characterized by very high yield (97%) in comparison with the conventional method using H_2SO_4[2,4] or a mixture of H_2SO_4 and CH_3CO_2H.[2]

Experimental

Melting points were determined on Yanaco melting point apparatus and are uncorrected. UV, IR and MS spectra were taken on Shimadzu UV-200, Jasco IRA-1 and JEOL JMS-D 100 machines, respectively. All solutions were dried over anhyd. $MgSO_4$.

Treatment of N-[α-(3,4-Dimethoxybenzyl)-3,4-dimethoxybenzyl]aminoacetal (1) Oxalate with $ClSO_3H$——1 oxalate (2.48 g, 4.7 mmol) prepared according to the method in the lit.[2] was added little by little to $ClSO_3H$ (3.1 ml) and the reaction mixture was held at −60——50° for 30 min with vigorous stirring, then allowed to stand at −15° for 3 hr in the absence of moisture. The reaction mixture was poured into 100 ml of ice-water and extracted with Et_2O to remove non-basic substances. The aq. layer was made alkaline with 10% aq. NaOH, then shaken with hot C_6H_6. The benzene solution was dried, and the solvent was distilled off. A basic substance was deposited which melted at 153.5—155°. This base was shown to be identical with an authentic sample of isopavine (3). Yield 1.57 g (97%). *Anal.* Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.94; H, 6.84; N, 4.10. MS: *m/e* (%), 156 (10.7), 190 (72), 191 (10.5), 269 (17.9), 281 (10.7), 312 (100), 313 (24.7), 314 (35.9), 341, M^+ (43.6).

Acknowledgment The authors are grateful to Mr. T. Miyazaki for elemental analyses and mass spectral measurement.

References and Notes

1) *a*) This paper forms Part IV of "Halosulfonic Acid as a Cyclizing Agent for Isoquinoline Synthesis"; *b*) Part III: K. Kido and Y. Watanabe, *Heterocycles*, **14**, 1151 (1980).
2) E. Waldmann and C. Chwala, *Ann. Chem.*, **609**, 125 (1957).
3) M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, 1972, pp. 112—113.
4) D.A. Guthrie, A.W. Frank, and C.B. Purves, *Can. J. Chem.*, 33, 729 (1955); A.R. Battersby and D.A. Yeowell, *J. Chem. Soc.*, **1958**, 1988.

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Studies on Ketene and Its Derivatives. CII.[1] Reaction of Diketene with Cyanamide Derivatives

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The reaction of diketene with cyanamide gave 2-amino-6-methyl-4*H*-1,3-oxazin-4-one, which was transformed to 6-methyluracil by refluxing it in acetic acid. Diketene also reacted with monosubstituted cyanamides to give 1,3-oxazin-4-one derivatives, which could be similarly converted into 1-substituted 6-methyluracils. The reaction of diketene with dicyanodiamide afforded 2-guanidino-6-methyl-4*H*-1,3-oxazin-4-one, which, on treatment with ammonia, afforded 2-guanidino-4-hydroxy-6-methylpyrimidine.

Keywords——diketene; cyanamide; monosubstituted cyanamides; 6-methyluracils; dicyanodiamide; 4*H*-1,3-oxazin-4-ones; ring transformation

It has been reported that diketene reacts with compounds having a C=N double bond, such as S-alkylthiourea,[2] diphenylguanidine,[3] N-trimethylsilylketimine,[4] and some Schiff bases[5] to give 6-methyl-4*H*-1,3-oxazin-4-one derivatives. Similarly, Gompper *et al.*[6] reported the reaction of diketene with disubstituted cyanamides, such as dimethyl-, diethyl-, and

diisopropyl-cyanamide, to give the corresponding 2-dialkylamino-6-methyl-4*H*-1,3-oxazin-4-one. Previously, we have reported that diketene reacts with ketimine[7] and imidates[8] to give 6-methyl-4*H*-1,3-oxazin-4-ones, which can be transformed to pyridone or pyrimidone derivatives.[9] The present paper reports the reaction of diketene with cyanamide (**1a**), monosubstituted cyanamides **1b**—**e**, and dicyanodiamide (**1f**) to give the 1,3-oxazine derivatives **2a**—**f**.

When diketene was allowed to react with cyanamide (**1a**), 2-amino-6-methyl-4*H*-1,3-oxazin-4-one (**2'a**) was obtained in 58% yield. As detailed in the experimental section, elemental analysis and spectroscopic data were consistent with the oxazine structure **2'a**. Similar reaction with monosubstituted cyanamides **1c**—**e** gave the corresponding 2-alkylamino-6-methyl-4*H*-1,3-oxazin-4-ones **2'c**—**e** in 49, 68, and 45% yields, respectively. The nuclear magnetic resonance (NMR) spectral study suggests that the adducts from **1a**, **1d**, and **1e** have the 2-amino-4*H*-1,3-oxazin-4-one structures **2'a**, **2'd**, and **2'e**, while the adduct from **1b** exists in the 2-imino-2,3-dihydro-4*H*-1,3-oxazin-4-one structure **2b**. As shown in Table I, the NMR spectra of **2'a**, **2'd**, and **2'e** show broad signals due to the 2-amino proton at 7.98 (2H), 8.30—8.85 (1H), and 8.92—9.40 ppm (1H), respectively. On the other hand, the NH proton of the adduct of **1b** shows its chemical shift at rather higher field (5.60—6.20 ppm), corresponding to the amide NH proton of the structure **2b**. In the case of the adduct from **1c**, its NMR spectrum indicated the presence of amino and amido protons at 9.00—9.51 and 6.10—6.90 ppm, respectively. However, on heating, the amino proton signal disappeared, indicating the imino structure **2c**. Similarly, **2'a** and **2'd** isomerized on heating to the 2-imino structures **2a** and **2d**, respectively.

2-Amino-6-methyl-4*H*-1,3-oxazin-4-one (**2'a**) was refluxed in acetic acid to give 6-methyluracil (**3a**) in 76% yield. Compounds **2'b**—**e** were similarly converted to the 1-substituted 6-methyluracils **3b**—**e**. The results are summarized in Table II.

The reaction of dicyanodiamide (**1f**) with diketene in acetic acid afforded 2-guanidino-6-methyl-4*H*-1,3-oxazin-4-one (**2f**) in 86% yield. Treatment of compound **2f** in refluxing

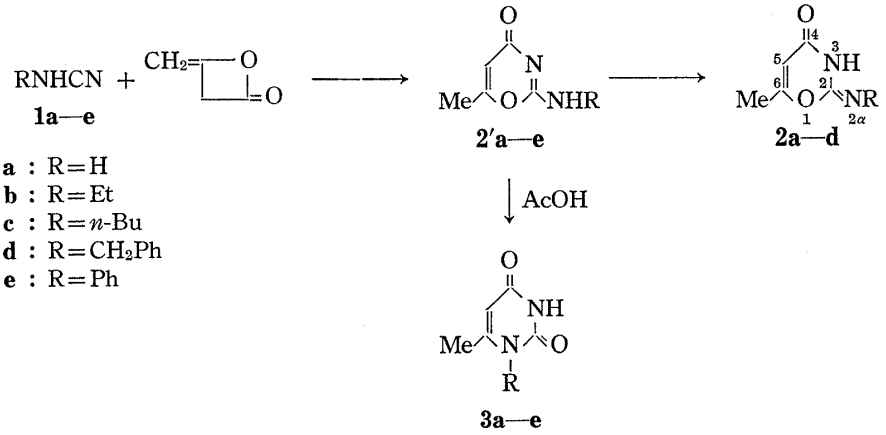


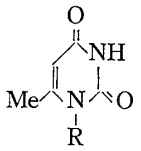
Chart 1

Table I. NMR Spectral Data for **2a**—**e** and **2'a**—**e** (δ in $CDCl_3$)

	2'a[a]	2'b	2'c	2'd	2'e
$N_{2\alpha}$–H	7.98	—	9.00—9.51	8.30—8.85	8.92—9.40
	2a[a]	**2b**	**2c**	**2d**	**2e**
N_3–H	6.40—6.70	5.60—6.20	6.10—6.90	6.15—6.72	—

a) Measured in DMSO-d_6.

TABLE II.



3a—e

Compd. No	Scale (mmol)	Product No	R	Yield (%)	mp (°C) (lit. mp (°C))	Crystal form (Recrystn. solvent)
2'a	1	**3a**	H	76	313 (dec.) (313—315 (dec.))[10]	Needles (EtOH)
2b	1	**3b**	Et	55	195—196 (195—196)[11]	Needles (EtOH)
2'c	1	**3c**	*n*-Bu	65	132—133 (133—136)[11]	Needles (*n*-hexane)
2'd	1	**3d**	CH_2Ph	58	230—231 (232—233)[11]	Needles (AcOEt)
2'e	1	**3e**	Ph	50	273 (dec.) (272—274)[11]	Prisms (AcOEt)

28% NH_4OH gave 2-guanidino-4-hydroxy-6-methylpyrimidine (**4**) in 55% yield; this product was identified by comparison with an authentic sample of **4** prepared from diketene and biguanide (**5**) according to the literature.[12]

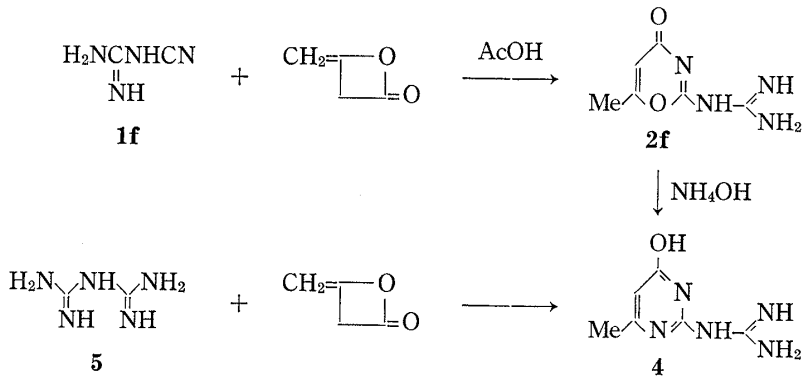


Chart 2

The formation of the 1,3-oxazin-4-ones **2a**—**f** can be rationalized as shown in Chart 3; namely, the carbodiimide intermediate **1'** is acylated with diketene to give the dipolar intermediate **A**, which cyclizes to the intermediate **B**. Prototropy gives rise to the oxazine **2**.

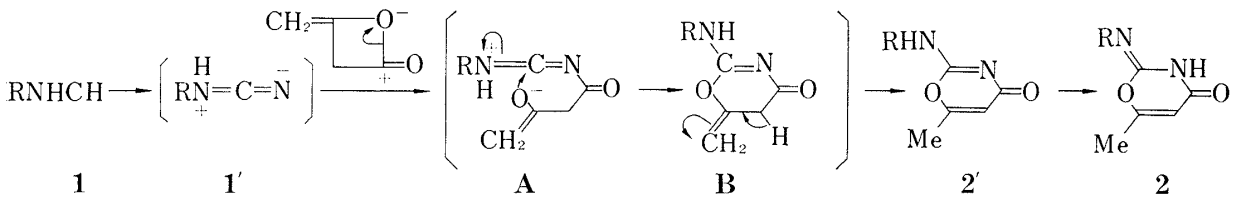


Chart 3

Experimental

Melting points are uncorrected. Proton NMR spectra were recorded on a Hitachi R-20 instrument with tetramethylsilane (or 3-(trimethylsilyl)propanesulfonic acid sodium salt) as an internal standard. IR spectra were taken on a JASCO IR-S spectrometer. UV spectra were taken on a Beckmann DB-G spectrometer. Mass spectra (MS) were obtained with a Hitachi M-52G spectrometer operating at an ionization potential of 15 eV.

Reaction of Cyanamide (1a) with Diketene——Diketene (9.2 g, 0.1 mol) was added dropwise to a solution of **1a** (4.2 g, 0.1 mol) in water (10 ml) at room temperature with stirring. After every 24 hr, additional diketene (4.6, 2.3, and 1 g) was added (total amount of diketene, 17.1 g, 0.2 mol). Crystals that separated were collected and recrystallized from methanol to give 2-amino-6-methyl-4*H*-1,3-oxazin-4-one (**2'a**), which isomerized to 3,4-dihydro-2-imino-6-methyl-2*H*-1,3-oxazin-4-one (**2a**) on heating at 150° for 3 hr; needles (from methanol), mp 287° (dec.). Yield, 7.3 g (58%). *Anal.* Calcd for $C_5H_6N_2O_2$: C, 47.81; H, 5.06; N, 22.45. Found: C, 47.62; H, 4.86; N, 22.22. UV $\lambda_{max}^{ethanol}$ nm (log ε): 219 (3.78), 300 (3.93). IR ν_{max}^{KBr} cm^{-1}: 3330, 3120, 1730, 1660. **2'a**: NMR (DMSO-d_6) δ: 2.01 (3H, s, CH_3), 5.42 (1H, s, C_5–H), 7.98 (2H, br, $N_{2\alpha}$–H). **2a**: NMR (DMSO-d_6) δ: 2.03 (3H, s, CH_3), 5.31 (1H, s, C_5–H), 6.40—6.70 (1H, br, N_3–H), 7.98 (1H, br, $N_{2\alpha}$–H).

Reaction of Ethylcyanamide (1b) with Diketene——Diketene (1.8 g, 0.02 mol) was added dropwise to **1b** (1.4 g, 0.02 mol) over a period of 2 hr. The mixture was stirred for 24 hr at room temperature, then concentrated under reduced pressure to give a crystalline product. Recrystallization from *n*-hexane gave 2-ethylimino-3,4-dihydro-6-methyl-2*H*-1,3-oxazin-4-one (**2b**) as prisms, mp 63.5—64.5°. Yield, 1.2 g (38%). *Anal.* Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.81; H, 6.51; N, 17.98. UV $\lambda_{max}^{ethanol}$ nm (log ε): 211 (3.98), 251 (3.36). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330, 2980, 1690, 1640. NMR ($CDCl_3$) δ: 1.22 (3H, t, J= 7 Hz, $NCH_2\underline{CH_3}$), 2.06 (3H, s, CH_3), 3.98 (2H, q, J=7 Hz, $N\underline{CH_2}CH_3$), 5.52 (1H, s, C_5–H), 5.60—6.20 (1H, br, N_3–H).

Reaction of *n*-Butylcyanamide (1c) with Diketene——*n*-Butylcyanamide (**1c**) (1.96 g, 0.02 mol) was dissolved in diketene (2.52 g, 0.03 mol), and the reaction mixture was stirred for 24 hr at room temperature. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography with ethyl acetate as an eluent to give a mixture of 2-*n*-butylamino-6-methyl-4*H*-1,3-oxazin-4-one (**2'c**) and 2-*n*-butylimino-3,4-dihydro-6-methyl-2*H*-1,3-oxazin-4-one (**2c**). This mixture was heated at 120° for 3 hr to give the iminooxazine **2c** as prisms (from ethyl acetate), mp 106—107°. Yield, 1.78 g (49%). *Anal.* Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.55; H, 7.70; N, 15.57. UV $\lambda_{max}^{ethanol}$ nm (log ε): 213 (4.28), 246 (sh) (3.81). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 3050, 1678, 1610. **2'c**: NMR ($CDCl_3$) δ: 0.92 (3H, t, J=6 Hz, $N(CH_2)_3\underline{CH_3}$), 1.03—1.78 (4H, m, $NCH_2(CH_2)_2\underline{CH_3}$), 2.12 (3H, s, CH_3), 3.40 (2H, t, J=7 Hz, $N\underline{CH_2}(CH_2)_2CH_3$), 5.74 (1H, s, C_5–H), 9.00—9.51 (1H, br, $N_{2\alpha}$–H). **2c**: NMR ($CDCl_3$) δ: 0.93 (3H, t, J=6 Hz, $N(CH_2)_3\underline{CH_3}$), 1.03—1.78 (4H, m, $NCH_2(\underline{CH_2})_2CH_3$), 3.40 (2H, t, J=7 Hz, $N\underline{CH_2}(CH_2)_2CH_3$), 5.72 (1H, s, C_5–H), 6.10—6.90 (1H, br, N_3–H).

Reaction of Benzylcyanamide (1d) with Diketene——Benzylcyanamide (**1d**) (1.32 g, 0.01 mol) was dissolved in diketene (1.68 g, 0.02 mol). The solution was stirred for 24 hr. Crystals that separated were collected and recrystallized from ethyl acetate to give 2-benzylamino-6-methyl-4*H*-1,3-oxazin-4-one (**2'd**), which isomerized to 2-benzylimino-3,4-dihydro-6-methyl-2*H*-1,3-oxazin-4-one (**2d**) on heating at 165° for 3 hr; prisms (from ethyl acetate), mp 164—164.5°, yield, 1.47 g (68%). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.73; H, 5.86; N, 13.00. UV $\lambda_{max}^{ethanol}$ nm (log ε): 209 (4.67), 250 (sh) (4.03). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 3010, 1680, 1610. **2'd**: NMR ($CDCl_3$) δ: 2.09 (3H, s, CH_3), 4.48 (2H, d, J= 7 Hz, NCH_2–), 5.67 (1H, s, C_5–H), 7.28 (5H, s, aromatic protons), 8.30—8.85 (1H, br, $N_{2\alpha}$–H). **2d**: NMR ($CDCl_3$) δ: 2.06 (3H, s, CH_3), 4.52 (2H, s, NCH_2–), 5.71 (1H, s, C_5–H), 6.15—6.72 (1H, br, N_3–H), 7.33 (5H, s, aromatic protons).

Reaction of Phenylcyanamide (1e) with Diketene——Phenylcyanamide (**1e**) (1.18 g, 0.01 mol) was dissolved in diketene (1.68 g, 0.02 mol). The solution was stirred for 24 hr at room temperature, and concentrated *in vacuo*. The resulting residue was recrystallized from ethyl acetate to give 6-methyl-2-phenylamino-4*H*-1,3-oxazin-4-one (**2'e**) as prisms, mp 180—181° (lit.[13] mp 177—178°). Yield, 0.9 g (45%). NMR ($CDCl_3$) δ: 2.12 (3H, s, CH_3), 5.87 (1H, s, C_5–H), 7.08—7.71 (5H, m, aromatic protons), 8.92—9.40 (1H, br, $N_{2\alpha}$–H).

1-Substituted-6-methyluracils 3a—e: General Procedure——The 1,3-oxazin-4-ones **2'a—e** (1 mmol) were dissolved in acetic acid (2 ml), and the mixture was refluxed for 24 hr. The mixture was concentrated under reduced pressure to give a crystalline substance. Recrystallization gave the uracils **3a—e**. The results are summarized in Table II.

2-Guanidino-6-methyl-4*H*-1,3-oxazin-4-one (2f)——Diketene (2.52 g, 0.03 mol) was added to a suspension of dicyanodiamide (**1f**) (2.1 g, 0.025 mol) in acetic acid (30 ml) with stirring at room temperature. The suspension changed into a solution. After 3 days, crystals that had separated were collected and washed with ether. Recrystallization from ethanol gave the product **2f** as needles, mp 240° (dec.). Yield, 3.6 g (86%). *Anal.* Calcd for $C_6H_8N_4O_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 43.04; H, 5.22; N, 32.93. IR ν_{max}^{KBr} cm^{-1}: 3320, 3100, 1655, 1640. NMR (DMSO-d_6) δ: 2.06 (3H, s, CH_3), 5.70 (1H, s, C_5–H), 6.94—8.44 (4H, br, NH_2 and 2×NH). MS *m/e*: 168 (M^+).

2-Guanidino-4-hydroxy-6-methylpyrimidine (4)——a) The guanidino-1,3-oxazinone **2f** (0.25 g, 1.5 mmol) was dissolved in 28% NH_4OH (10 ml). The mixture was refluxed for 4 hr, and concentrated under reduced pressure. The resulting residue was treated with Norit in methanol. The methanol solution gave the product **4** as pale yellow prisms, mp 305° (dec.) (lit.[14] mp 303° (dec.)). Yield, 0.14 g (55%).

b) According to the literature,[12] diketene (0.9 g, 11 mmol) was added dropwise to a solution of biguanide (**5**) (0.5 g, 5 mmol) in water (5 ml). The mixture was stirred at room temperature for 24 hr. Crystals that separated were collected and recrystallized from methanol to give the product **4**. Yield, 0.25 g (30%).

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References and Notes

1) Part CI: T. Kato, N. Katagiri, M. Tanaka, A. Wagai, and K. Harimaya, *Chem. Pharm. Bull.*, **28**, 2129 (1980).
2) R.N. Lacey, *J. Chem. Soc.*, **1954**, 839.
3) R.N. Lacey, *J. Chem. Soc.*, **1954**, 845.
4) H. Suzuki, I. Matsuda, K. Itoh, and Y. Ishii, *Bull. Chem. Soc. Jpn.*, **47**, 2736 (1974).
5) A. Maujean and J. Chuche, *Tetrahedron Lett.*, **1976**, 2905.
6) R. Gompper and J. Stetter, *Tetrahedron Lett.*, **1973**, 233.
7) T. Kato and T. Sakamoto, *Yakugaku Zasshi*, **87**, 1322 (1967).
8) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.*, **13**, 959 (1965); T. Kato, Y. Yamamoto, and M. Kondo, *ibid.*, **23**, 1873 (1975).
9) T. Kato and M. Kondo, *Chem. Pharm. Bull.*, **24**, 356 (1976).
10) Y. Iwakura and K. Nagakubo, *Kogyo Kagaku Zasshi*, **57**, 947 (1954).
11) V.I. Gunar and S.I. Zav'yalov, *Dokl. Akad. Nauk SSSR*, **158**, 1358 (1964).
12) M. Furukawa, T. Yoshida, M. Goto, and S. Hayashi, *Chem. Pharm. Bull.*, **21**, 2594 (1973).
13) A.C. Veronese and F. D'Angeli, *Ann. Chim.* (Rome), **60**, 374 (1970).
14) A.F. Crowther, F.H.S. Curd, and F.L. Rose, *J. Chem. Soc.*, **1948**, 586.

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Chemische und chemotaxonomische Untersuchungen von Filices. XXXV.[1] Chemische Untersuchungen der Inhaltsstoffe von *Polystichum tripteron* (Kunze) Pr.

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(Eingegangen am 10, September 1980)

From the fronds of *Polystichum tripteron* (Kunze) Pr. a new norcarotenoid glycoside was isolated and shown to be (6*R*, 7*E*, 9*R*)-9-hydroxy-megastigma-4,7-dien-3-one-9-O-β-D-glucoside. The fronds of *Dennstaedtia wilfordii* (Moore) Christ. contain the same glucoside.

Keywords——*Polystichum tripteron*; *Dennstaedtia wilfordii*; ferns; norcarotenoid glucoside; (6*R*,7*E*,9*R*)-9-hydroxy-megastigma-4,7-dien-3-one-9-O-β-D-glucoside

In Fortsetzung unserer chemischen und chemotaxonomischen Untersuchungen von Filices wurde *Polystichum tripteron* (Kunze) Pr. (jap. Name: Jyumonji-shida, Aspidiaceae) auf die Inhaltsstoffe untersucht. Die oberirdischen Teile enthalten ein bisher unbekanntes Glykosid (I) des Norcarotinoid–Typs. In dieser Mitteilung wird über die Struktur des Glykosids berichtet.

Das Glykosid (I), $C_{19}H_{30}O_7$, stellt farbloses Öl vom $[\alpha]_D^{20}$ +58.6° (c=1.5, MeOH) dar. Im PMR–Spektrum (100 MHz, C_5D_5N) erscheinen die Signale bei δ 3.72—4.70 (7H) und 4.90 (1H, d, J=7 Hz) für die Protonen des Zucker–Anteils und im ^{13}C-NMR–Spektrum die Signale