Kurze Mitteilungen

Bis zum 15. des Monats bei der Redaktion eingehende Kurze Mitteilungen werden in der Regel am 15. des folgenden Monats veröffentlicht. Es werden auch Manuskripte aus dem Ausland angenommen, Maximalumfang: 6 Schreibmaschinenseiten (alles inbegriffen).

Stereoselectivity in Enzymic Biotransformation of Chiral and Achiral 1,3-Dihydro-2 H-1,4-Benzodiazepin-2-ones *

Abstract

Enzymic biotransformation of chiral 1,4-benzodiazepin-2-ones (S and R forms) is found to be configuration dependent for hydroxylation in aromatic rings, but hydroxylation in position 3, as well as N^1-demethylation prooved to be nonstereospecific.

Most biotransformation products are known to be less biologically active than their parent compounds, but cases are known where such metabolites exibited increased therapeutic effect[1, 2], a fact which prompted us to get more insight into the biotransformation of chiral and achiral 3-substituted and unsubstituted 1,3-dihydro-2 H-1,4-benzodiazepin-2-ones. As a part of our studies[3–6] on psycho-pharmacologically active chiral 1,4-benzodiazepin-2-ones possessing a centre of chirality in position 3, we attempted to investigate their enzymic biotransformation *in vitro*. The investigation of pharmacological activities of compounds I to IV revealed the high activity of the compounds with (S)-configuration, while those with (R) configuration were almost inactive. Racemates showed about 30% activity of (S) enantiomers[6]. This study was undertaken in order to ascertain whether different biotransformation pathways exist for the enantiomeric compounds I to IV (S- and R-forms)[4, 5].

Hydroxylation reactions of aromatic and aliphatic compounds are known to be catalyzed by hepatic microsomal mixed function oxygenases[7]. Hepatic monooxygenases convert aromatic compounds to aren oxydes, which then undergo spontaneous isomerizations to phenols by "NIH" shift mechanism. Such isomerization is often accompanied by migration of deuterium, halo- and alkyl-substituents[8]. Therefore the experiments with compounds I to IV possessing both (S) and (R) configuration were performed *in vitro* using 9000 g centrifuged supernatant from liver of control and phenobarbital treated male rats.

To the treated animals three daily i.p. injections of 40 mg phenobarbital/kg were given, which has been found particularly effective in inducing drug metabolism. After the last injection, the animals fasted for 24 hrs and were sacrificed by decapitation. The liver of each animal was rinced in a cold water and homogenized in 2 volume ice-cold 0,2 M Tris (hydroxymethyl) methylamine buffer *p*H 7,4 in a Edmund Bühler homogenizer at 20000 r.p.m. for 60 seconds. Homogenates were maintained at 0 °C while centrifuged at 9000 g for 20 min. Supernatants were stored at − 20 °C until used within three months as enzyme sources[9, 10]. The incubation mixture contained the substrate, the enzyme source, pyridine nucleotides and NADPH generating system[9]. Incubation media were extracted three times with 2 volume of ethyl acetate. The combined extracts were evaporated to dryness and dissolved in a small volume of ethanol. The ethanol solution aliquots were analysed by thin-layer chromatography ("Merck" TLC plates Silica gel 60 F_{254}). The isolation of identified metabolites were performed by the preparative thick-layer chromatography ("Merck" PLC plates Silica gel 60 F_{254}), in the following solvents: chloroform : acetone (9 : 1), isopropanol : conc. ammonia (20 : 1), chloroform : heptane : ethanol : conc. ammonia (5 : 5 : 1 : 0,03), chloroform : ethanol (9 : 1) and chloroform : ethanol : acetone (8 : 1 : 1) respectively, Biotransformation products detected under uv light were scarped and eluted from silica gel with ethanol. The eluates were evaporated and biotransformation products examined by mass, uv and circular dichroism spectrometry.

Chromatographic separation revealed that the (3S)-enantiomer of I (molecular ion at *m*/e 284) was biotransformed into two (VI a, b) and those of (II) (molecular ion at *m*/e 298) into five (VI a, b; VII a, b; I) main metabolic products. The R_f value of I formed by biotransformation of II indicated and uv absorption, circular dichroism and mass spectra confirmed the identity of this biotransformation product with compound I (S) i.e. N^1-demethylation occured. Compounds VIa and VIb, well resolved by their R_f values and absorption spectra (Fig. 1), have proved to be common

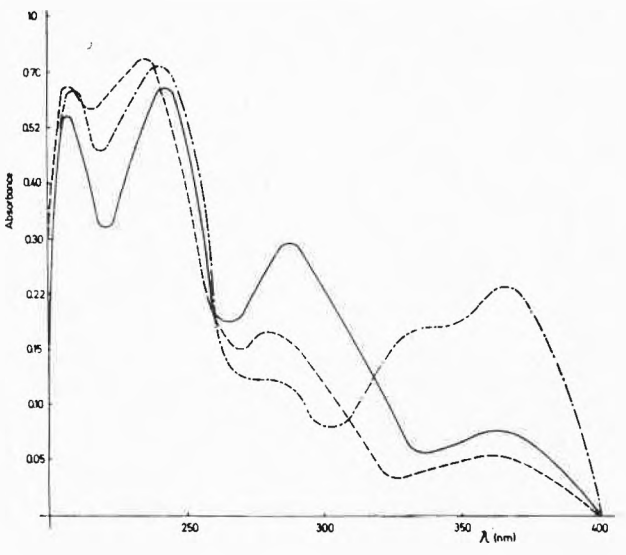


Fig. 1. Absorption spectra of chiral 3-substituted 1,4-benzodiazepin-2-one I and metabolites VIa and VIb in 0,1 N HCl: ——I, – – – –VIa, –·–·–·–VIb

* Received February 12, 1974.

metabolites of I (S) and II (S). On the other hand absorption spectra of compounds VIIa and VIIb, which are metabolites of II (S) showed remarkable resemblance to those of VIa and VIb, respectively. Circular dichroism spectra of VIa and VIb (Fig. 2), as well as those of

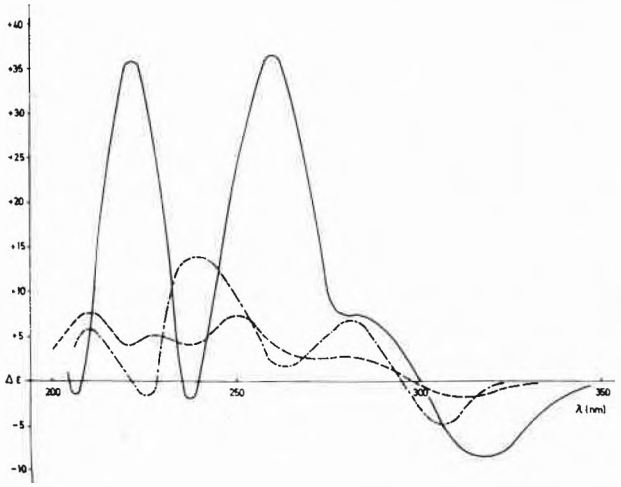
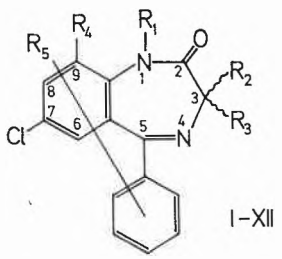


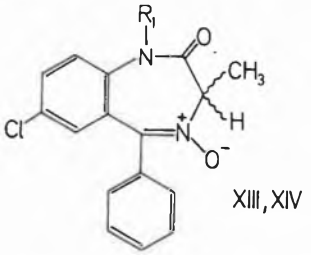
Fig. 2. Circular dichroism spectra of 3-substituted 1,4-benzodiazepin-2-one I –(S) and metabilites VIa and VIb in 96% ethanol (spectra of metabolites are qualitative):
——I, –(S), – – – –VIa, –·–·–·–VIb

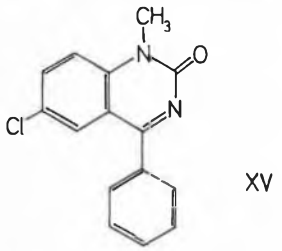
VIIa and VIIb, showed that optical activity was retained in the course of biotransformation. In the mass spectra of VIa and VIb the same molecular ion at *m*/e 300 and nearly identical fragmentation pattern was observed. The same was found for compounds VIIa and VIIb with molecular ion at *m*/e 314. This indicates that VI a/b and VII a/b are two constitutional isomeric pairs, which have one oxygen atom more than the parent compound and which mutually differ in the N^1-methyl group. Finding out where the oxygen atom is introduced into the molecules of the parent compounds needs some consideration. A possible N^4-oxyde structure could be excluded by comparison with authentic samples of N^4-oxydes XIII and XIV. Hydroxylation at position-3 and C-9 could also be excluded by comparison with the mass and uv spectra of the prepared authentic compounds VIII and XII.



Synthesis of some other possible aryl-hydroxy metabolites are in course.

Compound	R^1	R^2	R^3	R^4	R^5	Configuration
I	H	CH_3	H	H	H	(S) and (R)
II	CH_3	CH_3	H	H	H	(S) and (R)
III	H	$CH_2C_6H_5$	H	H	H	(S) and (R)
IV	CH_3	$CH_2C_6H_5$	H	H	H	(S) and (R)
V	CH_3	H	H	H	H	prochiral
VIa,b	H	CH_3	H	H	OH	(S)
VIIa,b	CH_3	CH_3	H	H	OH	(S)
VIII	CH_3	CH_3	OH	H	H	racemic[5]
IX	CH_3	H	OH	H	H	racemic
X	H	H	OH	H	H	racemic
XI	CH_3	CH_3	$OCOCH_3$	H	H	racemic
XII	CH_3	CH_3	H	OH	H	(S) and (R)





Compound	R^1	Configuration	
XIII	H	(S) and (R)	XV
XIV	CH_3	(S) and (R)	

The same experiments with (R)-enantiomers of I showed that they were not biotransformed at all. Compound II (R) demethylates into a metabolite which on isolation proved to be identical with I (R). Both (S)- and (R)-forms of II, as well as compound V, gave the same metabolite XV with a molecular ion at *m*/e 270. To clarify this finding experiments were performed without addition of 9000 g supernatant fraction of rat liver into the incubation media VIII, IX, XI, II (S- and R-forms) and V. Compound XV was isolated from the incubation media of 3-hydroxy compounds VIII, IX and of XI, but not from incubation media of 3-dehydroxy compounds II (S- and R-form) and V. This revelaled that XV can only be formed by nonenzymic

[1] V. D. Parke, *Chemistry in Britain 43* (1972) 102.
[2] H. G. Mandel, in *Fundamentals of Drug Metabolism and Disposition* (B. N. La Du, H. G. Mandel and E. L. Way, eds.), 2nd edition The Williams & Willkins Company, Baltimore 1972, p. 150.
[3] V. Šunjić, F. Kajfež, D. Kolbah and N. Blažević, *Croat. Chem. Acta 43* (1971) 205.
[4] V. Šunjić, F. Kajfež, I. Štromar, N. Blažević and D. Kolbah, *J. Heterocycl. Chem. 10* (1973) 591.
[5] V. Šunjić, F. Kajfež, D. Kolbah, H. Hofman and M. Štromar, *Tetrahedron Letters 34* (1973) 3209.
[6] V. Šunjić, J. Kuftinec and F. Kajfež, *Arzneimittel-Forsch.*, in press.
[7] G. S. Boyd in *Biological Hydroxylation Mechanisms* (G. S. Boyd and R. M. S. Smellie, eds.), Academic Press, London 1972, p. 1.
[8] J. W. Daly, D. M. Jerina and B. Witkop, *Experientia 28* (1972) 1129.
[9] M. S. Schwartz and E. Postma, *Biochem. Pharmac. 17* (1968) 2443.
[10] J.-P. Viau, J. E. Epps and F. J. Carlo, *Biochem. Pharmac. 21* (1972) 563.

rearrangement of intermediary 3-hydroxy compounds, indicating that 3-hydroxylation of chiral compounds is not stereoselective. In addition in experiments performing enzymic hydroxylation of prochiral compound V, metabolites VIII and IX were isolated which exibited no c.d. activity. Enzymic hydroxylation of V at position 3 has been observed earlier *in vivo* experiments[11,12]. Recently it has been found however that *in vitro* enzymic hydroxylation of C (3) deuterated V (both S- and R-forms) proceeds with a high degree of stereospecificity[13]. Optically inactive IX and X isolated in our experiments are therefore as likely to arise from *in vitro* racemisation, following stereospecific hydroxylation, as from non-specific hydroxylation.

Experiments performed with (S)- and (R)-enantiomers of III and IV indicated that these compounds were not biotransformed at all. It is possible that a benzylic group at position 3 inhibited metabolic reactions probably generating steric hindrances for binding on the enzyme surface.

From the ohter results it can further be concluded that chirality of position 3 causes stereoselectivity during enzymic aromatic hydroxylation but is of minor importance for N^1-demethylation and 3 hydroxylation of chiral 1,4-benzodiazepin-2-ones.

S. Rendić, V. Šunjić, F. Kajfež, L. Klasinc and P. Mildner

CRC (Compagnia di Ricerca Chimica), CH-6830 Chiasso (Switzerland), and Institute of Organic Chemistry and Biochemistry, Zagreb (Yugoslavia)

[11] M.A. Schwartz, B.A. Koechlin, E. Postma, S. Palmer and G. Krol, *J. Pharm. Exper. Ther. 149* (1965) 423.
[12] M.A. Schwartz, P. Bommer and F.M. Vane, *Atch. Biochem. Biophys. 121* (1967) 508.
[13] A. Corbella, P. Gariboldi, G. Jommi, A. Forgione, F. Marcucci, P. Martelli, E. Mussini and F. Mauri, *J. Chem. Soc. Chem. Comm. 1973*, 721.

Herstellung von Estern der Cyanessigsäure mit sekundären Alkoholen durch Umesterung*

Summary

The ester-alcohol interchange reaction (alcoholysis) has been used for the preparation of some new esters of cyanoacetic acid. Aluminium isopropoxide was used as catalyst.

Die Herstellung von Estern der Cyanessigsäure mit sekundären Alkoholen, in der Folge kurz sekundäre Ester genannt, wird durch direkte Verrsterung erreicht. Cyanessigsäure – aus Chloressigsäure und Natriumcyanid gewonnen – wird mit dem entsprechenden sekundären Alkohol in Abwesenheit[1] oder meist in Gegenwart von Brönsted-Säuren, z.B. Schwefelsäure[2,3] durchgeführt. Ein anderer Weg führt über die Veresterung von Chloressigsäure und anschließende Cyanidierung des sekundären Esters der Chloressigsäure[4].

Bei allen diesen Methoden sind zahlreiche Operationen durchzuführen. Dazu kommt noch, daß die Veresterungsgeschwindigkeit mit steigendem Molgewicht des sekundären Alkohols abnimmt.

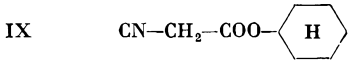
Aus diesen Gründen war es angebracht, eine einfache Methode zur Herstellung von sekundären Cyanessigestern zu suchen. Im Hinblick darauf, daß entsprechende Ester niedriger Alkohole leichter zugänglich sind als die freie Säure, eröffnet die Umesterungsmethode besonders einfache und günstige Möglichkeiten. Die Übertragung dieser Methode auf die Cyanessigester ist noch nicht beschrieben. Diese Arbeit zeigt, daß dies bei entsprechender Katalysatorwahl für viele dieser «schwierigen» Ester mit gutem Erfolg durchgeführt werden kann. Die Umesterung kann durch Säuren oder Basen katalytisch beschleunigt werden. Bekannt ist der Einsatz folgender Verbindungen: Natrium- oder Kaliumalkoholate, Magnesiumalkoholate[5], Tetraalkyltitanate[5,6], Aluminiumalkoholate[7,8,9], Zinksalze[10], Schwefelsäure u.a. Der Zusatz von Aluminiumisopropylat hat sich bei der Umesterung von Methylcyanacetat mit sekundären Alkoholen bewährt. Er wird in Mengen von 1 bis 5 Mol-%, bezogen auf Methylcyanacetat, zugesetzt. Die Reaktionstemperatur kann innerhalb eines Bereiches von 0 bis 70 °C über dem Siedepunkt des entsprechenden sekundären Alkohols gewählt werden.

Zur Umesterung ist eine Apparatur notwendig, welche aus Blase, Kolonne und Kühler besteht. In die Blase werden Methylcyanacetat, der entsprechende sekundäre Alkohol im Überschuß und Aluminiumisopropylat eingefüllt und auf die gewünschte Temperatur erhitzt. Das entstehende Methanol wird am Kopf der Kolonne laufend abgetrennt. Nachdem die theoretische Menge an Methanol abdestilliert ist (2 bis 8 Stunden), wird das Reaktionsgemisch unter vermindertem Druck fraktioniert.

Nach dieser Methode wurden die folgenden Ester hergestellt (Schema 1):

Die Ester III bis VIII wurden von uns neu hergestellt. Ihre Struktur wurde spektroskopisch bestätigt.

Diese Methode eignet sich auch zur Herstellung von alizyklischen Estern der Cyanessigsäure, z.B. Cyclohexylcyanacetat,

IX 

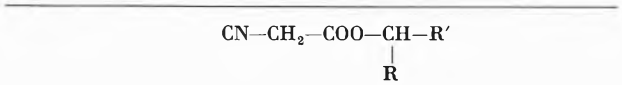
* Eingegangen am 1. März 1974.

Tabelle 1

Ester Nr.	Name	Molverhältnis Methylcyanacetat zu Alkohol	Reaktionsbedingungen Temperatur °C	Dauer h	E : R	Ausbeute %	Sdp. °C/Torr	n_D^{20}
II	2-Pentylcyanacetat	1 : 3	140–150	6	1 : 15	96	110–111/12	1,4243
III	4-Methyl-2-pentylcyanacetat	1 : 2	150–160	3½	1 : 15	95	115/12	1,4261
IV	5-Methyl-2-hexylcyanacetat	1 : 2	170–180	3½	1 : 4	93	129/12	1,4299
V	5-Methyl-3-heptylcyanacetat	1 : 2	180–200	3	–	91	135–136/12	1,4350
VI	2-Octylcyanacetat	1 : 2	200–210	1½	–	94	143–144/12	1,4340
VII	6-Methyl-5-hepten-2-yl-2-cyanacetat	1 : 2½	180–210	2	–	89	98–100/0,1	1,4515
VIII	1-Hexin-3-yl-3-cyanacetat	1 : 2	170–185	3	1 : 3	85	131–132/12	1,4483
IX	Cyclohexylcyanacetat	1 : 2½	125–160	1¼	–	92	138/12 *	1,4612

* (Lit. [11]: 103 bis 108 °C/0,5 Torr)

Schema 1



wobei bei

I	R = $-CH_3$	R′ = $-CH_2-CH_3$
II	$-CH_3$	$-CH_2-CH_2-CH_3$
III	$-CH_3$	$-CH_2-CH(CH_3)_2$
IV	$-CH_3$	$-(CH_2)_2-CH(CH_3)_2$
V	$-CH_2-CH_3$	$-CH_2-CH(CH_3)-CH_2-CH_3$
VI	$-CH_3$	$-(CH_2)_5-CH_3$
VII	$-CH_3$	$-(CH_2)_2-CH=C(CH_3)_2$
VIII	$-CC\equiv H$	$-CH_2-CH_2-CH_3$

Experimenteller Teil

Sek. Butylcyanacetat (I): In einem 1-Liter-Rundkolben, versehen mit Thermometer und einer Füllkörperkolonne mit versilbertem Vakuummantel (500 × 30 mm mit V_4A-Maschendrahtring-Füllung 4 × 4 mm), werden 198 g (2 Mol) Methylcyanacetat, 444 g (6 Mol) sek. Butanol und 10 g (0,05 Mol) Aluminiumisopropylat vorgelegt und mit einem Ölbad erhitzt. Wenn eine Kopftemperatur von 65 °C erreicht ist, wird das gebildete Methanol unter geregelter Entnahme (E : R = 1:15) abgetrennt. Die Badtemperatur wird langsam von 125 °C auf 140 °C erhöht. Nach 8 Stunden erreicht die Kopftemperatur den Siedepunkt des sekundären Butanols.

Das Reaktionsgemisch wird unter vermindertem Druck fraktioniert, wobei zunächst der überschüssige Alkohol und anschließend der Ester abdestillieren. Ausbeute: 273,5 g (97 %). Sdp. 100 bis 101 °C/12 Torr (Lit.[1]: 116 °C/20 Torr). n_D^{20} : 1,4210.

Die Bedingungen für die analoge Herstellung sowie Ausbeuten, Siedepunkte und Brechungsindizes der Ester II bis IX sind in Tabelle 1 zusammengefaßt. Die N-Bestimmungen ergaben innerhalb der üblichen Fehlergrenzen die den Formeln entsprechenden Werte.

Adel Said
Lonza AG, Werk Visp

[1] M. Yonezawa, S. Suzuki, H. Ito und K. Ito, *Yuki Gosei Kagaku Kyokai Shi 24* (1966) 580; *Chem. Abstr. 65* (1966) 18443.
[2] E. G. Somogyi, US Pat. 2553065 (1951).
[3] K. Tarui und S. Morimoto, Jap. Pat. 3418 (1956).
[4] Lonza AG, Werk Visp, unveröffentlichte Arbeit.
[5] Chemische Werke Witten, Belg. Pat. 660259 (1964).
[6] E. König, Schweiz. Pat. 540257 (1973).
[7] B. E. Sorenson, US Pat. 2251765 (1941).
[8] P. K. Mulvany, W. W. West und A. Goldschmidt, US Pat. 2891990 (1959).
[9] C. E. Rehberg und C. H. Fischer, *J. Org. Chem. 12* (1947) 226.
[10] Chemische Werke Witten, DWP 31540 (1963).
[11] M. S. Newman, B. J. Magerlein und Wm. B. Wheatley, *J. Amer. Chem. Soc. 68* (1946) 2112.

The Reaction of 2-Aminopyridines with Ethyl Diazoacetate*

Summary

It has been found that ethyl diazoacetate reacted with 2-amino-pyridines to give the corresponding 2-carbethoxymethylaminopyridines (**1**). In *m*-xylene as solvent, thermal decomposition of the diazo ester proceeded with preferential attack on *m*-xylene to give a mixture of isomeric ethyl dimethylcycloheptatrienecarboxylates (**2**, **3** and **4**).

There have been several reports concerning the reaction of diazoacetic ester with heterocyclic compounds under thermal, catalytic or photochemical conditions, in particular in the azole series.[1] In the pyridine series, ethyl diazoacetate was reacted with pyridones to give the corresponding N- or O-carbethoxymethyl derivatives.[2,3]

We have studied thermal and catalyzed reaction of ethyl diazoacetate with 2-aminopyridines. It is well established that ethyl diazoacetate loses nitrogen under

* Received March 4, 1974.

[1] V. Dave and E. W. Warnhoff, *Organic Reactions*, Vol. 18, Wiley, New York 1970, p. 217.
[2] M. P. Cava and N. K. Bhattacharryya, *J. Org. Chem. 23* (1958) 1614.
[3] J. Maas, G. B. R. de Graaff and H. J. den Hertog, *Rec. Trav. Chim. Pays-Bas 74* (1955) 175.

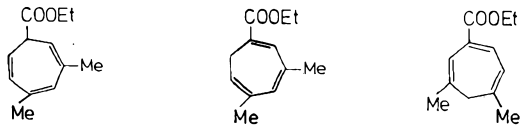
the influence of heat to give carbethoxy carbene[4,5] which is the reactive species. The decomposition may be catalyzed by metal salts or metals, in particular copper.

Ethyl diazoacetate smoothly decomposed in a boiling solution of 2-aminopyridine in benzene in the presence of anhydrous copper (II) sulfate. The reaction afforded 2-carbethoxymethylaminopyridine (**1**, R = H, R_1 = OEt) as the sole product,[6] b.p. 112 to 115°/1.8 mm (lit.[7] gives b.p. 156 to 160°/13.5 mm) (yield 13%; nmr ($CDCl_3$) τ 3.70 (H_3, *ddd*), 2.75 (H_4, *ddd*), 3.54 (H_5, *ddd*), 2.05 (H_6, *ddd*), 5.85 (*d*, $-CH_2-$), 5.83 (*q*, CH_2CH_3), 8.20 (*t*, CH_2CH_3), 4.9 (broad, NH), $J_{3,4}$ = 6.7, $J_{4,5}$ = 6.9, $J_{3,6}$ = 0.9, $J_{4,6}$ = 2.0, $J_{5,6}$ = 5.1, $J_{3,5}$ = 1.6, J_{Et} = 7.2 Hz.

1

In a similar fashion the reaction of 6-methyl-2-aminopyridine with ethyl diazoacetate gave the anticipated carbethoxymethylamino compound (**1**, R = Me, R_1 = OEt; b.p. 105 to 112°/1.5 mm; yield 9.7%; nmr ($CDCl_3$) τ 3.95 (*d*, H_3), 2.90 (*t*, H_4), 3.72 (*d*, H_5), 7.70 (*s*, 6-Me), 5.90 (*q*, CH_2CH_3), 8.75 (*t*, CH_2CH_3), 4.95 (broad, NH), $J_{3,4}$ = 7.5, $J_{4,5}$ = 7.2, J_{Et} = 7.2, J_{CH_2NH} = 6.0 Hz) in addition to a mixture of diethyl fumarate and maleate. It is well known, that all catalyzed decompositions of ethyl diazoacetate are accompanied by the formation of the aforementioned unsaturated esters which are generated from dimerization of ethoxycarbonylcarbene. In the case of 4-methyl- and 5-methyl-2-aminopyridines, the crude products on attempted purification by distillation decomposed into the starting amines.

We also studied the thermal decomposition of ethyl diazoacetate in the absence of a catalyst. When the reaction was conducted in boiling *m*-xylene (1.5 hr), 2-aminopyridine did not react and *m*-xylene was attacked perferentially to give a mixture of ethyl dimethylcycloheptatrienecarboxylates.[8] The mixture was separated by vpc[14] into several fractions. On the basis of high resolution mass spectra and nmr spectra, it was established that the first fraction consisted of a mixture of ethyl 3,5-dimethyl-2,4,6-cycloheptatrienecarboxylate (**2**) and ethyl 3,5-dimethyl-1,3,5-cycloheptatrienecarboxylate (**3**) (M^+ : *m*/e = 192.11527; calculated 192.11502). The second fraction consisted of pure 4,6-dimethyl-1,3,6-cycloheptatrienecarboxylate (**4**) (M^+ : *m*/e = 192.11679, calculated 192.11502; nmr ($CDCl_3$) τ 5.80 (*q*, CH_2CH_3), 8.68 (t, CH_2CH_3), J_{Et} = 7.2 Hz; τ 2.63 (*d*, H_2), 4.02 (*d*, H_3), 3.65 (*s*, H_7), 7.72 (*s*, 5-CH_2), 8.02 (broad *s*, 4-Me and 6-Me), $J_{2,3}$ = 6.5 Hz). The nmr spectrum of compound **4** exhibited a very close pattern to that as observed with the known corresponding acid.[13] The third fraction was ethyl 3,5-dimethyl-1,3,5-cycloheptatrienecarboxylate (**3**; M^+ : *m*/e = 192; nmr ($CDCl_3$) τ 2.80 (*s*, H_2), 3.70 (*s*, H_4), 4.60 (*t*, H_6), 7.75 (*d*, 7-CH_2), 8.0 (*s*, 3-Me), 8.09 (*s*, 5-Me), 5.76 (*q*, CH_2CH_3), 8.67 (*t*, CH_2CH_3), J_{Et} = 7.2, $J_{6,7\text{-}CH_2}$ = 6.0 Hz).



2 3 4

Carbethoxymethylaminopyridines were converted to the corresponding hydrazides (**1**, R = H, R_1 = $NHNH_2$; m.p. 90°, from ethyl acetate and *n*-hexane; M^+ : *m*/e = 166; nmr (DMSO-d_6) τ 3.5 (*m*, H_3, H_5), 2.70 (*m*, H_4), 2.10 (*m*, H_6), 6.15 (*d*, CH_2), 1.0 (broad, NH) 6.1 (broad, $NHNH_2$), or **1**, R = Me, R_1 = $NHNH_2$; mp 132°, from ethyl acetate and *n*-hexane; M^+ : *m*/e = 180°) or acid (**1**, R = H, R_1 = OH; mp 172–175° (lit.[15] gives mp 168 to 170°); nmr (DMSO-d_6) τ 3.17 (*m*, H_3), 2.40 (*m*, H_4), 3.35 (*m*, H_5), 2.10 (*m*, H_6), 5.90 (*s*, CH_2), 1.2 broad, NH); M^+ : *m*/e = 152) in the usual manner. An attempt to from the imidazo (1,2-a) pyridine system from 2-carbethoxymethylaminopyridine in the presence of polyphosphoric acid was not successful and the starting compound was recovered.

The authors acknowledge support of this work by a Boris Kidrič Foundation research grant. Our thanks are due also to Dr. V. Kramer, Institute J. Stefan, for recording high resolution mass spectra.

B. Doma, B. Verček, B. Stanovnik and M. Tišler

Department of Chemistry, University of Ljubljana
61000 Ljubljana (Yugoslavia)

[4] M. Jones and R. A. Moss, *Carbenes*, Wiley-Interscience, New York 1973, p. 95.
[5] W. Kirmse, *Carbene, Carbenoide und Carbenanaloge*, Verlag Chemie, Weinheim 1969.
[6] Melting points were determined on a Kofler micro hot stage. Nmr spectra were taken on a JEOL-C-60 HL spectrometer (TMS as internal standard). Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L instrument and high resolution mass spectra on a CEC 21-110C instrument. Freshly dehydrated copper(II) sulfate was used as catalyst. All compounds analyzed satisfactorily.
[7] E. B. Knott, *J. Chem. Soc. 1956*, 1644.
[8] The thermal and photochemical decomposition of methyl or ethyl diazoacetate has been reported[9–11] and structures for four products have been proposed.[12] In a recent report[13] *m*-xylene was reacted with ethyl diazoacetate at 145°. Vpc analysis revealed 5 peaks, but on a preparative scale only 4,6-dimethyl-1,3,6-cycloheptatrienecarboxylic acid was isolated and characterized.
[9] G. O. Schenk and H. Ziegler, *Ann. Chem. 584* (1953) 221.
[10] E. Buchner and K. Delbruck, *Ann. Chem. 358* (1907) 1.
[11] K. Alder, R. Muders, W. Krane and P. Wirtz, *Ann. Chem. 627* (1959) 59.
[12] G. O. Schenck and A. Ritter, *Tetrahedron Letters 1968*, 3189.
[13] S. Hanessian and G. Schütze, *J. Org. Chem. 34* (1969) 3196.
[14] Column length was 3 m, filled with Chromosorb A A/W, 45/60 mesh, impregnated with SE 30 (10%); flow 12 ml/min, 150°. Fractions with t_1 = 38, t_2 = 57 and t_3 = 69 min were used for structural determination.
[15] M. Augustin and H. Dehne, *J. prakt. Chem. 13* (1961) 118.

The acid dissociation constant of triethylsilanol in aqueous solution*

Summary

The acid dissociation constant of $(C_2H_5)_3SiOH$ in aqueous solution was evaluated with the aid of a distribution method using CCl_4 and an aqueous phase of constant ionic strength as solvents. The experimental results led to a value of $pK_a = 13.63$ ($\pm$ 0.07) (25 °C, I = 1 M Na[ClO_4]).

The increased aciditiy of silanols compared to alcohols was first observed by SOMMER *et al.*[1] who found that triethylsilanol is converted into its sodium salt by 12 M NaOH. ALLRED, ROCHOW and STONE[2] deduced from n.m.r. spectra that the hydroxyl proton in trimethylsilanol is less shielded than in *t*-butyl alcohol. This observation was attributed to $d\pi-p\pi$ bonding. Qualitative information on the acid strength of carbinols and silanols was obtained from i.r. spectra[3]. The shift of the OH stretching band on hydrogen bonding to organic bases such as ether or mesitylene indicates the following series of increasing acidity: Alkylcarbinols < arylcarbinols < alkylsilanos < arylsilanols. These observations were supplemented by direct measurements of the Brønsted acidity in pyridine solution[4]. The observed half neutralisation potentials suggest that triphenylsilanol is a somewhat weaker acid than phenol; alkylsilanols were found to be too weak for titration in this solvent.

In recent studies of the properties of surface OH groups, we observed that silanol groups at amorphous silica surfaces exhibit a surprisingly high acidity[5]. The intrinsic microscopic acidity constant $K_a = 1.6 \times 10^{-7}$ (25 °C, I = 1 M $NaClO_4$) is considerably larger than the microscopic acidity constant of H_4SiO_4[6] ($K_a = 8.4_5 \times 10^{-11}$, 25 °C, I = 1 M $NaClO_4$). Thus, it was of interest to evaluate K_a for some simple alkylsilanols and alkoxysilanols in the same solvent.

This paper reports the determination of the acid dissociation constant of triethylsilanol (BH) in aqueous solution using a distribution method. Solutions of BH in CCl_4 were equilibtrated with aqueous solutions S of the general composition $[Na^+] = 1M$, $[OH^-] = CM$, $[ClO_4^-] = (1\text{-}C)M$. The total concentrations of BH in CCl_4 (B_0) and S (B) were evaluated by gas chromatography. In order to minimize the effect of a possible association of BH in CCl_4[7], B_0 was kept low and almost constant. The measurements were carried out at 25.0 $\pm$ 0.5 °C.

Assuming that the aqueous phase containes no associated silanol species, the overall distribution coefficient D is given by

$$D = \frac{B}{B_0} = \frac{[BH]_{aq} + [B^-]_{aq}}{B_0}. \qquad (1)$$

At constant ionic strength, K_a is defined by

$$K_a = \frac{[H^+]_{aq}\,[B^-]_{aq}}{[BH]_{aq}} = K_w \frac{[B^-]_{aq}}{[OH^-]_{aq}\,[BH]_{aq}}, \qquad (2)$$

where

$$K_w = [H^+]_{aq}[OH^-]_{aq} = 1.698(\pm 0.038) \times 10^{-14}$$

(25 °C, I = 1 M $NaClO_4$).[6]

Hence

$$D = K_d + \frac{K_a \cdot K_d}{K_w}[OH^-]_{aq}, \qquad (3)$$

where $K_d = [BH]_{aq}/B_0$.

Since the initial concentration of OH^- in the aqueous phase is only little changed by the deprotonation of BH, a plot of D against C results in a straight line (Fig. 1).

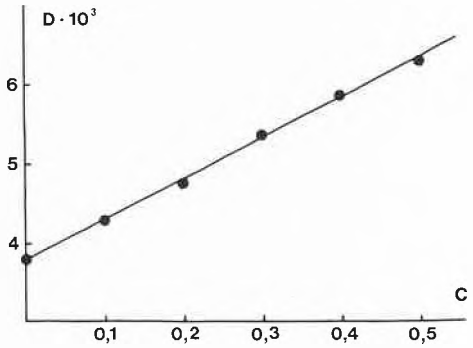


Fig. 1. The overall distribution coefficient D as a function of the OH^--concentration (C) of the aqueous phase. The straight line was calculated with $K_d = 3.78 \times 10^{-3}$ and $K_a = 2.29 \times 10^{-14}$

K_d and thus K_a are then calculated from intercept and slope respectively:

Experimental results (in molar units)

C	B_0	$B \times 10^3$
0	0.3346	1.226
0.100	0.3552	1.522
0.200	0.3535	1.677
0.300	0.3690	1.981
0.400	0.3710	2.176
0.500	0.3696	2.326

* Received March 22, 1974.

[1] L.H.SOMMER, E.W.PIETRUSZA and F.C.WHITMORE, *J. Amer. Chem. Soc. 68* (1946) 2282.
[2] L.ALLRED, E.G.ROCHOW and F.G.A.STONE, *J. Inorg. Nucl. Chem. 2* (1956) 416.
[3] R.WEST and R.H.BANEY, *J. Amer. Chem. Soc. 81* (1959) 6145.
[4] R.WEST and R.H.BANEY, *J. Inorg. Nucl. Chem. 7* (1958) 297.
[5] H.HOHL, L.SIGG and P.W.SCHINDLER, unpublished results.
[6] P.SANTSCHI and P.W.SCHINDLER, *Dalton Transactions 1974*, 181.
[7] K.LICHT and H.KRIEGSMANN, *Z. anorg. Chem. 323* (1963) 239.

$$\log K_a = -13.63\,(\pm 0.07)$$

(25 °C, I = 1M $Na[ClO_4]$).

The error limits correspond to 2σ.

Experimental

Triethylsilanol was prepared according to SOMMER *et al.*[1] and purified by preparative gas chromatography.

B.p.: 77.5° (28 torr). $n^{20} = 1.4329$, $d^{20} = 0.8638$.

Acknowledgments: Part of the experimental work was carried out by A. SAXER and H. KOHLER. The work was financially supported by the Swiss National Foundation.

H. ARM
Department of organic chemistry, University of Bern

K. HOCHSTRASSER and P. W. SCHINDLER*
Department of inorganic chemistry, University of Bern

* To whom correspondence may be addressed.

Sekundärionenmassenspektroskopische Untersuchungen an einem Zinkoxid-Katalysator*

Summary

Surface studies of ZnO catalysts using secondary ion mass spectroscopy (SIMS) showed that under dehydrogenation conditions a certain amount of the surface-zinc oxide is reduced to zinc.

Leitfähigkeitsmessungen an Zinkoxid-Katalysatoren[1] führten zur Annahme, daß bei der Dehydrierung von Alkoholen über Zinkoxid die Kontaktoberfläche teilweise in reduzierter Form vorliege. Da die Sekundärionenmassenspektroskopie (SIMS)[2–4] eine chemische Analyse der obersten Atomlagen der Oberfläche erlaubt, wurden Zinkoxid-Katalysatoren in frischem und gebrauchtem Zustand nach dieser Methode untersucht. Bei der SIMS-Analyse von Zinkoxid muß beachtet werden, daß Zink aus 6 Isotopen mit den folgenden Massenzahlen und Häufigkeiten besteht:

Massenzahl (g/mol)	64	66	67	68	70
Häufigkeit (%)	48,89	27,81	4,11	18,57	0,62

Im Sekundärionenmassenspektrum einer Zinkoxid-Oberfläche sind folgende Mehrfachkombinationen der Oberflächenbausteine zu erwarten:

$$Zn_aO_bH_c$$

a, b, c = 0, 1, 2, 3, 4, 5

Mit zunehmender Größe der Indizes a, b und c nimmt die Wahrscheinlichkeit für das Auftreten der entsprechenden Masse im SIMS stark ab. Die große Isotopenzahl des Zinks erzeugt aber eine breite Massenverteilung einer gegebenen Zink/Sauerstoff/Wasserstoff-Kombination.

Tritt im Verlauf der Dehydrierungsreaktion eine partielle Reduktion des Zinkoxid-Katalysators auf, so müßte an der Oberfläche eine Zinkanreicherung beobachtet werden können. Im Sekundärionenmassenspektrum sollte daher im Vergleich zum ungebrauchten Katalysator eine verstärkte Zinkionenemission festgestellt werden bzw. der Index a müßte sich auf Kosten des Sauerstoffindex b vergrößern. Die in Abb. 1 gezeigte schematische Darstellung der Katalysatoroberfläche verdeutlicht die steigende Emissionswahrscheinlichkeit von zinkreicheren Bruchstücken mit zunehmendem Reduktionsgrad.

* Eingegangen am 25. März 1974.

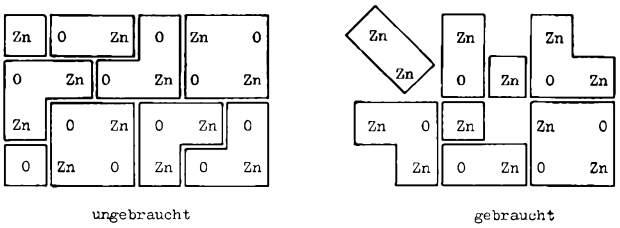


Abb. 1. Schematische Darstellung der von der Katalysatoroberfläche emittierten Bruchstücke

Wie die in Tabelle 1 zusammengestellten Signalhöhenverhältnisse zeigen, nimmt die Wahrscheinlichkeit für das Benachbartsein von Zink und Sauerstoff beim Vergleich von ungebrauchten und gebrauchten Katalysatoren ab, wodurch beispielsweise das Zn^+/ZnO^+-Verhältnis beim frischen Katalysator mit 1,9 kleiner ist als dasjenige des gebrauchten Kontaktes mit 4,3.

Tabelle 1. Signalverhältnis von Sekundärionen bei frischen und gebrauchten Zinkoxid-Katalysatoren

Signalverhältnis	Katalysator frisch	gebraucht
Zn^+ / ZnO^+	1,9	4,3
Zn^+ / ZnO_2^+	23,7	18,1
Zn_2^+ / ZnO^+	4,2	12,5
Zn_2^+ / Zn_2O^+	0,65	1,1
Zn_2^+ / Zn_2O_2	0,96	2,17
Zn_2O^+ / $Zn_2O_2^+$	1,5	2,1

Durch diese vergleichende Messung kann die unterschiedliche Emissionswahrscheinlichkeit der einzelnen Partikel eliminiert werden. Mit Hilfe der SIMS-Methode konnte somit eindeutig gezeigt werden, daß der für die Dehydrierung eingesetzte Katalysator bei den gegebenen Reaktionsbedingungen (T = 350 °C, Substrat = Methylcyclohexanol) teilweise reduziert wurde.

Experimentelles

Das SIMS-Verfahren beruht darauf, daß ein Festkörper im Hochvakuum mit Primärionen (Argon) beschossen wird, die während der Implantation in den Kristall ihre Energie an die sie umgebenden Gitteratome abgeben. Durch einen komplexen

Stoßkaskadenprozeß können nun Partikel (Neutralteilchen oder Ionen), die sich an der Oberfläche befinden, soviel Energie aufnehmen, daß sie sich von dieser lösen. Die Sekundärionen werden dann in einem Quadrupolmassenfilter nach ihren Massen aufgetrennt und mit einem Sekundärelektronenvervielfacher nachgewiesen.

[1] P. FONTANA. Diss. ETH, Zürich, Nr. 5210 (1973).
[2] A. BENNINGHOVEN, *Z. Physik 230* (1970) 403.
[3] A. BENNINGHOVEN, *Physic. Letters 32 A* (1970) 427.
[4] A. BENNINGHOVEN und E. LOEBACH, *Rev. Sci. Instr. 42* (1971) 49.

Der Firma Balzers AG, insbesondere dem Applikationslaboratorium für Oberflächenuntersuchungen, sei für die Durchführung der SIMS-Analysen bestens gedankt.

P. FONTANA und G. GUT

Technisch-Chemisches Laboratorium der Eidgenössischen Technischen Hochschule, 8006 Zürich