ACETOFORMIC ANHYDRIDE IN THE SYNTHESIS OF CHROMONES. 1. SYNTHESIS OF 3-HETARYLCHROMONES

V. G. Pivovarenko and V. P. Khilya

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It was shown that the reaction of α-(het)aryl-2,4-dihydroxy- and 2,4,6-trihydroxyacetophenones with acetoformic anhydride catalyzed by sodium formate is an effective method for the preparation of chromones containing a heteroaromatic residue at the 3-position. The yield of the chromone and the rate of the reaction increase with increase in the π-deficiency of this residue or in the presence of a hydroxy group in the 6-position of the starting acetophenone. In the last case the method is also applicable to the preparation of the difficulty available 3-aryl-5,7-dihydroxychromones. Chromones with a nitrogen-containing residue are formed without the use of any catalyst.

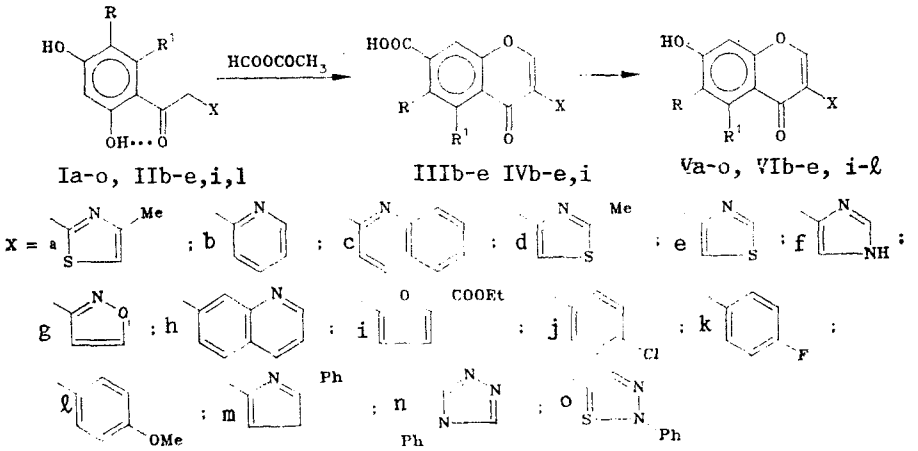
The increased interest with respect to flavonoids and isoflavonoids is explained by the important role played by these compounds in life processes of plant and animal organisms and by their high and diverse biological activity. The principal elements of the chemical structure of flavonoids and isoflavonoids are the heterocyclic systems of chromone and coumarin.

Up to the present time, the most universal and effective method used for the syntheses of 2-R-chromones remains the Kostanetskii—Robinson method — a reaction of 2-hydroxyacetophenones with anhydrides or acid chlorides of carboxylic acids in the presence of salts of these acids or tertiary amines [1]. Several difficulties arise in the synthesis of terminal chromones (R = H) by this method, to overcome which fairly effective solutions have been worked out. The best of these involve the use of ethyl orthoformate [2], dimethylformamide [3], dimethoxydimethylaminomethane [4], and acetoformic anhydride [5, 6]. However, each of the above-mentioned methods has drawbacks, which in some specific cases impede its application. For example, ethyl orthoformate is inapplicable for the preparation of polyhydroxychromones and dimethylformamide — in the synthesis of compounds with substituents unstable to acids, dimethoxydimethylaminomethane is difficultly available, while the use of acetoformic anhydride was limited only to 3-R-chromones with strong electron-acceptor substituents (R = NO_2, SO_2R^1, SOR^1, COR^1, 5-tetrazolyl, etc.).

We have previously reported the results of the first experiments on the reactions of certain α-aryl- and α-hetaryl-2-hydroxyacetophenones with acetoformic anhydride [7, 8]. The aim of the present publication was, on the basis of the available data, to present a more comprehensive concept for this reaction.

The chemical properties of acetoformic anhydride (unstable at a temperature above 5°C, even weak acids and bases accelerate its decomposition) make necessary the use of mild conditions in its reaction with the starting 2-

Scheme 1



I, V a R=*n*-Pr, b-f, h-n R=H, g R=Me, o R=*n*-Hex; a—o R^1=H; II, VI b-e, i-l R=H, R^1=OH; III b-e, R=R^1=H; IV b-e and R=H, R^1=HCOO

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TABLE 1. Reaction of Ketones Ia-*l*, IIb-e,i-*l* with Acetoformic Anhydride in the Presence of Catalyst

Starting compound	Time of reaction, h	Degree of conversion into chromone, %*	Reaction product	Yield, %**	Starting compound	Time of reaction h	Degree of conversion into chromone, %*	Reaction product	Yield, %**
Ia	0,3	100	Va	98	Ik	120	10	Vk	—
Ib	0,3	100	Vb	99	Il	120	5	Vl	—
Ic	0,5	100	Vc	86	IIb	0,2	(100)	VIb	(84)
Id	5	100	Vd	96	IIc	0,25	(100)	VIc	(80)
Ie	5	100	Ve	91	IId	1	(100)	VId	(99)
If	5	100	Vf	93	IIi	(50)	(90) 100	VIi	(80) 92
Ig	5	100	Vg	84	IIj	25	(40) 100	VIj	92
Ih	30	80	Vh	74	IIh	25	(30) 70	VIk	—
Ii	120	20	Vi	—	IIl	25	(10) 50	VIl	—
Ij	120	10	Vj	—					

*According to TLC data.

**In brackets, data are given which were obtained on using 0.1 mole of sodium formate. In the remaining cases, it was used in a sixfold molar excess.

hydroxyacetophenones, while the conversion of the latter into chromones often requires the use of strong acids, bases, or elevated temperatures. We believe that the behavior of 2-hydroxyacetophenones containing an aromatic substituent at the α-position should be placed within the intermediate scope of investigation of this reaction.

In the first series of experiments we studied the reaction of 2,4-dihydroxyacetophenones Ia-*l* and 2,4,6-trihydroxyacetophenones IIb-e,i-*l* with acetoformic anhydride. It was found that of the two catalysts used in the reaction (pyridine and sodium formate) the latter is super. For example, 3-thiazolylchromone Vd was obtained in the presence of the same amount of sodium formate, the yield was 96%.

It was found in subsequent experiments that in the presence of sodium formate, acetoformic anhydride can be successfully used only for the cyclization of ketones with increased mobility of the α-methylene unit protons. Of the 2,4-dihydroxyacetophenones, the cyclization proceeds most rapidly in the case of compounds Ia-c (Table 1). Compounds Vi-*l* could not be obtained in satisfactory yields under these conditions.

Compared with 2,4-dihydroxy derivatives, the degree of conversion of substituted 2,4,6-trihydroxyacetophenones into chromones VIb-e,i-*l* is considerably higher, even in the presence of small amounts of sodium formate. Thus, according to the TLC data, ketones IIb-f convert quantitatively under these conditions into chromones VIb-f, while the yields of chromones in the VIi-*l* series decrease.

The use of an excess of sodium formate as a catalyst leads to increase in the reaction rate and the yields of the desired end products, which made it possible to convert into chromones those ketones containing a π-excessive furan ring in the α-position (IIi) and even an aromatic residue (IIj, k). However, in the case of a ketone containing a methoxy group in the aromatic ring (III), the desired conversion occurred only to the extent of 50%.

The mechanism of formation of chromones in the reaction of acetoformic anhydride with 2-hydroxyacetophenones should not be substantially different from that for other anhydrides [9]. It is clear that the first stage of the reaction of these compounds under the conditions of catalysis by weak bases is an exhaustive O-formylation of the hydroxyl groups of the ketone. This phenomenon is confirmed by the TLC data, according to which after some time from the beginning of the reaction, none of the products present in the reaction mixture gives coloration with an alcoholic solution of ferric chloride. The formation of an enol-formate most probably does not occur. This may be confirmed by the fact that pyridyl ketone Ib, present in the ketonic form to the extent of 90%, reacts 1.5-2 times more rapidly than the quinoline analog Ic, which exists entirely in the form of the enol [10]. Then follows the splitting by a base of an α-proton and conversion of the carbanion (2) formed into the cyclic product (3). The formation of the carbanion is the limiting stage of the process, as confirmed by the faster conversion, compared with the corresponding 6-hydro analogs (5), of the 2,6-diformyloxy ketones (1) into the corresponding chromones. Here also the more prevalent residence of 2,6-diformyloxyacetophenone in a conformation favorable for the cyclization (each of the two formyloxy groups can be included into the hetero ring) and the stabilization of this conformation in compound (4) due to the formation of an intramolecular hydrogen bond between the carbonyl and hydroxy groups may exert an influence (see Scheme 2).

The base catalyzed dissociation of formyloxyacetophenones to the starting hydroxy analogs under the conditions studied is the process which competes with the heterocyclization. This is the main (and only) side reaction limiting

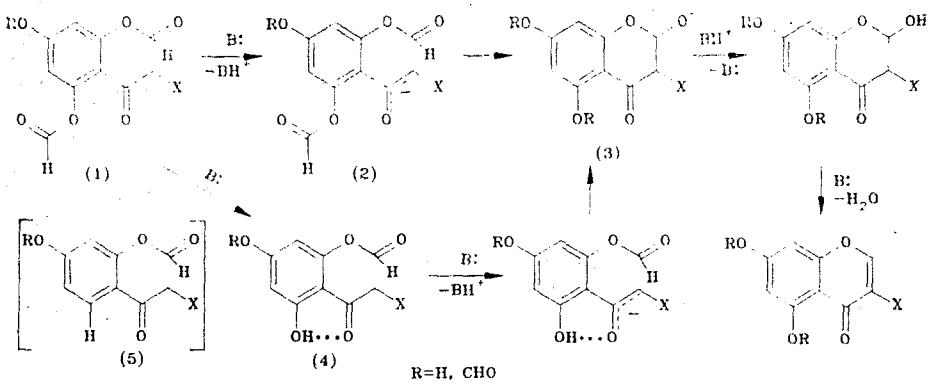
TABLE 2. Reaction of Ketones Ia-i,m-o and IIb-d with Acetoformic Anhydride in the Absence of Catalyst

Starting compound	Time of reaction, h	Degree of conversion into chromone %*	Reaction product	Yield, %	Starting compound	Time of reaction, h	Degree of conversion into chromone %*	Reaction product	Yield, %
Ia	0,2	100	Va	98	Ii	100	0	Vi	0
Ib	0,5	100	Vb	99	Im	25	90	Vm	73
Ic	0,5	100	Vc	86	In	1	100	Vn	95
Id	25	95	Vd	84	Io	70	40	Vo	—
Ie	25	95	Ve	93	IIb	0.2	100	VIb	88
If	5	100	Vf	93	IIc**	0,5	100	VIc	76
Ig	30	70	Vg	60	IId	1	100	VId	99
Ih	30	85	Vh	73					

*According to TLC data.

**An unpurified ketone was used.

Scheme 2



the applicability of the method. In practice it is manifested by an increase in the content of the starting compound in the mixture approximately 24 h after the beginning of the reaction.

Many of the 2-hydroxyacetophenones that we studied include a nitrogen-containing hetero ring, and hence are bases. This suggested to us the study of the reaction of compounds Ia-h,m-o and Ii (for comparison) with acetoformic anhydride in the absence of any catalyst. Thus, in those cases where the basic nitrogen atom and the α-methylene group of the ketone are adjacent to one another, an intra- and intermolecular catalysis by the hetero ring fragment is also possible.

The results show (Table 2) that most of the 3-hetarylchromones with a nitrogen-containing ring can be obtained without the addition of the catalyst. Those 2-hydroxyacetophenones which are characterized by insufficient mobility of the α-methylene unit protons or by the low basicity of the meterocyclic residue (Vg,h,o) convert incompletely under these conditions into the corresponding chromones. Chromones which do not contain the basic atom are not formed (Vi, VIi). The process limiting the use of the method also when the catalyst is used is the dissociation of the intermediate compound — 2-formyloxyacetophenone.

Thus, we have not detected any substantial differences in the conditions of the synthesis of azahetarylchromones in the presence of sodium formate and in its absence. The somewhat lower yield of the chromones in the latter case can be explained by the lower concentration of the base (1:1 compared with 1:6 when sodium formate is used), and its relatively low effectiveness as a catalyst. On the basis of these data, we believe that no particular conclusions can be made on the specifics of the cyclization mechanism. The steric models of the ketones containing a nitrogen atom of the hetero residue adjacent to an α-methylene group, show that the key stage of the cyclization (the splitting off of an α-proton) can be an intramolecular process. During the formylation of the hydroxy group at the 2-position, an intramolecular catalysis may also occur. However, in both reactions an intermolecular reaction is also conceivable.

Depending on the conditions of separation used in the method under consideration, the hydroxychromone can be obtained either in a free state or in the form of a formyloxy derivative. Formyloxychromones IIIa-e, IVb,d,i are weakly stable compounds which lose the formyloxy group rapidly, even on boiling in ethanol. In contrast to the hydroxy analogs, they are soluble in chloroform, which can be taken advantage of during their purification. Almost all the

TABLE 3. Characteristics of Synthesized Compounds

Compound	Empirical formula	Mp, °C	IR spectrum, cm^{-1}		PMR spectrum, δ, ppm					
					chromone fragment					
			$\nu_{C=O}$, $\nu_{C=O}$ of chromone	$\nu_{C=O}$, of formyloxy group (ν_{OH})	1H, s, 2-H	1H, 5-R'	6-R	1H, s, 7-HCOO	1H, d, 8-H	X
IIb	$C_{13}H_{11}NO_4$	330*1 (dec)	1625*2 —	(3340)	—*3	—	—	—	—	7,32 (1H, dd, 3-H); 7,72 (1H, m, 4-H); 7,27 (1H, m, 5-H); 8,47 (1H, dd, 6-H)
IId	$C_{12}H_{11}NO_4S$	244	1630*2 —	(3380)	—*4	—	—	—	—	2,61 (3H, s, 2-CH_3); 7,16 (1H, s, 5-H)
IIIb	$C_{15}H_9NO_4$	180*1 (dec)	1650, 1625	1730	8,68	8,08, d	7,13 (1H, dd)	8,27	7,32	8,28 (1H, dd, 3-H); 7,74 (1H, m, 4-H); 7,25 (1H, m, 5-H); 8,55 (1H, dd, 6-H)
IIIc	$C_{19}H_{11}NO_4$	180*1 (dec)	1650, 1620	1750	8,89	8,32, d	7,17 (1H, dd)	8,32	7,39	8,32 (2H, m, 3-H, 4-H); 7,48...8,13 (4H, m, 5-H...8-H)
IIId	$C_{14}H_9NO_4S$	180*1 (dec)	1625	1745	8,92	8,31, d	7,18 (1H, dd)	8,31	7,35	2,73 (3H, s, 2-CH_3); 8,31 (1H, s, 5-H)
IIIe	$C_{13}H_7NO_4S$	175*1 (dec)	1645, 1620	1750	8,94	8,28, d	7,15 (1H, dd)	8,24	7,31	8,70 (1H, s, 2-H); 8,51 (1H, s, 5-H)
IVb	$C_{16}H_9NO_6$	175*1 (dec)	1645, 1625	1740	8,83	8,30, s	6,70 (1H, d)	8,30	6,87	8,30 (1H, dd, 3-H); 7,80 (1H, m, 4-H); 7,27 (1H, m, 5-H); 8,62 (1H, dd, 6-H)
IVc	$C_{20}H_{11}NO_6$	175*1 (dec)	1640, 1620	1740	8,81	8,61, s	6,70 (1H, d)	8,96	7,07	8,34 (1H, d, 3-H); 8,11 (1H, d, 4-H); 7,40...8,10 (4H, m, 5-H...8-H)
IVd	$C_{15}H_9NO_6S$	175*1 (dec)	1650, 1625	1750	8,93	8,31, s	6,91 (1H, d)	8,31	7,36	2,70 (3H, s, 2-CH_3); 8,31 (1H, s, 5-H)
IVi	$C_{18}H_{12}O_9$	178	1650, 1615	1740	8,66	8,32, s	7,40 (1H, d)	8,36	7,23	7,01 (1H, d, 3-H); 7,40 (1H, d, 4-H); 4,25 (2H, q, OCH_2), 1,43 (3H, t, CH_3)
Va	$C_{16}H_{15}NO_3S$	267	1645, 1620	(3450)	9,05	7,87, s	2,68 (2H, t, Ar—CH_2); 1,69 (2H, m, CH_2); 0,97 (3H, t, CH_3)	11,05*5	6,98	2,47 (3H, s, 4-CH_3); 7,32 (1H, s, 5-H)
VIb	$C_{14}H_9NO_4$	248	1665, 1625	(3320)	8,81	12,89, s	6,29 (1H, d)	11,02*5	6,45	8,21 (1H, dd, 3-H); 7,87 (1H, m, 4-H); 7,39 (1H, m, 5-H); 8,62 (1H, dd, 6-H)
VIc	$C_{18}H_{11}NO_4$	248	1655, 1625	(3430)	8,83	12,77, s	6,27 (1H, d)	10,91*5	6,41	8,35 (1H, d, 3-H); 8,13 (1H, d, 4-H); 7,40...8,10 (4H, m, 5-H...8-H)
VId	$C_{13}H_9NO_4S$	251	1650, 1625	(3500)	8,78	12,73, s	6,21 (1H, d)	10,81*5	6,34	2,70 (3H, s, 2-CH_3); 8,08 (1H, s, 5-H)
VIi	$C_{16}H_{12}O_7$	262	1650, 1625	(3400)	8,65	12,42, s	6,26 (1H, d)	10,85*5	6,42	7,20 (1H, d, 3-H); 7,30 (1H, d, 4-H); 4,36 (2H, q, OCH_2); 1,36 (3H, t, CH_3)

*1Spectra of compounds IIb,d, IVc, Va, VIb-i were measured in DMSO-D_6, IIIb-e, IVb-d,i in $CDCl_3$.

*2$\nu_{C=O}$ of ketone.

*3Signals of the phenol fragment: 12.23 (2H, s, 2-OH); 5.86 (2H, s, 3-H, 4-H).

*4Signals of the phenol fragment: 4.53 (2H, s, α-CH_2); 12.20 (2H, s, 2-OH, 6-OH); 5.86 (2H, s, 3-H, 5-H); 4.44 (2H, s, α-CH_2).

*5Signal of 7-OH proton.

hydroxychromones are soluble in the reaction mixture, while the formyloxy derivative precipitate from it in the form of colorless crystals, which assisted in the purification of the desired end compounds in those cases where the starting ketones were insufficiently purified. A convenient advantage of the reaction is the separation of desired chromones from the reaction mixture in the form of pure compounds. This is the result of the mild reaction conditions, due to which the starting 2-hydroxyacetophenones do not undergo any side transformations.

The structure of the new compounds was confirmed by the IR and PMR spectroscopy data (Table 3). The previously unknown formyloxychromones IIIb-e, IVb-e,i deserve special attention. In the PMR spectra of these compounds recorded in deuterochloroform, the singlets at 8.27-8.32 ppm belong to the formyloxy group protons, and those at 8.68-8.92 ppm to the 2-H chromone ring signal. In the IR spectra there is an intense band in the 1725-1750 cm^{-1} region corresponding to the C=O stretching vibrations in the formyloxygroups.

EXPERIMENTAL

The course of the reaction and the purity of the compound obtained was monitored by TLC on Silufol UV-254 plates in the chloroform—methanol (9:1 or 85:15) and benzene—ethanol (95:5) systems. The PMR spectra were recorded n ZKR-60 and Bruker-CXP-200 spectrometers at 20°C, using TMS as internal standard. The IR spectra were recorded in KBr tablets on a Specord IR 71 spectrophotometer.

The starting ketones (except for IIb-d) containing 95-99% of the main compound, were synthesized by known methods [10-18]. A "pure" grade sodium formate was preliminarily dried in vacuo.

The elemental analysis data for C, H, N, and S corresponded to the calculated values.

Acetoformic Anhydride. A test tube 40 mm in diameter containing 46 g (37.7 ml, 0.001 mmole) of "analytically pure" grade formic acid was placed in an ice bath. Ketene obtained by pyrolysis of acetone was passed through a capillary reaching the bottom of the test tube until the pH of the mixture raised to 4.5 (a dry universal indicator paper thus ceases to be pink-colored). The liquid obtained (80 ml, n_D^{20} 1.379) was used without further purification. The material was stored at 0-4°C in a hermetically closed vessel.

TLC Analysis of the Reaction Mixture for the Content of Chromone and Ketone. The reaction mixture was placed at the start (a few points with a different amount of the material). Before elution, the plate was held for 15 min at 100-120°C. The chromatogram obtained was compared visually with a chromatogram of a set of standard mixtures of 2-hydroxyacetophenone (*Il* and II*l*) and chromone (V*l* or VI*l*). An additional comparison was carried out after treating the chromatograms with an alcoholic solution of ferric chloride.

α-2-(Pyridyl)-2,4,6-trihydroxyacetophenone (IIb, $C_{13}H_{11}NO_4$). A current of a dry hydrogen chloride was passed with stirring into a solution of 13.6 g (108 mmoles) of phloroglucinol and 10.2 g (98 mmoles) of 2-pyridylacetonitrile in 50 ml of dry DMFA, up to complete saturation of the reaction mixture. After a day, the mixture was poured into 0.5 liter of hot water, the mixture was boiled for 1 h and neutralized with a 25% aqueous solution of ammonium hydroxide to pH 6. The precipitate that separated out was filtered off. Yield 13 g (75%) of a chromatographically pure orange compound, which was additionally purified from ethanol.

α-(2-Quinolyl)-2,4,6-trihydroxyacetophenone (IIc, $C_{17}H_{13}NO_4$). A current of dry hydrogen chloride was passed, with stirring, at 0°C into a solution of 6.3 g (50 mmoles) of phloroglucinol and 8.4 g (50 mmoles) of 2-(quinolyl)acetonitrile in 50 ml of dry DMFA up to complete saturation of the reaction mixture. After 2 days, the mixture was poured into 0.5 liter of water, the mixture was boiled for 1.5 h, and neutralized with an aqueous solution of ammonium hydroxide. The precipitate that separated out was filtered off and dried. Yield 10.5 g (71%) of compound IIc containing about 20% of impurities. It was used further without purification.

α-(2-Methyl-4-thiazolyl)-2,4,6-trihydroxyacetophenone (IId, $C_{12}H_{11}N_4S$) was obtained in a similar way as compound IIb from 0.76 g (6 mmoles) of phloroglucinol, 0.69 g (5 mmoles) of (2-methyl-4-thiazolyl)acetonitrile and 5.0 ml of DMFA in a yield of 1.28 g (97%).

General Method of the Preparation of Chromones Va-*l*, VIb-e,i-*l* under Catalysis Conditions with Sodium Formate. A 408 mg portion (6 mmoles) of sodium formate was added to a mixture of 1 mmole of 2-hydroxyacetophenone and 1 ml (11 mmoles) of acetoformic anhydride and the mixture was stirred to complete dissolution of the reagents. Samples of the reaction mixture (1-5 μliter) were withdrawn after 0.25, 0.5, 1, 2, 4, 6, 12, and 24 h. If after 24 h the starting ketone was detected in the mixture (preparation of chromones Vh-*l*), 1 ml of acetoformic anhydride was added. The last operation was repeated 5 times at periods of 24 h. The reaction mixture was then boiled for 20 min and poured into 50 ml of hot water. After neutralization of the mixture with an aqueous ammonia solution, the crystals that separated out were filtered off and recrystallized from ethanol.

General Method of Preparation of 3-hetarylchromones without Addition of the Catalyst. A suspension of 5 mmoles of 2-hydroxyacetophenone (Table 2) in 5 ml of acetoformic anhydride was stirred at room temperature. Samples of the reaction mixture were withdrawn after 0.25, 0.5, 1, 2, 4, 6, 12, and 24 h. After stabilization of the

composition of the reaction mixture, it was heated to 100°C, 10 ml of hot water was added, and the mixture was boiled for 1 h. It was then diluted with 50 ml of hot water, neutralized with an aqueous ammonia solution to pH 6, and cooled. The crystals that separated out were filtered off and crystallized from ethanol.

General Method of Preparation of Formyloxychromones IIIb-e, IVb-d. A suspension of 5 mmoles of 2-hydroxyacetophenone (Ib-e or IIb-i) in 5 ml of acetoformic anhydride was stirred for 0.5-0.25 h (Table 2), and then was diluted with 20 ml of acetone. The precipitate that separated out was filtered off and, if necessary, was recrystallized from a mixture of chloroform and acetone.

3-(5-Ethoxycarbonyl-2-furyl)-5,7-diformyloxychromone (IVi). A 0.007 g portion (0.1 mmole) of sodium formate was added to a suspension of 0.0306 g (1 mmole) of compound IIi in 1 ml (11 mmoles) of acetoformic anhydride and the mixture was stirred to its complete homogenization. After 40 h, the precipitate that separated out was filtered off. Yield 0.09 g (24%) of compound IVi.

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