are summarized in Table 10.

2-Alkoxy-2-alkyl- (38) and 2-Alkylidene-6-methyl-tetrahydro-1,3,6-dioxazocines (39); General Procedure[43]: The compound **37** (0.4 mol) is dissolved in methanol or ethanol (100 ml). A solution of sodium (0.4 g-atom) in the same alcohol (150 ml) is added dropwise with stirring at 60° and the mixture is held at 60° for a further 2 hr. After cooling, precipitated sodium methyl sulfate is filtered off, the excess alcohol is distilled off via a column, and the residue is fractionally distilled in vacuo via a spinning-band column.

A further transannular ring-opening reaction of the N-alkylation products **37** is brought about by potassium cyanide[44].

The reaction of the N-alkylation products **37** (where $R \neq H$, the crude reaction mixtures from the methylation are used without isolation of the products **37**) with potassium cyanide in methanol affords 6-methyl-2-cyano-tetrahydro-1,3,6-dioxazocines (**40**), the structure of which has been confirmed by elemental analysis, molecular-weight determination, and I.R. and N.M.R. spectra, as well as by hydrolysis with concentrated hydrochloric acid to give α-oxocarboxylic acids and methyl-bis-[2-hydroxyethyl]-amine or its derivatives.

Table 11 gives a summary of the 6-methyl-2-cyano-tetrahydro-1,3,6-dioxazocines **40** obtained from **37** and potassium cyanide.



37 **40**

Table 10. Tetrahydro-1,3,6-dioxazocines **38c,d** and **39c,d** from **37c,d** and Sodium Alkoxides

37	R^2	Yield %		b.p./mm		n_D^{20}	
		38	**39**	**38**	**39**	**38**	**39**
c	CH_3	38	< 5	57°/3		1.4546	
c	C_2H_5	20	< 5	50°/1		1.4490	
d	CH_3	42	5	66°/2	54°/2	1.4556	1.4780
d	C_2H_5	10	37	70°/2	54°/2	1.4522	1.4780

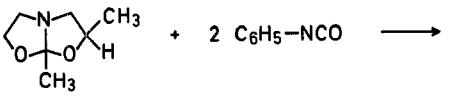
2-Cyano-6-methyl-tetrahydro-1,3,6-dioxazocines (40); General Procedure[44]: The N-alkylation product **37** (0.22 mol) is dissolved in methanol (150 ml); a solution of potassium cyanide (0.2 mol) in methanol (300 ml) is slowly added with stirring at room temperature. The mixture is subsequently stirred at room temperature for a further 2 hr, then cooled with ice/sodium chloride. The precipitated potassium methyl sulfate is filtered off. Methanol is removed from the filtrate in vacuo and the residue distilled via a spinning-band column.

Table 11. 2-Cyano-6-methyl-tetrahydro-1,3,6-dioxazocines (**40**) from **37** and Potassium Cyanide

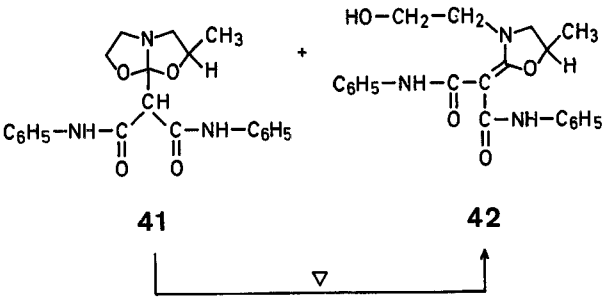
R	R^1	Yield %	b.p./mm	n_D^{20}
CH_3	H	15	63°/2	1.4555
C_2H_5	H	44	78°/4	1.4569
n-C_3H_7	H	36	96°/3	1.4572
i-C_3H_7	H	64	78°/2	1.4571
CH_3	CH_3	14	72°/4	1.4525
C_2H_5	CH_3	55	99°/5	1.4534

2.3. Other Reactions

A few reactions of bicyclic amide acetals (**3**) having a methyl group in the 5-position are indicative of a certain acidity of the hydrogen atoms of the methyl group. Thus, for example, phenyl isocyanate reacts with **3b** in dichloromethane at room temperature to give a mixture of a crystalline (30% yield) and an amorphous (60% yield) 2:1 addition product, both of which give malonic acid dianilide on hydrolysis[40]. The crystalline addition product rearranges to the amorphous addition product on heating. The analytical data make the structure **41** probable for the crystalline adduct and the structure **42** probable for the amorphous product:



3b



41 **42**

Thermally unstable 1:1 addition products obtained from **3c** and 1,2-diketones[40] likewise point to a reaction at the 5-methyl group of **3c**, since the unchanged ring structure of **3c** is recognized in the I.R. spectra of the reaction products.

Reactions with CH-acidic compounds, which are known in the case of dimethylformamide dimethyl acetals (**1a**, see Ref.[3]), do not lead to isolable reaction products with the bicyclic amide acetals **3**, although vigorous reactions are observed in some cases[40].

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[38] R. FEINAUER, Angew. Chem. **79**, 189 (1967); Angew. Chem., Internat. Edit. **6**, 178 (1967).
[39] H. VORBRÜGGEN, Angew. Chem. **75**, 296 (1963).
[40] R. FEINAUER, unpublished work.
[41] H.E. WYNBERG, J.E. CARNAHAN, D.D. COFFMAN, M. BROWN, J. Amer. Chem. Soc. **87**, 2055 (1965).
[42] H. VORBRÜGGEN, Steroids **1**, 45 (1963).
[43] R. FEINAUER, Angew. Chem. **80**, 703 (1968); Angew. Chem., Internat. Edit. **7**, 731 (1968).
[44] R. FEINAUER, Synthesis **1969**, 40.

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