Acetylation of 2-Acyl-1,3-indandiones with Ketene and Determination of the Structure of Products

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Acetylation of 2-acyl-1,3-indandiones with ketene was performed. There was found regioselective and quantitative *O*-acetylation, with formation of the corresponding 2-(1-acetoxyalkylidene)-1,3-indandiones. The structure of products was determined on the basis of data gained from ^1H and ^{13}C NMR spectra.

2-Acyl-1,3-indandiones attracted the interest of chemists as early as forty years ago, since some of them exhibited remarkable physiological, in particular anticoagulant, properties and found use in practice as rodenticides [1—3]. Their chemical properties, however, have been scarcely studied. It is known for example that they exist in a diketo-enol form. Nevertheless, existence of two structures *A* and *B* can be assumed, *A* representing enolization of an acyl carbonyl group and *B* an enol form of a carbonyl belonging to 1,3-indandione skeleton. In both enol forms, stabilization *via* the hydrogen bond and formation of a favoured six-membered ring is feasible.

Evidence gained from the examination of IR spectra demonstrated the preference of the diketoenol form *A* with an exocyclic enol arrangement [4]. Studying properties of cyclic 1,3-diketones, we were interested lately in their acylation with various acylating agents, as in some cases their behaviour is different from that of acyclic 1,3-diketones.

In this paper, our results obtained from acetylation of 2-acyl-1,3-indandiones (acyl = acetyl *I*, propionyl *II*, isovaleryl *III*, pivaloyl *IV*, benzoyl *V*) with ketene are presented. From the theoretical point of view, acetylation of 2-acyl-1,3-indandiones can possibly afford a product of *C*-acetylation at C-2 atom of the indandione moiety and two products of *O*-acetylation: either at an oxygen of the carbonyl group which forms a part of the indandione skeleton or at an oxygen atom of the substituent. It is worth mentioning that acylations of 2-acyl-1,3-indandiones have not been performed so far. The acetylation with ketene carried out

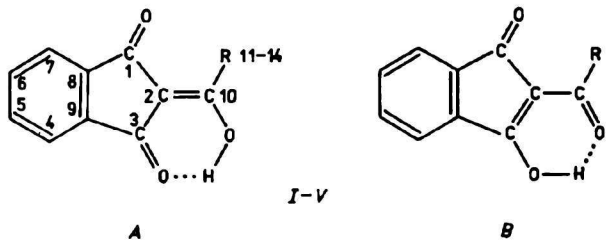


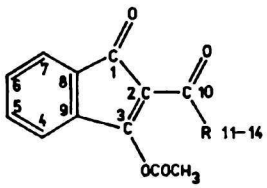
Table 1. Characteristic Data of Synthesized 2-(1-Acetoxyalkylidene)-1,3-indandiones *VI*—*X*

Compound	R	Formula M_r	M.p. °C	R_f[a]	t[b] min	$\tilde{\nu}$/cm^{-1}		
						ν_{as}(C=O)[c]	ν_s(C=O)[c]	ν(COO)[c]
VI	CH_3	$C_{13}H_{10}O_4$ 230.22	93—95	0.72	130	1688	1732	1776
VII	CH_3CH_2	$C_{14}H_{12}O_4$ 244.24	73—75	0.80	150	1686	1734	1778
VIII	$(CH_3)_2CHCH_2$	$C_{16}H_{16}O_4$ 272.30	77—78	0.88	140	1692	1732	1788
IX	$(CH_3)_3C$	$C_{16}H_{16}O_4$ 272.30	107—111	0.88	300	1686	1730	1776
X	C_6H_5	$C_{18}H_{12}O_4$ 292.28	98—100	0.60	60	1686	1732	1774

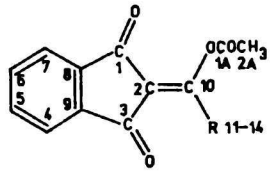
a) Eluent: petroleum ether—ethyl acetate (φ_r = 2 : 1); *b*) the reaction time. *c*) Spectra were taken in $CHCl_3$, 0.1 mm NaCl cells.

by us gives quantitative yield of the single product of the reaction.

The course of the reaction was monitored by TLC. IR and ^{1}H NMR spectra of the product revealed *O*-acetylation. Determination of the direction of acetylation — to the oxygens of 1,3-indandione carbonyls (*C*) or to the oxygen of an acyl group (*D*) — proved to be a more complex



C



VI–X
D

problem. IR and ^{1}H NMR spectra of both types of compounds are quite similar (Tables 1 and 2). Certain clue to the solution of a problem can lie in comparison of chemical shifts of the aromatic protons of 1,3-indandione (*XI*) (^{1}H NMR spectrum taken in $CDCl_3$, a solvent in which this compound is in a diketo form), 2-acyl-1,3-indandiones *I*—*V*, the products of their acetylation with ketene (*VI*—*X*), and 3-acetoxy-2-inden-1-one (*XII*) prepared for the sake of comparison according to the described procedure [5]. Almost identical chemical shifts of multiplets of aromatic protons (Table 2) of *I*—*V*, structure *A* (δ = 7.43—8.17), and their *O*-acetylated derivatives *VI*—*X* (δ = 7.43—8.07) indicate their mutual structural likeness which is comparable with the diketo arrangement of the unsubstituted 1,3-indandione (*XI*) (δ = 7.70—8.20). On the other hand, the multiplet of aromatic protons of the model compound *XII*, the structure of which represents a ketoenol form of 1,3-indandione trapped by acetyl group, is shifted to the value of δ = 7.20—7.46.

For the unambiguous determination of the structure of *VI*—*X*, their ^{13}C NMR spectra as well as those of the starting compounds *I*—*V* served much better than the ^{1}H NMR spectra (Table 3). Should the acetylation of *I*—*V* take place at the oxygen of 1,3-indandione carbonyls (*C*), the signal of the carbonyl C-10 must be present in the spectra of *VI*—*X* and its chemical shift would be strongly affected by the substituent R which is in a close vicinity of this carbonyl group. ^{13}C NMR spectra of compounds *VI*—*X* possess two signals of C-1 and C-3 characteristic of the carbonyl carbons. Chemical shifts of these carbon atoms are almost identical (δ = 189 and 187) for all the compounds. Unchanged position of these two signals apparently indicates remoteness of both carbonyl carbon atoms from the influence of the substituent R and therefore it confirms the structure *D* for all the acetylated compounds. On the other hand, a signal belonging to sp^2 hybridized carbon C-10 is found in the spectra of products *VI*—*X*. Its position is greatly influenced by the substituent R directly connected to the sp^2 carbon atom. Chemical shift of this carbon atom is dependent on the substituent in an analogous way also with the starting compounds *I*—*V*, structure *A*.

The further evidence, supporting the idea of direction of acetylation, *i.e.* the structure *D*, 2-(1-acetoxyalkylidene)-1,3-indandiones *VI*—*X*, comes from the downward tendency of differences be-

Table 2. ^{1}H NMR Spectral Data (δ) of Compounds *I*—*XII*

Compound	H_{arom}		H_{alkyl}		H_{enol}	H_{2A}
I	7.80—8.00 (m, 4H)	2.71 (s, 3H)	—	—	12.73 (s, 1H)	—
II	7.46—7.91 (m, 4H)	3.00 (q, 2H, J = 7 Hz)	1.28 (t, 3H, J = 7 Hz)	—	12.87 (s, 1H)	—
III	7.50—7.91 (m, 4H)	2.86 (d, 2H, J = 7 Hz)	2.16 (m, 1H)	1.04 (d, 6H, J = 7 Hz)	12.21 (s, 1H)	—
IV	7.45—7.85 (m, 4H)	1.43 (s, 9H)	—	—	16.00 (s, 1H)	—
V	7.43—8.17 (m, 9H)	—	—	—	13.87 (s, 1H)	—
VI	7.70—7.98 (m, 4H)	2.63 (s, 3H)	—	—	—	2.41 (s, 3H)
VII	7.60—8.00 (m, 4H)	3.08 (q, 2H, J = 7 Hz)	1.23 (t, 3H, J = 7 Hz)	—	—	2.42 (s, 3H)
VIII	7.60—8.07 (m, 4H)	3.00 (d, 2H, J = 7 Hz)	2.06 (m, 1H)	1.04 (d, 6H, J = 7 Hz)	—	2.41 (s, 3H)
IX	7.57—8.02 (m, 4H)	1.43 (s, 9H)	—	—	—	2.43 (s, 3H)
X	7.43—7.93 (m, 9H)	—	—	—	—	2.47 (s, 3H)

Compound *XI*: 7.70—8.20 (m, 4H), 3.20 (s, 2H). Compound *XII*: 7.20—7.46 (m, 4H), 6.02 (s, 1H), 2.40 (s, 3H).

Table 3. ^{13}C NMR Spectral Data (δ) of Compounds *I*—*XII*

Carbon	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*	*XI*	*XII*
C-1	196.8	197.1	197.1	199.1	198.8	189.5	189.3	189.2	188.5	188.1	197.2	195.7
C-2	108.9	108.0	109.1	107.1	107.6	119.8	118.9	119.9	120.3	119.0	45.0	107.9
C-3	188.5	188.4	188.2	186.9	186.5	187.2	187.5	187.2	187.3	187.1	197.2	167.6
C-4	122.5	122.4	122.4	122.1	122.3	123.1	123.2	123.1	123.0	123.0	123.1	130.2
C-5	134.1	134.0	134.0	133.6	134.1	135.1	135.1	135.0	134.9	135.3	135.5	118.8
C-6	135.0	134.9	134.9	134.8	135.2	135.3	135.3	135.2	135.0	135.3	135.5	122.0
C-7	122.7	122.7	122.7	122.6	122.8	123.2	123.2	123.1	123.0	123.2	123.1	132.8
C-8	140.8	140.8	140.9	139.7	140.1	141.4	141.4	141.3	141.0	140.9	143.4	140.2
C-9	138.1	138.3	138.2	137.4	137.8	140.5	140.7	140.5	140.4	140.7	143.4	130.6
C-10	183.7	188.2	187.0	198.4	179.5	166.9	171.9	170.5	179.3	163.2	–	–
C-11	19.2	25.9	27.6	39.8	131.3	19.8	26.1	27.5	39.7	131.8	–	–
C-12	–	10.1	40.9	26.2	130.3	–	10.2	40.9	26.9	130.6	–	–
C-13	–	–	22.6	–	128.0	–	–	22.6	–	128.0	–	–
C-14	–	–	–	–	133.6	–	–	–	–	132.8	–	–
C-1A	–	–	–	–	–	167.7	167.0	166.7	167.0	167.4	–	166.3
C-2A	–	–	–	–	–	21.0	21.0	21.0	20.8	21.1	–	21.5

tween the chemical shifts of parallel aromatic carbon atoms in indandione skeleton of acetylated compounds (Table 4) in comparison with the starting 2-acyl-1,3-indandiones or 3-acetoxy-2-inden-1-one (*XII*).

Such a trend indicates that the environment accounting for nonequivalency of these carbon atoms is far away from them with its diminished influence as a consequence.

Experimental results demonstrate approximately 2.5 times extended reaction period for acetylation of 2-pivaloyl-1,3-indandione (*IV*) with ketene. This can be explained by bulkiness of the *tert*-butyl group which hinders an approach of ketene to the oxygen atom of the enolic hydroxyl group. Such experimental finding corresponds best to the structure *A* of the starting 2-acyl-1,3-indandiones as well as to the reaction site.

Finally, we can conclude that 2-acyl-1,3-indandiones *I*—*V* react with ketene regioselectively under formation of 2-(1-acetoxyalkylidene)-1,3-indandiones *VI*—*X* as the only products.

EXPERIMENTAL

Starting 2-acyl-1,3-indandiones *I*—*V* were synthesized according to the published procedure [1]. Prior to use they were recrystallized from ethanol. 1,3-Indandione was purified by sublimation under reduced pressure (80 °C/13 Pa)

Table 4. Differences of ^{13}C NMR Chemical Shifts of Parallel Aromatic Carbon Atoms

$\Delta\delta$	*VI*—*X*	*I*—*V*	*XII*
$\delta_{C-8} - \delta_{C-9}$	0.2—0.9	2.3—2.7	9.6
$\delta_{C-7} - \delta_{C-4}$	0.0—0.2	0.2—0.5	2.6
$\delta_{C-6} - \delta_{C-5}$	0.0—0.2	0.9—1.1	3.2

3-Acetoxy-2-inden-1-one (*XII*) as a model compound was prepared by acetylation of 1,3-indandione with isopropenyl acetate [5].

Melting points were determined on a Kofler hot-stage. NMR spectra were measured on an instruments BS-487 (80 MHz, Tesla) and VXR-300 (Varian) with 299.93 MHz frequency for protons and 75.43 MHz frequency for carbon atoms in deuterated chloroform with TMS as an internal standard. IR spectra were taken on a Specord IR-80 instrument in the region of $\tilde{\nu}$ = 400—4000 cm^{-1} in chloroform. The course of the reactions and their termination was monitored by TLC using Silufol UV-254 plates (Kavalier, Sázava, CSFR) with petroleum ether (b.p. = 30—55 °C)—ethyl acetate mixture as eluent. Ketene lamp producing 0.45 mol of ketene per hour described by *Handford et al.* [6] was used as a source of ketene. Any impurities were frozen out from it at – 45 °C. The reactions were carried out in a 100 cm^3 flask equipped with a condenser, a sintered inlet tube for introducing ketene and a septum for withdrawal samples for TLC.

2-(1-Acetoxyalkylidene)-1,3-indandiones *VI*—*X*

Into a solution of 2-acyl-1,3-indandione *I*—*V* (2 mmol) in chloroform (80 cm^3) ketene was introduced at room temperature over a period given in Table 1. The solvent was removed at room temperature and at a pressure of water pump and the last traces of volatile materials were removed at the pressure of 13 Pa. The oily residue was dissolved in a mixture of ether and petroleum ether and allowed to crystallize at – 20 °C. The precipitate was filtered off by suction, washed with petroleum ether and dried. In all cases the yields were quantitative.

REFERENCES

1. Kilgore, L. B., Ford, J. H., and Wolfe, W. C., *Ind. Eng. Chem. 34,* 494 (1942).
2. Hassal, C. H., *Experientia 6,* 462 (1950).
3. Correll, J. J., Coleman, L. L., Long, S., and Willy, R. F., *Proc. Soc. Exp. Biol. Med. 80,* 139 (1952).
4. Gren, E. J., *Izv. Akad. Nauk Latv. SSR, Ser. Khim. 5,* 600 (1965).
5. Šraga, J. and Hrnčiar, P., *Chem. Papers 40,* 807 (1986).
6. Handford, W. E. and Sauer, J. C., *Organic Reactions III,* pp. 108—149. J. Wiley & Sons, New York, 1946.

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Reactions of 2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene with Nitrogen Nucleophiles

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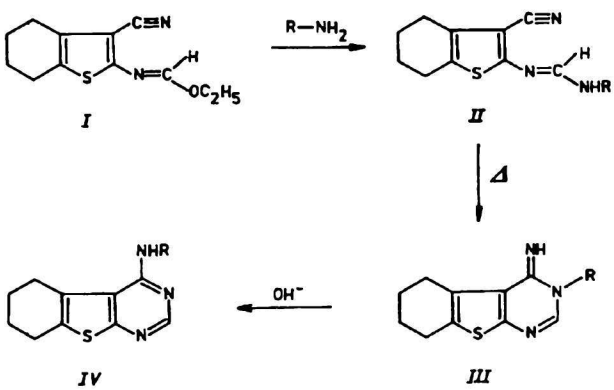
2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene gave in the reaction with nitrogen nucleophiles corresponding formamidines that under heating cyclized to 3-substituted 4-imino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-3,4-dihydropyrimidines. These under a base catalysis underwent Dimroth rearrangement to 4-substituted 5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines.

2-Ethoxymethyleneamino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene (*I*) is mentioned in the paper [1] as a substrate in the reaction with methylamine and in the paper [2] its reaction with hydrazine hydrate leading to the product of the type of formamidines is described. This was then employed for the preparation of a fused heterocyclic derivative — triazolo[2,3-*c*]pyrimidine.

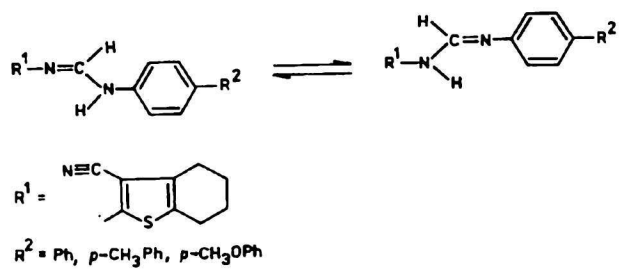


R		R	
a	CH_3CH_2	*e*	*p*-NO_2Ph
b	Ph	*f*	NH_2
c	*p*-CH_3Ph	*g*	PhNH
d	*p*-CH_3OPh	*h*	NH=C(NH_2)

Scheme 1

The aim of our work was to check the behaviour of *I* against a broader scale of nucleophile representatives and compare their reaction conditions.

There are two reactive centres sensitive to nucleophilic attack in the structure of used compound *I*. But in all our tested cases of the reaction of *I* with nitrogen nucleophiles the only attack on the double bond C=N was observed under formation of formamidines *II* (Scheme 1). The reactions were carried out with ethylamine, aniline, *p*-toluidine, *p*-anisidine, *p*-nitroaniline, hydrazine, phenylhydrazine, guanidine, and urea.



Scheme 2

In case of the reaction of compound *I* with strong nucleophiles the formed formamidines (compounds *IIf*—*IIh*) could not be isolated because