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THE REACTION OF METHYL DIAZOACETATE WITH 4,4-DIMETHYL-2-PENTYN-1-AL AND RELATED COMPOUNDS

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Summary

Methyl 2-diazo-3-hydroxy-6,6-dimethyl-4-heptynoate was prepared by treating 4,4-dimethyl-2-pentyn-1-al with methyl diazoacetate at room temperature in the absence of catalysts. In the case of related aldehydes, RC≡CCHO (R = n-Bu, Me_3Si, Et_3Si, Et_3Ge), this unusual reaction is partially or completely suppressed by a competing 1,3-cycloaddition process. The latter leads to a mixture of isomeric 3- and 4-formylpyrazole, one of which cyclodimerizes to form tricyclic hemiaminal.

Introduction

4,4-Dimethyl-2-pentyn-1-al (Ia) has broad synthetic applicability as a synthon since it posseses two reaction sites. For example, the carbonyl group and the carbon—carbon triple bond are reactive towards diazo compounds. The reaction of diazomethane and its derivatives with aldehydes has been shown to give corresponding epoxides and/or ketones [1]. Dipolar addition of diazo compounds to carbon—carbon multiple bonds is also well known [2]. Thus, when propynal was treated with ethyl diazoacetate in ether, only 3-formyl-4-(ethoxycarbonyl)pyrazole was isolated in 86% yield [3]. We describe below a study of the scope of the reaction between acetylenic aldehydes and methyl diazoacetate *.

Results and discussion

Methyl diazoacetate can react with aldehydes of general formula R—C≡CCHO (Ia—Ie) in different ways: 1,3-cycloaddition and/or addition to the

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* Preliminary communication, see ref. 4.

carbonyl group (Scheme 1). Typical reaction conditions involve treatment of aldehyde with one equivalent of the diazo ester in ether at room temperature in the dark. Under these conditions 4,4-dimethyl-2-pentyn-1-al (Ia) was converted exclusively to an aldol-type adduct. The analytical data obtained for the adduct were compatible with the formulation of the product as methyl 2-diazo-3-hydroxy-6,6-dimethyl-4-heptynoate (Va). This reaction is particularly surprising in view of the stability of the triple bond towards the diazo ester. Moreover, this bond in Ia is apparently more stable to methyl diazoacetate than the carbon—oxygen multiple bond. For this compound the explanation may lie in shielding of the triple bond by the bulky tert-butyl group. In accord with this conclusion, addition of methyl diazoacetate to an ether solution of n-BuC$\equiv$CCHO (Ib) under conditions similar to those used for Ia causes the formation of isomeric pyrazoles IIb and IIIb together with methyl 2-diazo-3-hydroxy-4-nonynoate (Vb) (see Table 1).

SCHEME 1

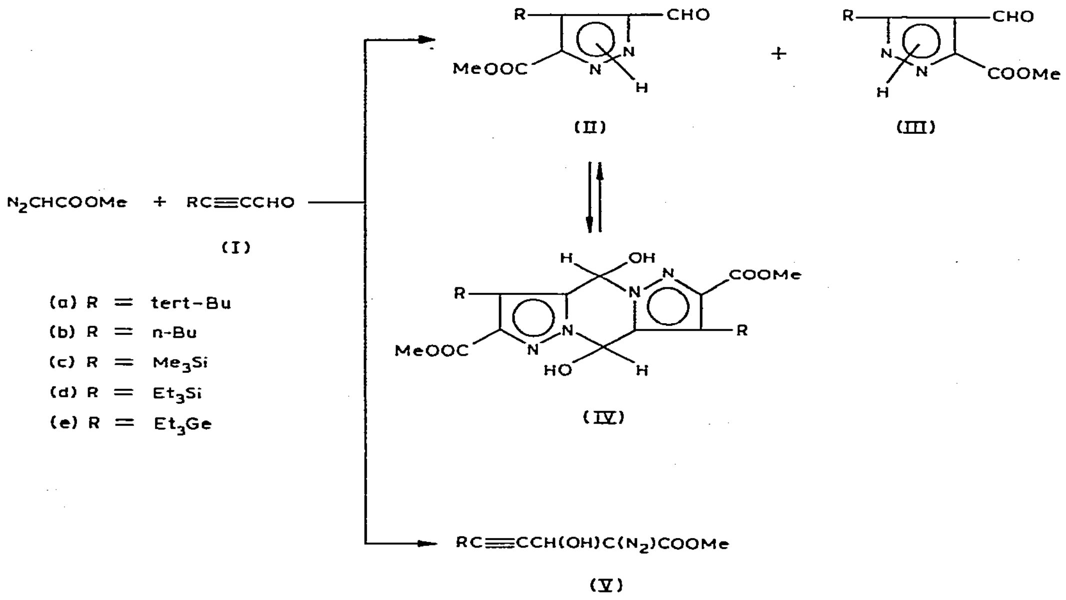


TABLE 1

REACTION OF 4,4-DIMETHYL-2-PENTYN-1-AL AND RELATED COMPOUNDS (Ia—Ie) WITH METHYL DIAZOACETATE

Starting reagent	Products (%) [a]			
	II	III	IV	V
t-BuC$\equiv$CCHO (Ia)	—	—	—	100
n-BuC$\equiv$CCHO (Ib)	5	4	38	53
Me$_3$SiC$\equiv$CCHO (Ic)	15	50	35	—
Et$_3$SiC$\equiv$CCHO (Id)	—	45	10	45
Et$_3$GeC$\equiv$CCHO (Ie)	10	35	25	35

[a] Determined by ^{1}H NMR spectroscopy.

TABLE 2

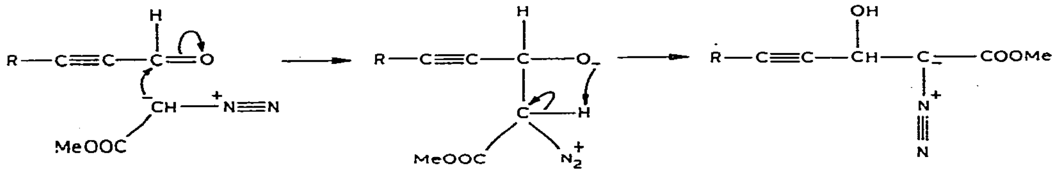
ANALYTICAL AND OTHER DATA FOR THE COMPOUNDS PREPARED IN THIS INVESTIGATION

Compound	R	Yield (%)	m.p. (°C)	n_D^{20}	Analysis, found (calcd.) (%)			
					N	C	H	Si/Ge
IIIc	Me_3	43	152–153		12.47 (12.37)	47.62 (47.74)	6.32 (6.24)	12.53 (12.41)
IIId	Et_3Si	25	98–99		10.68 (10.44)	53.94 (53.70)	7.50 (7.51)	10.57 (10.46)
IIIe	Et_3Ge	33	108–109		8.62 (8.45)	45.84 (46.07)	6.35 (6.40)	23.54 (23.22)
IVb	n-Bu	19	89–90		13.21 (13.33)	57.08 (57.14)	6.78 (6.67)	
IVc	Me_3Si	23	52–53		12.18 (12.37)	47.86 (47.74)	6.44 (6.24)	12.24 (12.41)
IVe	Et_3Ge	35	138–139		8.99 (8.95)	46.04 (46.07)	6.24 (6.40)	23.16 (23.22)
Va	t-Bu	88	oil	1.4866	13.20 (13.32)	57.21 (57.13)	6.59 (6.71)	
Vb	n-Bu	33	oil		13.01 (13.32)	57.48 (57.13)	6.82 (6.71)	
Vd	Et_3Si	54	oil	1.5030	10.34 (10.44)	53.52 (53.70)	7.50 (7.51)	10.21 (10.46)
Ve	Et_3Ge	28	oil	1.5040	7.17 (6.95)	46.09 (46.07)	6.43 (6.40)	23.08 (23.22)
VII	Et_3Ge	100	89–90		7.43 (7.27)	46.97 (46.79)	7.43 (7.33)	[a]
VIII	Et_3Ge	26	180–182		14.01 (13.94)	53.31 (53.65)	6.31 (6.56)	18.12 (18.01)
IX	Et_3Ge	76	93–94.5		7.93 (7.80)	46.73 (46.85)	7.08 (7.30)	19.99 (20.22)

[a] Si 7.28 (7.29) %; Ge 18.70 (18.85) %.

It is also well known that propynal reacts with ethyl diazoacetate [3], diazoethane [5] and phenyldiazomethane [6] to give mainly the products of dipolar addition of diazo compounds to the triple bond. These results indicate that the steric effect of the R group attached to the *sp* carbon of the acetylenic aldehyde plays an important role in the regioselectivity. Similarly, α-diazo-β-hydroxy esters (Vd, e) were formed along with mixtures of the corresponding pyrazoles in the reactions of triethylsilyl- and triethylgermylpropynal with methyl diazoacetate. The esters (Va—Ve) are new compounds and appear to be the first compounds isolated containing both a diazo group and a carbon—carbon triple bond. This type of reaction seems to be a convenient method for the preparation of diazo compounds containing four different functional groups. Compounds of type V probably result from initial attack of methyl diazoacetate at the carbonyl group of I to give the dipolar intermediate VI [cf. 1,7], which is followed by fast proton migration (Scheme 2)

SCHEME 2



(VI) (V)

The structure of the product Va could be assigned unambiguously from its IR and ^{1}H NMR spectra (Table 3). For example, the IR spectrum shows a strong band at 1700 cm^{-1} attributable to the ester carbonyl group, a diazo group band at 2110 cm^{-1}, a strong band at 2250 cm^{-1} [ν(C≡C)], and a hydroxy group band at 3450 cm^{-1}.

Similar carbonyl addition reactions of diazo compounds with aldehydes and ketones have appeared in a number of reports [8]. For example, 2,2,2-trifluorodiazoethane has been recently shown to react with F_3CCHO and Cl_3CCHO with an intermediate formation of relatively stable α-diazo-β-hydroxy alkanes [9]. Similarly, ethyl diazoacetate was shown to add to the carbonyl group of alloxane and related compounds [10].

The reaction of $LiC(N_2)COR$ and $LiC(N_2)COOR$ with aldehydes or ketones is the most fundamental one for the preparation of α-diazo-β-hydroxy ketones and β-hydroxy-α-diazo esters, respectively [11—16]. The best yields of α-diazo-β-hydroxy esters or α-diazo-β-hydroxy ketones are obtained when ethyl lithiodiazoacetate (or lithiodiazoacetone) is generated in situ by adding to the mixture of aldehyde and ethyl diazoacetate (or diazoacetone) a solution of lithium diisopropylamide in THF at low temperature [12,14,16—21]. The base-catalysed reaction between aldehydes and ethyl diazoacetate (or α-diazoacetone) has been reported to yield aldol-type products [18,22—26].

The reaction between trimethylsilylpropynal (Ic) and methyldiazoacetate does not give the corresponding β-hydroxy-α-diazo ester (Vc) but instead gives 3(5)-formyl-4-trimethylsilyl-5(3)-methoxycarbonylpyrazole (IIc) together with

TABLE 3

SPECTROSCOPIC PROPERTIES OF THE COMPOUNDS PREPARED IN THIS INVESTIGATION

Compound	IR, ν (cm^{-1})					NMR, chemical shifts (ppm)						
	C=N	CH=O	OC=O	N≡N	C≡C	OH(NH)	MR$_3$	MeOCO	OH	CH	CHO	NH
IIIc	1525	1685	1730			3130	0.96t	3.95s			10.48s	
IIId	1530	1640	1730			3150	0.56m 0.95m	3.98s			10.48s	
IIIe	1540		1720									
IVc	1530		1725			3380	0.96s				10.48s	
IVe	1530		1725			3370	1.05t	3.92s	4.90d [d]	6.82d [d]		
Va			1700	2110	2250	3450	1.19s	3.75s	3.35s	5.46s		
Vb			1695	2125	2240	3380	0.88m 1.48m 2.25m	3.80s	3.25s	5.48s		
Vd			1700	2120	2190	3300	0.56m 0.95s	3.74s	3.87s	5.54s		
Ve			1710	2115	2180	3360	1.00m	3.77s	3.87s	5.54s		
VII	1530		1720				1.15m 0.10s [b]	4.02s		6.92s		
VIII [a]	1525		1735			3040 3230	1.05m	3.86s				7.98s
IX [c]	1540		1720			3260	1.00m	3.85s		5.44s		11.89s

[a] δ(CH=) 7.61s, ν(Ph) 1690. [b] OSiMe$_3$. [c] δ(OCH$_3$) 3.26s, [d] ^3J = 5.0 Hz.

its isomer (IIIc) and a tricyclic hemiaminal (IVc). This reaction has been found to proceed in two stages: the addition of $N_2CHCOOMe$ to the triple bond to give IIc and IIIc and subsequent cyclodimerization of pyrazole IIc to give hemiaminal (Scheme 1). Dimerization of this type is not unexpected. It is known [6] that 5-phenyl-3-formylpyrazole prepared from propynal and phenyldiazomethane is converted to the corresponding hemiaminal. Moreover, it has been established that such cyclic hemiaminal formation might also occur with aldehydes of other *N*-substituted azoles such as 2-formylbenzimidazole [27—29], 3-formyl-1,2,4-triazoles [6,30,31]. With 5-formyl-5-methyl-1-pyrazolines the cyclodimerization is a highly stereospecific process [32—35].

The compounds IVc—IVe prepared by us represent the first organometallic hemiaminals. Their structure has been determined by elemental analysis and IR and NMR spectroscopy. Thus, the IR spectrum of 4H,9H-2,7-dimethoxycarbonyl-3,8-bis(triethylgermyl)dipyrazolo[1,5-a:1′,5′-d]pyrazine-4,9-diol (IVe) shows no formyl group, i.e. (C=O), absorption. There are, however, characteristic frequencies at 1530 cm^{-1} (C=N), 1725 cm^{-1} (the ester carbonyl group), and a broad band with a maximum at 3370 cm^{-1} attributed to OH stretching vibrations [cf. 36]. The ^{13}C NMR spectrum of the above compound containing a natural abundance of ^{13}C shows signals at δ 166.1 (CO), 151.2, 145.6, 117.5 (C of pyrazole cycles), 79.0 (CHOH), 54.0 (OCH_3), 11.4 (CH_3 attached to C) and 7.4 ppm (CH_2). The mass spectrum of IVe shows the fragment ions at *m/e* 757 ($M^+ - CH_3$) and 743 ($M^+ - C_2H_5$).

On the other hand, the ^1H NMR and IR spectroscopic data indicate that a reversible conversion of the dimeric hemiaminal to a monomeric pyrazole IVe $\rightleftharpoons$ IIe occurs in solution. We have found that the IVe $\rightleftharpoons$ IIe reversible conversion occurs even at room temperature under appropriate polar conditions, as observed previously for 3-formyl-5-phenylpyrazole [6]. The data on the IVe : IIe ratio in organic solvents are summarized in Table 4. These data indicate that the pyrazole IIe content of solvents such as tetrahydrofuran, chloroform, dioxan does not exceed 28%. More polar solvents (methanol, hexamethylphosphoramide, dimethylsulfoxide) contain predominantly pyrazole IIe. Heating of IVe in dimethylsulfoxide to 60°C is accompanied by disappearance of the signals

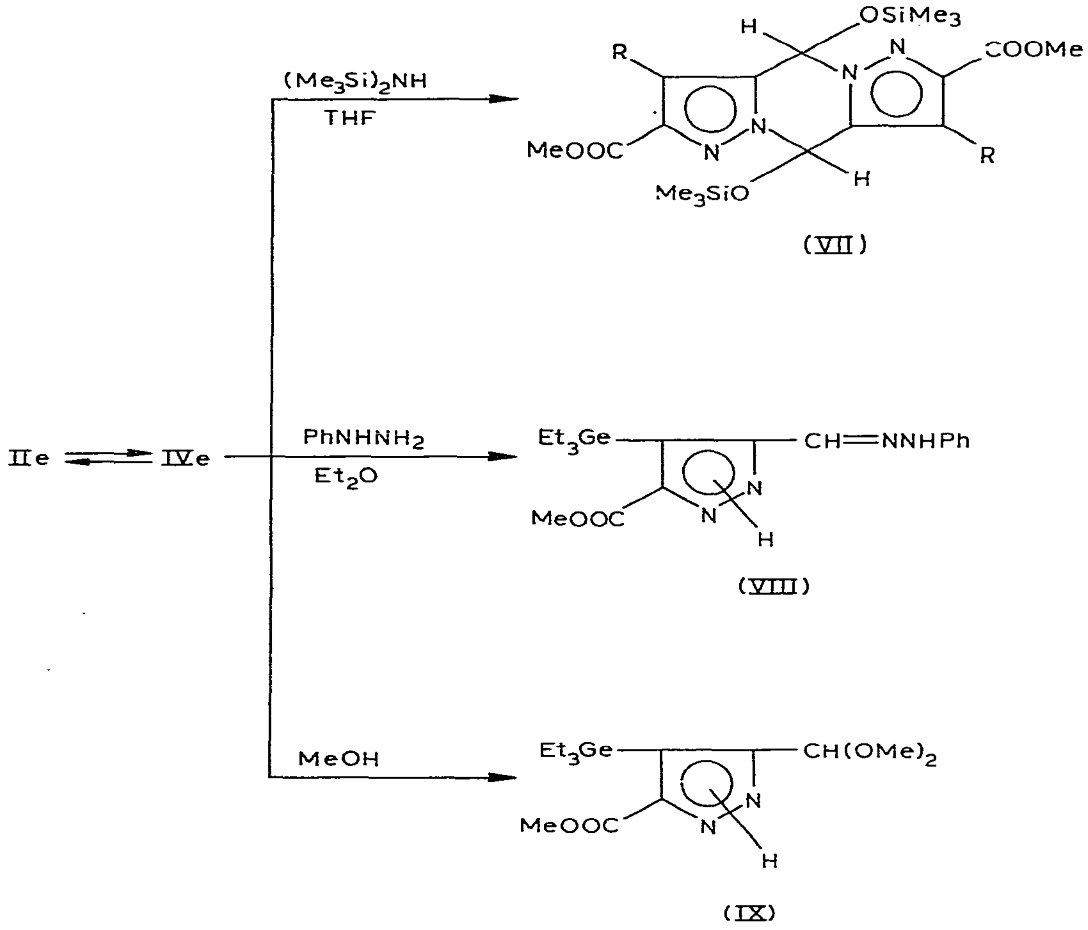
TABLE 4

INFLUENCE OF THE REACTION CONDITIONS ON THE IVe : IIe RATIO

Solvent	IVe : IIe ratio (±10%)	
	Determined by ^1H NMR	Determined by IR
tetrahydrofuran	90 : 10	
chloroform	80 : 20	87 : 13
dioxan	80 : 20	72 : 28
pyridine		74 : 26
dimethylsulfoxide	25 : 75	
methanol	25 : 75	
hexamethylphosphoramide	10 : 90	

Isomerization time 3 h; reaction temperature 20°C; Measured for 0.1—0.3 *M* solution of compounds.

associated with the CH—OH group and an increase in the aldehyde proton signal intensity. Subsequent cooling of the solution to room temperature reduces the IVe : IIe ratio observed before heating. This demonstrates reversibility of the IVe $\rightleftharpoons$ IIe conversion. In agreement with the above conclusion, hemiaminal IVe exhibits a dual reactivity. Thus, its reaction with excess hexamethyldisilazane in THF produces bistrimethylsilyl ether (VII) in almost quantitative yield. In contrast, the reaction of IVe with phenylhydrazine in diethyl ether provides a phenylhydrazone (VIII). Treatment of IVe with methanol in the presence of a catalytic amount of hydrochloric acid gave dimethylacetal (IX), which was isolated and characterized.



The hydrolysis of acetal IX by 5% HCl in THF leads to the dimer IVe.

Experimental

Triethylgermyl-, trimethyl- and triethylsilyl-propynals were prepared by oxidation of the corresponding acetylene carbinols with pyridinium chlorochromate [37].

The IR spectra were recorded on a UR-20 spectrometer. NMR spectra were run on Tesla BS 487C (^1H, 80 MHz) or Varian XL 100/12 (^{13}C, 25.2 MHz) spectrometers. All chemical shifts are measured in ppm (δ scale) relative to hexamethyldisiloxane as internal standard. The ^{13}C NMR spectra are proton noise decoupled. Mass spectra were obtained on an MX-1303 spectrometer.

All starting materials and solvents were distilled before the experiments. All reactions were performed under an atmosphere of dry argon. Typical experiments are given below. Analytical data are collected in Table 2 and infrared and ^1H NMR spectroscopic data in Table 3.

Reaction of 1-(trimethylsilyl)prop-1-yn-3-al (Ic) with methyl diazoacetate

A solution of 2.3 g (23 mmol) of methyl diazoacetate and 2.9 g (23 mmol) of propynal Ic in 6 ml of diethyl ether was kept in the dark at room temperature under argon for 45 days. The precipitate formed was filtered off and washed with ether to give 1.2 g (23.1%) of the product (IVc) in an analytically pure condition, m.p. 52—53° C. The filtrate was concentrated at reduced pressure to afford crude pyrazole (IIIc) as a thick yellow oil. The product was chromatographed on an alumina column with elution with $CHCl_3$ to yield 2.2 g (42.5%) of pyrazole IIIc as a white solid, m.p. 152—153°C.

Reaction of 1-(triethylgermyl)prop-1-yn-3-al (Ie) with methyl diazoacetate

A solution of 3.11 g (14.6 mmol) of propynal Ie and 1.46 g (14.6 mmol) of methyl diazoacetate in anhydrous ether (10 ml) was kept under argon for 14 days at 20—25°C. The crystalline precipitate was filtered off, washed with ether and dried to give 1.6 g (35.0%) of the hemiaminal IVe. Workup as above and chromatography on an alumina column, eluting with chloroform, afforded diazo ester Ve as a yellow clear oil (1.3 g, 28.1%), n_D^{20} 1.5040. Continued elution gave the pyrazole IIIe as colorless crystals (1.5 g, 32.8%), m.p. 108—109°C.

Methyl 6,6-dimethyl-3-hydroxy-2-diazo-4-heptynoate (Va)

A solution of 3.1 g (31 mmol) of methyl diazoacetate and 3.4 g (31 mmol) of 4,4-dimethylpent-2-yn-1-al (Ia) in 15 ml of ether was kept in the dark at room temperature under argon for 60 days. The solution was filtered and concentrated to an oil. This oil was chromatographed on an alumina column with elution by chloroform to yield 5.7 g (87.8%) of diazo ester Va as a yellow viscous oil, n_D^{20} 1.4866.

4H,9H-2,7-Dimethoxycarbonyl-3,8-bis(triethylgermyl)dipyrazolo[1,5-a:1',5'-d]-4,9-bis(trimethylsiloxy)-pyrazine (VII)

A solution of 0.62 g (1.0 mmol) of cyclic hemiaminal IVe was treated with 2 ml of hexamethyldisilazane. The resulting mixture was kept under the same conditions for 1 day. The solvent and excess of $(Me_3Si)_2NH$ were evaporated under reduced pressure, and the resulting solid was triturated with hexane to provide 0.74 g (ca. 100%) of disilylated hemiaminal VII as a solid, m.p. 89—90°C.

3(5)-Formyl-4-triethylgermyl-5(3)-methoxycarbonylpyrazolephenylhydrazone (VIII)

A mixture of 0.91 g (1.45 mmol) of hemiaminal IVe and 0.31 g (2.9 mmol) of phenylhydrazine in anhydrous ether (10 ml) was stirred for 22 h at room temperature under argon. The solution was concentrated to give a solid. The solid was recrystallized from benzene/heptane to give phenylhydrazone VIII (0.31 g, 26.3%), m.p. 180—183°C.

3(5)-Dimethoxymethyl-4-triethylgermyl-5(3)-methoxycarbonylpyrazole (IX)

A solution of 0.81 g (1.3 mmol) of hemiaminal IVe and a catalytic amount of concentrated hydrochloric acid in 10 ml of methanol was refluxed for 6 h and cooled. The resulting crystalline precipitate was collected by filtration and recrystallized from pentane to yield 0.71 g (75.5%) of dimethylacetal IX, m.p. 93—94.5°C.

Hydrolysis of dimethylacetal (IX)

A mixture of 0.41 g (1.1 mmol) acetal (IX) obtained as above and refluxed with 7 ml of 5% aqueous hydrochloric acid for 5 h. The resulting mixture was cooled and extracted with ether. The extract was washed with water, dried over magnesium sulfate and concentrated to a solid. Recrystallization from ether gave 0.14 g (39.4%) of hemiaminal IVe, m.p. 136—138°C.

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