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Synthesis of *N*-Acylacetoacetamide using 2,2,6-Trimethyl-1,3-dioxin-4-one

Masayuki Sato, Norio Kanuma, and Tetsuzo Kato*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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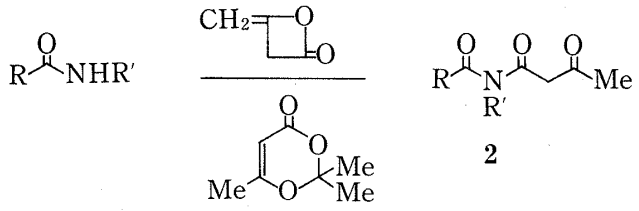
Diketene–acetone adduct (2,2,6-trimethyl-1,3-dioxin-4-one) **1** reacts with amide NH to give the corresponding *N*-acetoacetates **2**. Formamide and basic amides such as picolinamide, on treatment with the adduct, are transformed to the *N*-acyl-2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxamide (**4a** and **4p**) together with the corresponding *N*-acetoacetates.

Keywords——diketene–acetone adduct; 1,3-dioxin-4-one; acetylketene; diketene; acetoacetylation; 4-pyrone derivatives; *N*-acylacetoacetamide

Perekalin *et al.* reported that amides reacted with diketene in the presence of a catalytic amount of pyridine to give *N*-acylacetoacetamides.[1] Gunar *et al.* reported the reaction of diketene with formamide under similar conditions to give a 14% yield of 3-acetyl-4-hydroxy-6-methyl-2(1*H*)-pyridone (**3**), which was also formed from acetamide in a very low yield.[2] Previously, we re-investigated these reactions and found that only benzamide was acylated with diketene under the reported conditions to give *N*-benzoylacetoacetamide (**2k**: R=Ph, R′=H) in poor yield (9%, lit. 43%), while other amides such as acetamide and phenylacetamide did not give the corresponding *N*-acylamides. In acetic acid, acetamide and benzamide reacted with diketene to give the corresponding *N*-acylacetoacetamide in *ca.* 40% yield. Phenylacetamide gave a poor yield of *N*-(phenylacetyl)acetoacetamide (**2f**: R=PhCH$_2$, R′=H). Formamide, in acetic acid, was transformed to the pyridone **3**, and cyanoacetamide and malonamide were not acylated resulting in the recovery of the starting materials.[3]

Although several other procedures for the synthesis of such *N*-acylacetoacetamides are available, they do not always give satisfactory results.[4] The present paper reports a novel and facile method for the preparation of *N*-acylacetoacetamides using a diketene–acetone adduct, 2,2,6-trimethyl-1,3-dioxin-4-one (**1**), which is easily prepared from diketene and acetone in the presence of an acidic catalyst such as *p*-toluenesulfonic acid.[5]



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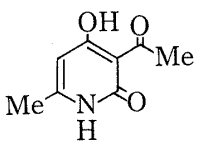

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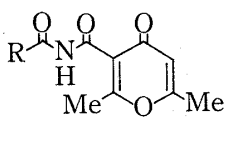

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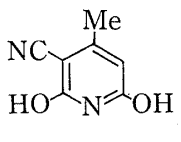

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Chart 1

When formamide and the adduct **1** were heated in xylene under reflux, *N*-formylacetoacetamide (**2a**) was obtained in 68% yield along with a small amount of 3-acetyl-4-hydroxy-6-methyl-2(1*H*)-pyridone (**3**). Reaction of the adduct **1** with formamide without solvent gave the acetoacetamide **2a** in low yield (12%), besides the pyridone **3** (20%) and *N*-formyl-2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxamide (**4a**) (7%).

Similarly, various amides were treated with the adduct **1** in xylene (method A) or without solvent (method B) to produce the corresponding acetoacetamides (**2b**—**2r**). The results are summarized in Table I.

Table I. *N*-Acylacetoacetamides (**2**)

Compound No.	Substituent R	Substituent R′	Yield (%) Method A	Yield (%) Method B	Recryst. solvent[a]	mp (lit.) °C
2a	H	H	68	12	A	56—58
2b	Me	H	73	59	B	84—86 (86—88)[b]
2c	Et	H	70	63	A	115—117 (116—117)[c]
2d	Pr	H	85	70	A	96—97
2e	Iso-Pr	H	80	74	A	69—70 (81—82)[c]
2f	$PhCH_2$	H	79	73	C	150—152 (147—148)[d]
2g	$ClCH_2$	H	90	51	D	139—140
2h	EtO_2CCH_2	H	84	53	E	57—58 (65—67)[c]
2i	CH_2=CH	H	20	48	C	120—122
2j	PhCH=CH	H	84	70	C	115—116
2k	Ph	H	78	82	C	123—125 (123—124)[e]
2l	$-(CH_2)_3-$		84	83	E	49—52 (52—53)[f]
2m	$-(CH_2)_4-$		71	78	E	40—42 (41—42)[f]
2n	$-(CH_2)_5-$		70	74	E	41—42 (46—47)[f]
2o	$NCCH_2$	H	18	36	C	119—120
2p	2-Pyridyl	H	78	24	D	108—110
2q	3-Pyridyl	H	32	0	A	122—123
2r	4-Pyridyl	H	30	0	F	195—197

a) Solvents: A=dichloromethane–hexane, B=ether, C=ethyl acetate, D=benzene, E=ether–hexane, F=ethyl acetate–hexane.
b) Reference 3).
c) T. Kato, Y. Yamanaka, Y. Yamamoto, and M. Kondo, *Yakugaku Zasshi*, **92**, 886 (1972).
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e) Reference 1).
f) Reference 4*a*).

Generally, both methods gave a good yield of the product **2**, but method A generally gave rather better results. Reactions of some amides under similar conditions proceeded in different fashions to give varied products. For instance, reaction of cyanoacetamide with the adduct **1** by method A or B yielded the acetoacetamide **2o** (R=CN·CH_2, R′=H) and 2,6-dihydroxy-4-methylnicotinonitrile (**5**), which was formed from the product acetoacetamide **2o**.

On heating without solvent, picolinamide gave a 24% yield of the acetoacetate **2p** and a 6% yield of 4-pyrone derivative (**4p**), while nicotinamide and isonicotinamide gave only the corresponding pyrones **4q** and **4r** in 21 and 13% yields, respectively. When the reaction of picolinamide was carried out in an organic solvent such as xylene, the acetoacetate **2p** was obtained in 78% yield. Similarly, nicotinamide gave the acetoacetate **2q** and the pyrone

4q in 32 and 12% yields, respectively, while isonicotinamide gave, under the same conditions, the acetoacetate **2r** in 30% yield.

Next, the reactions of acetoacetamides with the adduct **1** were investigated.

Table II. IR Spectral Data and Elemental Analyses of Compound **2**

Compound No.	R	IR $\nu_{max}^{CHCl_3}$ cm^{-1} NH	IR C=O	Formula	Analysis (%) Calcd (Found) C	H	N
2a	H	3420, 3300	1700, 1700, 1620	$C_5H_7NO_3$	46.51	5.47	10.85
					(46.70	5.39	10.65)
2d	Pr	3400, 3250	1720, 1690, 1620	$C_8H_{13}NO_3$	56.12	7.65	8.18
					(55.88	7.81	8.15)
2g	$ClCH_2$	3420	1730, 1715	$C_6H_8ClNO_3$	40.58	4.54	7.89
					(40.85	4.59	7.90)
2i	CH_2=CH	3440, 3320	1725, 1695, 1625	$C_7H_9NO_3$	54.19	5.85	9.03
					(54.67	5.93	8.62)
2j	PhCH=CH	3420, 3280	1720, 1685, 1630	$C_{13}H_{13}NO_3$	67.52	5.67	6.07
					(67.52	5.79	5.98)
2o	$NCCH_2$	3320, 3200	1750, 1730, 1705[a]	$C_7H_8N_2O_3$	50.00	4.80	16.66
					(50.33	4.89	16.91)
2p	2-Pyridyl	3360	1730, 1700, 1630	$C_{10}H_{10}N_2O_3$	58.25	4.89	13.58
					(58.35	4.83	13.66)
2q	3-Pyridyl	3400, 3260	1715, 1695, 1620	$C_{10}H_{10}N_2O_3$	58.25	4.89	13.58
					(58.13	4.88	13.53)
2r	4-Pyridyl	3390, 3260	1718, 1690	$C_{10}H_{10}N_2O_3$	58.25	4.89	13.58
					(58.33	4.71	13.76)
2s	$CH_3CO \cdot CH_2CO$	3370, 3240	1720, 1695	$C_8H_{11}NO_4$	51.88	5.99	7.56
					(51.89	5.99	7.50)

a) Taken as Nujol mull.

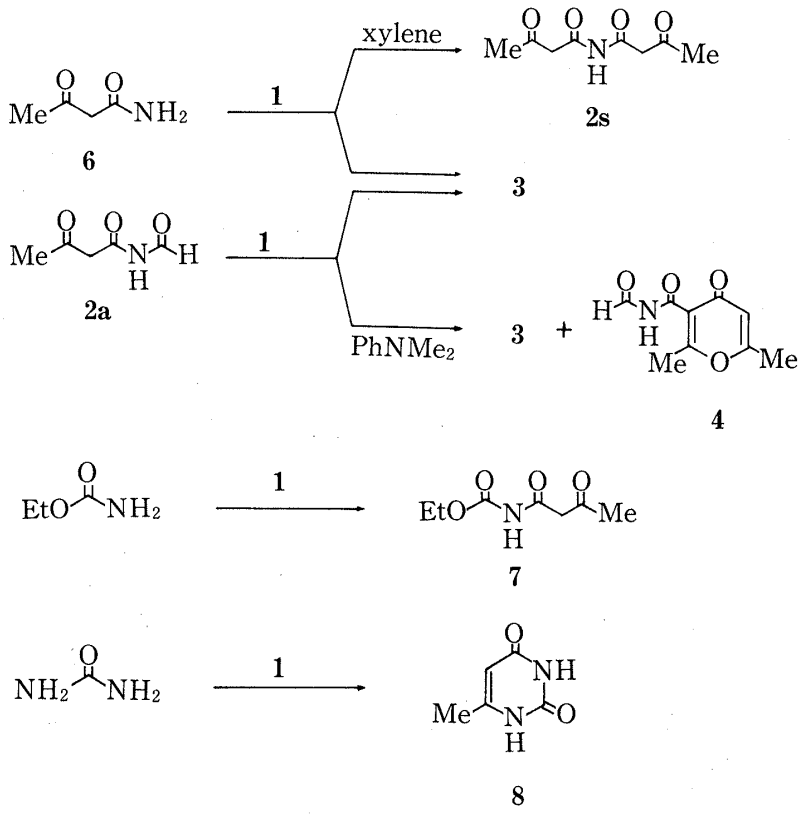
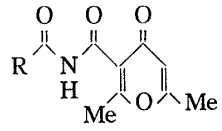


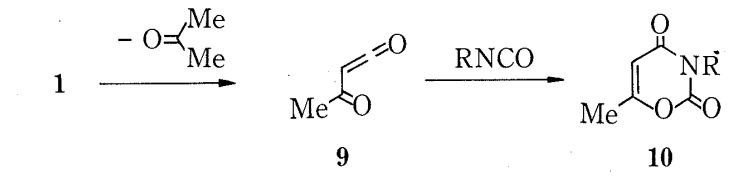
Chart 2

Thus, heating of acetoacetamide **6** with the adduct in xylene gave diacetoacetylamine **2s**, while heating without solvent gave the pyridone **3**. The pyridone **3** was also formed in 50% yield when *N*-formylacetoacetamide **2a** was treated with the adduct **1**. Heating of **2a** with

Table III. Spectral Data and Elemental Analysis of Pyrone Derivatives **4**



Compound No.	R	IR $\nu_{max}^{CHCl_3}$ cm^{-1} C=O	^{1}H-NMR ($CDCl_3$) δ 6-Me	2-Me	5-H	NH	Formula	Analysis (%) Calcd (Found) C	H	N
4a	H	1732, 1680	2.34	2.79	6.30	12.1	$C_9H_9NO_4$	55.38 (55.34	4.65 4.75	7.18 7.32)
4p	2-Pyridyl	1740, 1680, 1660	2.32	2.80	6.32	13.9	$C_{14}H_{12}N_2O_4$	61.76 (61.62	4.44 4.57	10.29 10.08)
4q	3-Pyridyl	1745, 1665	2.37	2.87	6.36	13.7	$C_{14}H_{12}N_2O_4$	61.76 (61.84	4.44 4.36	10.29 9.99)
4r	4-Pyridyl	1743, 1660	2.40	2.90	6.33	13.8	$C_{14}H_{12}N_2O_4$	61.76 (61.50	44.4 4.47	10.29 10.19)



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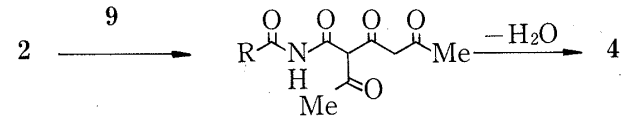

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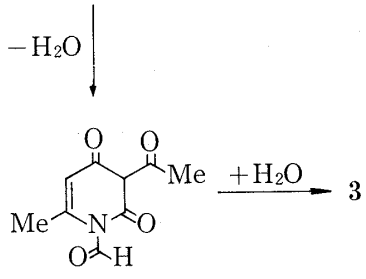

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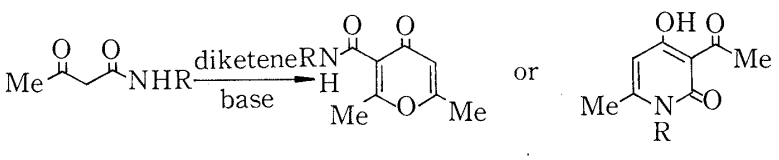

13 **14**

Chart 3

the adduct in the presence of *N*,*N*-dimethylaniline gave the pyridone **3** and the pyrone **4a**, in 60 and 21% yields, respectively.

It was also found that the adduct **1** reacts with urethane and urea to form *N*-ethoxycarbonylacetoacetamide (**7**) and 6-methyluracil (**8**), respectively.

Jäger and Wenzelburger[6] reported reaction of the adduct **1** with isocyanates to give the 1,3-oxazine derivatives **10**; they presumed that the first stage of this reaction might involve the pyrolysis of the adduct concomitant with addition to isocyanate. In our reaction, the acetoacetylation of amides with the adduct **1** might also involve the acetylketene intermediate **9**. The formation of the pyrones **4** and the pyridones **3** could be explained as follows; that is, the *N*-acetoacetate **2** is further acylated to give a *C*-acetoacetyl intermediate **11**, which cyclizes to the pyrones **4**. In the case of *N*-formylacetoacetamide (**2a**), cyclization would occur in a different fashion to give the *N*-formylpyridone **12**, which would be hydrolyzed to give the product **3**.

As reported previously, diketene reacted with acetoacetamides to give the 4-pyrone **13** and 2-pyridone **14** derivatives.[7] As a result of the present investigation, it can reasonably be concluded that the adduct **1** should have reactivity similar to that of diketene towards acetoacetamide derivatives. However, the adduct **1** is much more reactive towards amides, giving the acetoacetyl derivatives **2** in good yields.

Experimental[8]

Reaction of Amides with Diketene-Acetone Adduct (1) to give the Acetoacetates 2b—2n. Method A——A mixture of the amide (30 mmol) and the adduct **1**[5] (36 mmol) in xylene (30 ml) was heated under reflux for 30 min. Removal of the solvent by evaporation *in vacuo* gave a crude substance, which was purified by recrystallization to give the product (**2**).

Method B——A mixture of amide (30 mmol) and the adduct **1** (36 mmol) was heated at 120—130°C on an oil bath for 30 min. The reaction mixture was cooled to give a crystalline substance. Purification by recrystallization afforded the product **2**. The results are summarized in Table I, and IR spectral data and elemental analyses of new compounds are shown in Table II.

Reaction of Formamide with the Adduct 1——a) A solution of formamide (1.8 g, 40 mmol) and the adduct **1** (6.8 g, 48 mmol) in xylene (40 ml) was refluxed for 30 min. After removal of the solvent by evaporation *in vacuo*, ethyl acetate was added to the residue. Separated crystals were collected by suction, and washed with ethyl acetate to give 3-acetyl-4-hydroxy-6-methyl-2(1*H*)-pyridone (**3**) as needles of mp 260—265°C (dec.) (lit.[9] 256°C (dec.)). Yield, 0.5 g (7%). The IR spectrum was identical with that of an authentic sample.[9] Concentration of the ethyl acetate soluble fraction gave a crystalline residue. Recrystallization from dichloromethane–hexane gave *N*-formylacetoacetamide (**2a**) as leaves of mp 56—58°C. Yield, 3.5 g (68%). IR spectral data and elemental analyses are shown in Table II.

b) A mixture of formamide (1.8 g, 40 mmol) and the adduct **1** (6.8 g, 48 mmol) was heated at 120°C for 30 min. Ethyl acetate was added to the reaction mixture, and insoluble crystals were collected by suction to give compound **3**, 0.68 g (20%). The ethyl acetate soluble fraction was concentrated and the residue was subjected to silica gel (35 g) column chromatography. Elution with hexane–ether (2: 3) gave a crystalline substance, which was recrystallized from dichloromethane–hexane to give the product **2a**, 0.6 g (12%). Subsequent elution with ether gave *N*-formyl-2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxamide (**4a**) as prisms of mp 121—122°C (from dichloromethane–hexane). Yield, 0.5 g (7%). Spectral data and elemental analyses are shown in Table III.

Reaction of Cyanoacetamide with the Adduct 1——a) A mixture of cyanoacetamide (3.36 g, 40 mmol) and the adduct **1** (6.8 g, 48 mmol) was refluxed in xylene (40 ml) for 30 min. After removal of the solvent by evaporation, ethyl acetate (100 ml) was added, and the mixture was boiled for one minute. Insoluble crystals were collected by suction and recrystallized from methanol to give 2,6-dihydroxy-4-methylnicotinonitrile (**5**) as needles of mp 310—315°C (dec.) (lit.[10] mp 300—310°C (dec.)). Yield, 1.1 g (18%). The ethyl acetate-soluble fraction was concentrated and the crystalline residue was purified by recrystallization to give *N*-acetoacetylcyanoacetamide (**2o**). Yield, 1.24 g. IR spectral data and elemental analyses are shown in Table II.

b) A mixture of cyanoacetamide (1.68 g, 20 mmol) and the adduct **1** (3.4 g, 24 mmol) was heated at 120—130°C for 30 min. The reaction mixture was cooled, and ether was added. Insoluble crystals were collected by suction, washed with a few ml of water to remove the unreacted amide, dried, and purified by fractional recrystallization to give compound **5** (0.15 g, 5%) and compound **2o** (1.2 g, 36%).

Reaction of Picolinamide with the Adduct 1——a) Employing the general method A given for compound **2**, picolinamide (1.22 g, 10 mmol) was allowed to react with the adduct **1** (1.99 g, 14 mmol). After removal

of the solvent by evaporation, the residue was purified by recrystallization to give *N*-acetoacetylpicolinamide (**2p**) as needles. Yield, 1.6 g (78%).

b) Employing the general method B described above, picolinamide (1.22 g) was allowed to react with the adduct **1** (1.99 g, 14 mmol). The reaction mixture was subjected to silica gel (25 g) column chromatography. Elution with hexane–ethyl acetate (3: 2) gave a crystalline substance, which was recrystallized to give compound **2p**. Yield, 0.5 g (24%). Subsequent elution with hexane–ethyl acetate (1: 1) gave picolinamide (0.46 g). Elution was continued with ethyl acetate to give 2,6-dimethyl-*N*-picolinoyl-4-oxo-4*H*-pyran-3-carboxamide (**4p**) as needles of mp 198—200°C. Yield, 0.15 g (6%).

Reaction of Nicotinamide with the Adduct 1——a) Employing the general method A, nicotinamide (2.44 g) was allowed to react with the adduct **1** (1.99 g). The reaction mixture was subjected to silica gel (50 g) column chromatography. Elution with ethyl acetate gave *N*-acetoacetylnicotinamide (**2q**) as needles of mp 123°C (from dichloromethane–hexane). Yield, 1.3 g (32%). Subsequent elution with ethyl acetate–methanol (95: 5) gave 2,6-dimethyl-*N*-nicotinoyl-4-oxo-4*H*-pyran-3-carboxamide (**4q**) as needles of mp 170—171°C. Yield, 0.65 g (12%).

b) Employing the general method B, nicotinamide (1.22 g) was allowed to react with the adduct **1** (1.99 g). A few ml of water was added to the reaction mixture. Insoluble crystals were collected by suction, treated with charcoal in methanol, and purified by recrystallization from methanol to give compound **4q**. Yield, 0.58 g (21%).

Reaction of Isonicotinamide with the Adduct 1——a) Isonicotinamide (1.22 g) was allowed to react with the adduct **1** (1.99 g) according to the general method A. The reaction mixture was subjected to silica gel (10 g) column chromatography. Elution with hexane–ethyl acetate (5: 2) gave *N*-acetoacetylisonicotinamide (**2r**) as needles. Yield, 0.61 g (30%).

b) Isonicotinamide (1.22 g) was allowed to react with the adduct **1** (1.99 g) according to the general procedure B. Water was added to the reaction mixture and insoluble crystals were collected by suction. Recrystallization from methanol gave *N*-isonicotinoyl-2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxamide (**4r**) as needles of mp 195—197°C. Yield, 0.7 g (38%).

Reaction of Acetoacetamide (6) with the Adduct 1——a) Acetoacetamide (1.01 g) was allowed to react with the adduct **1** (1.99 g) according to the general method A. The reaction mixture was cooled in an ice-water bath and the precipitated crystals were collected by suction. Crystals were washed with a mixture of ether–ethyl acetate (2: 1), giving crude diacetoacetylamine (**2s**). Yield, 1.32 g (71%). This crude product (0.2 g) was dissolved in a small amount of acetic acid. Ether was added to this solution to give pure compound **2s** as needles of mp 136—137°C (dec.). Yield, 90 mg. IR spectral data and elemental analyses are shown in Table II.

b) Acetoacetamide (1.01 g) was allowed to react with the adduct **1** (1.99 g) according to the general method B. Ethyl acetate was added to the reaction mixture and insoluble crystals were filtered off. Recrystallization from methanol gave compound **3** as needles of mp 260—265°C (dec.). Yield, 0.77 g (46%).

Reaction of Compound 2a with the Adduct 1——a) A mixture of compound **2a** (516 mg, 4 mmol) and the adduct **1** (568 mg, 4 mmol) was heated at 120—130°C for 20 min. Ethyl acetate was added to the reaction mixture and insoluble crystals were collected by suction to give compound **3**, 335 mg (50%).

b) A mixture of compound **2a** (516 mg, 4 mmol), the adduct **1** (1.14 g, 8 mmol), and *N*,*N*′-dimethylaniline (242 mg, 2 mmol) was heated at 120—130°C for 20 min. Ethyl acetate was added to the reaction mixture, and the insoluble pyridone **3** was collected by suction. Yield, 0.4 g (60%). The ethyl acetate-soluble fraction was condensed. The residue was subjected to silica gel (10 g) column chromatography using ether as an eluent to give compound **4a**. Yield, 0.15 g (21%).

Reaction of Urethane with the Adduct 1——According to the general method B, urethane (0.89 g) was treated with the adduct **1** to give *N*-ethoxycarbonylacetoacetamide (**7**) as needles of mp 74—76°C (from benzene) (lit.[11] mp 77—78°C). Yield, 1.45 g (84%).

Reaction of Urea with the Adduct 1——A mixture of finely powdered urea (0.6 g, 10 mmol) and the adduct **1** (1.99 g, 14 mmol) was heated at 120—130°C for 30 min. Recrystallization of the solidified substance from water gave 6-methyluracil (**8**) as needles of mp 310—315°C (dec.). Yield, 0.855 g (68%). The IR spectrum was identical with that of an authentic sample.[12]

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