ALKYLATION AND SOME PHYSICOCHEMICAL CHARACTERISTICS OF 6,7- AND 7,8-DIHYDROXYCOUMARINS

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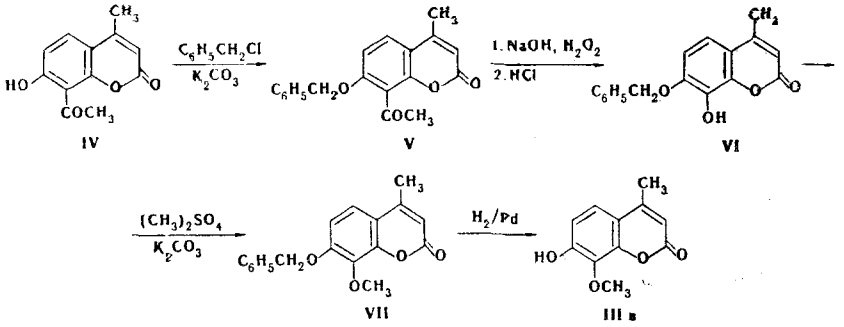
The lower selectivity of the methylation of 4-methyl-7,8-dihydroxycoumarin as compared with the methylation of 6,7-dihydroxycoumarins is explained by means of the pK_a values and data from the PMR and IR spectra by the slight difference in the acidity of the hydroxyl groups in the 7- and 8-positions.

The alkylation of esculetin, i.e., 6,7-dihydroxycoumarin (Ia), and 4-methyl-6,7-dihydroxycoumarin (IIa) proceeds primarily at the oxygen atom in the 7- or 6-position, depending on whether 1 or 2 moles of alkali, respectively, is used [1, 2]. This is explained by the fact that mainly the monophenoxide ion is formed under the influence of 1 mole of alkali due to the more acidic hydroxyl group in the 7-position; however, if there is sufficient alkali for conversion of both hydroxyl groups to anions, the more basic (and in this case more nucleophilic) anion in the 6-position is primarily alkylated.

We have carried out the methylation of 4-methyl-7,8-dihydroxycoumarin (4-methyldaphnetin) (IIIa) with dimethyl sulfate and the methylation of Ia, IIa, and IIIa with diazomethane.

To facilitate the identification of the products of methylation of IIIa, we synthesized its 7- and 8-monomethyl ethers (IIIb, c, respectively). Compound IIIb was obtained by a known method [3]. The synthesis of IIIc was accomplished by a new method, inasmuch as the methods described in the literature are either too complex or lead to one of the isomeric ethers of insufficiently definite structure [4, 5]. We obtained IIIc from the accessible 4-methyl-7-hydroxy-8-acetylcoumarin [6] (IV) via the following scheme:



The intermediates (V-VII) have not been described in the literature. Substance IIIc differs from IIIb with respect to its IR spectrum, pK_a value, and chromatography on paper and Silufol.

The results of the methylation of IIIa in the presence of 1 mole of NaOH proved to be somewhat unexpected: a mixture of approximately equal amounts of isomeric ethers IIIb, c (in yields of 9.1 and 13.1%, respectively, together with 7.9% IIId) was formed. The yields of ethers IIIb, c (7.1 and 13.8%) also differed only slightly in the presence of 2 moles of NaOH, and it was even more difficult to evaluate the relative re-

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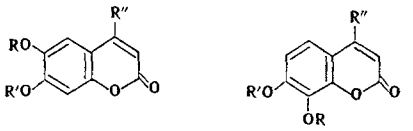
TABLE 1. pK_a Values and Data from the IR Spectra of Hydroxycoumarins

Compound	pK_a in 70% alcohol[a]	IR spectra		
		recording conditions	ν_{OH}, cm^{-1}	$\nu_{C=O}$, cm^{-1}
Xa[b]	9,22			
VIIIa	9,35	$CHCl_3$,[c] $c=10^{-3}$ M, $d=1$ cm	3600, narrow	
XIa[b]	10,40			
IXa	10,56	$CHCl_3$, $c=10^{-3}$ M, $d=1$ cm	3602, narrow	1723
Ia	8,60			
IIa	8,76			
Ic	8,96			
IIc	8,90	CCl_4, $c\leq10^{-4}$ M, $d=5$ cm	3550, narrow	1733, inflect. 1752
Ib	10,40			
IIb	10,57	CCl_4, $c=10^{-4}$ M[d], $d=5$ cm	3570, narrow	1742 and 1731, doublet with equally intense components
XIIa[b]	9,00			
IIIa	9.15	$CHCl_3$, $c=10^{-3}$ M, $d=1$ cm	3552, broad; shoulder at 3615	1735
IIIc	8,99	CCl_4, $c=10^{-4}$ M[d] $d=5$ cm	3518, narrow	1744
IIIb	10,02	CCl_4, $c=10^{-4}$ M[e], $d=5$ cm	3565	1749

[a]The standard error in the determination was no more than 0.06 pK_a units in all cases.
[b]Compounds Xa, XIa, and XIIa are, respectively, 7-hydroxy-, 6-hydroxy-, and 7,8-dihydroxycoumarins.
[c]In CCl_4 solution (c 10^{-4} M, d = 5 cm), ν_{OH} 3600 cm^{-1}.
[d]When c = 10^{-3} M, the indicated frequencies do not change.
[e]When c = 10^{-3} M, the frequencies are 3560 and 1748 cm^{-1}, respectively.

activities of the 7- and 8-phenoxide ions in this case in view of the fact that a considerable portion of the starting material is converted to the diether (21.6%), and it is not known which monoether is its precursor,



I, II a-d III a-d

I R″ = H; II, III R″ = CH_3; I-III a R = R′ = H; b R = H, R′ = CH_3; c R = CH_3, R′ = H; d R = R′ = CH_3

The results of the methylation of Ia and IIa under the same conditions as those in the preparation of IIIa (the yields of the reaction products in all of these experiments were determined by means of the PMR spectra) are in agreement with earlier data obtained when the reaction products were analyzed by paper chromatography [1, 2]. Thus, the following compounds (yields in percent given) are formed in the methylation of Ia and IIa with 1 mole of alkali: Ib 40.2, Ic 4.6, Id 5.4, IIb 20.6, IIc 2.6, and IId 2.4. When 2 moles of alkali are used, the following compounds are formed (yields in percent given): Ib 6.6, Ic 36.3, Id 13.2, IIb 6.2, IIc 31.2, and IId 13. Moreover, the errors in the determination are such that they do not affect the conclusions regarding the primary direction of alkylation (see the experimental section).

In order to attempt to explain the indicated behavior of IIIa in alkylation reactions we determined the ionization constants of IIIa and its isomeric ethers IIIb and IIIc and compared them with the ionization constants of Ia and IIa and their monoethers (Table 1). An examination of the pK_a values makes it possible to conclude that the 7-hydroxy derivatives with a methoxy group in the 6- or 8-position are stronger acids than the 6-hydroxy- or 8-hydroxy derivatives with a 7-CH_3O group. This corresponds to the difference in the acidity between 7- and 6-monohydroxycoumarins, and the experimentally found pK_a values of o-dihydroxycoumarins, consequently, are related to the 7-OH group. The second ionization constant is not determined by potentiometry in an aqueous alcohol medium; as in pyrocatechol [7], it possibly corresponds to $pK_a \geq 12$. The 4-methyl-substituted compounds have higher numerical pK_a values than the corresponding 4-unsubstituted hydroxycoumarins: on the average, the difference in the pK_a values of the corresponding hydroxy derivatives is 0.15. Compound IIIb is a stronger acid than IIb, which may be explained by the elec-

tron-acceptor effect of the ring-ester group. The introduction of CH_3O or HO groups into the 6- (or 8-) position of 4-methyl-7-hydroxycoumarin (VIIIa) intensitifes the acidity of the hydroxyl group in the 7-position, and the effect of the 6-OH group in the esculetin series is stronger than the effect of the $6\text{-}OCH_3$ group, but the reverse tendency exists in the dephnetin series: the pK_a of IIIa is 9.15, while the pK_a of IIIc is 8.99. It is true that the errors in the measurements may level out this small yet appreciable difference. It may be assumed that the CH_3O group in 8-methoxy derivative IIIc is partially removed from conjugation with the benzene ring as a consequence of steric hindrance (which is observed in molecular models). However, the presence of a CH_3O group in the 7-position of the 4-methyl-6-hydroxycoumarin (IIa) molecule does not change the pK_a value. In the benzene series, the introduction of a methoxy group into the ortho position relative to the phenolic OH group also does not change the pK_a value, but the presence of an ortho hydroxyl group increases the acidity. One may therefore, with a certain degree of caution, assume that 4-methyl-8-hydroxycoumarin, the ionization constant of which has not been determined (because of the low accessibility of this substance or its 4-unsubstituted homolog), is close in acidity to IIIb ($pK_a \sim 10$). Thus, the less-expressed selectivity of the alkylation of IIIa as compared with Ia and IIa in the presence of 1 or 2 moles of alkali should be explained by the smaller differences in the acidities of the hydroxyl groups in the 7- and 8-positions. This is also in agreement with the results of methylation by diazomethane: the yields of IIIb and IIIc are 8.7 and 6.5%, respectively (IIId 1.5%), while Ic and IIc are not formed at all under these conditions, and the yields of Ib and IIb are 10.8 and 12%, respectively (Ib 3.4% and IId 2.4%).

As in the case of pyrocatechol monoether [8, 9], the presence of intramolecular hydrogen bonding was observed in a study of the IR spectra (in $CHCl_3$ and CCl_4) of monoether derivatives of II and III. The intramolecular hydrogen bond in monoethers IIb, c and IIIb, c is characterized by an energy that corresponds to a band shift of 30-80 cm^{-1} in CCl_4 or $CHCl_3$ solutions if it is supposed that the free hydroxyl groups of the monoethers should have approximately the same stretching vibration frequencies, i.e., ~3600 cm^{-1}, as monohydroxycoumarins (for example, VIIIa and IXa).

The hydrogen bond in 7-hydroxy derivatives IIc and IIIc is stronger than in 6(8)-hydroxy derivatives IIb and IIIb, inasmuch as IIc and IIIc are relatively stronger acids, and the oxygen atoms of the CH_3O groups in IIc and IIIc bear relatively higher electron densities than in IIb and IIIb. The hydrogen bond is stronger in IIIc than in IIc; this may be associated with the high electron density on the oxygen atom of the methoxy group of IIIc, confirming our assumption of removal of this group from conjugation with the benzene ring. The frequency of the OH group in 8-hydroxy derivative IIIb is somewhat lower than in 6-hydroxy derivative IIb, and this corresponds to the higher acidity of IIIb. However, it is difficult to sufficiently accurately estimate the relative electron densities on the carbon atoms in the CH_3O groups of IIb and IIIb. On the basis of indirect data, namely, from the pK_a values of 7-hydroxy derivatives IIc and IIIc, it can be stated that there should not be a substantial difference in the electron-donor character of the oxygen atoms of these groups with respect to the proton. It follows from quantum-chemical calculations* by the simple Hückel method with Pullman parameters [10], without introduction of an auxiliary inductive parameter, that the residual charge on the oxygen atoms of the 6-OH and 7-OH groups of Ia is 1.9319 and 1.9222, respectively, as compared with 1.9105 and 1.8987 for 6,7-dimethoxycoumarin, 1.9320 and 1.8986 for Ib, and 1.9104 and 1.9224, respectively, for Ic. All of these values are in agreement with the ionization constants and the IR spectra in the region of the stretching vibrations of OH groups. However, in the 7,8-dihydroxycoumarin series the quantum-chemical calculations by the indicated method frequently do not correspond to these experimental data, apparently mainly because the inductive effect of the heteroatoms and the steric factors were not taken into account in the calculations. We note that the oxygen atom of the heteroring, as was assumed for 7,8-dihydroxy- or 7-methoxy-8-hydroxychromones [11], rather than that of the CH_3O group may participate in the formation of an intramolecular hydrogen bond in IIIb. The test with $FeCl_3$ serves as a confirmation of the fact that in compounds of the IIIa, b type there is a possibility for coordination of the proton of the 8-OH group with the heterocyclic O atom. In concentrated alcohol solutions, 7-ether IIIb gives a green coloration with $FeCl_3$. In contrast to this, esculetin monoethers of the Ib, c and IIb, c type do not give a color reaction with $FeCl_3$.

The intramolecular hydrogen bonds in monoethers IIb, c and IIIb, c and also in IIIa and VIIIa-IXa are disrupted in tetrahydrofuran (THF) solution, and the stretching vibrations of the OH groups in the IR spectra (c 0.1 M) appear as broad bands at 3200-3230 cm^{-1} for IIb, c; IIIb, c; IIIa; and VIIIa; and at 3263 cm^{-1} for IXa. The intramolecular hydrogen bonds of compounds of the indicated type are evidently completely disrupted in aqueous and alcohol solutions and therefore do not affect the ionization constants under these

*The calculations were made by M. E. Perel'son, to whom the authors exprss their gratitude.

conditions. As in THF, primarily intermolecular hydrogen bonds are formed in the crystalline state. For example, the IR spectra of Ic, IIa, IIIa, IIIb, IXa, and VIIIa are characterized by broad ν_{OH} bands at 3333, 3280, 3100-3450, 3200-3445 (and 3550), 3330, and 3150 cm^{-1}, respectively. Of the spectral characteristics of monoethers II and III we also note the higher values of the frequencies of the stretching vibrations of the C=O group in the III series as compared with II.

EXPERIMENTAL*

Leningrad "slow" paper impregnated with 0.1 M sodium borate solution was used for paper chromatography by the method in [12]; the system for ascending chromatography was butanol saturated with water, and the chromatograms were developed with UV light. Genuine individual substances or their artificial mixtures were used in all cases for monitoring.

The yields of reaction products were determined from the PMR spectra with a Varian T-60 spectrometer. A genuine sample of N-methyl-N-phenylbenzenesulfonamide with mp 78.5-79.5° served as the reference compound. The CH_3O groups were identified by the addition of genuine samples of the ethers in model and working experiments.

The acid dissociation constants were determined potentiometrically in 70% ethanol (by volume). The solution concentrations for titration were $1 \cdot 10^{-3}$ M, and the pH values were measured with a PHM-26 pH-meter.

Methylation of 4-Methyl-7,8-dihydroxycoumarin (IIIa). A) A total of 1.89 g (15 mmole) of dimethyl sulfate was added in three portions in the course of 3 h with stirring at 0° to a solution of 0.96 g (5 mmole) of IIIa and 0.6 g (15 mmole) of NaOH in 8 ml of water, and the mixture was stirred for another hour and filtered to give 0.35 g of the known diether (IIId) with mp 131.5-133° [9]. The alkaline filtrate was acidified to give 0.43 g of a precipitate containing (according to paper chromatography) IIIc with R_f 0.47, IIIa (at the start), and traces of IIId with R_f 0.91. The precipitate was treated with ~50 ml of hot toluene, and the toluene extract was cooled and filtered. The filtrate was evaporated to one-third of its original volume and allowed to stand to give 0.1 g (10%) of IIIc with mp 156-157.5° containing traces of IIIa (no more than 0.5%). The IIIc obtained in this manner was identical to a genuine sample.

B) A 0.96-g sample of IIIa was methylated by means of dimethyl sulfate in acetone containing K_2CO_3 by the method in [10]. The crude product, which, according to paper chromatography, contained both monoethers, a diether, and the starting substance, was treated with 5% NaOH, and the mixture was filtered to give 0.22 g of IIId. The alkaline filtrate was acidified to give 0.45 g of a precipitate, which was treated with toluene as described above to give 5% of IIIb with mp 155-156.5° containing traces of IIIc and IIIa; IIIb depressed the melting point of a genuine sample of IIIc and was identical to a genuine sample of IIIb obtained by the method in [9].

C) A 1.89-g (15 mmole) sample of dimethyl sulfate was added to a solution of 2.88 g (15 mmole) of IIIa and 0.6 g (15 mmole) of NaOH in 180 ml of alcohol, and the mixture was stirred at 20° for 5 h and allowed to stand for ~16 h. It was then acidified (with respect to Congo red) with HCl, and the liquid was removed completely by vacuum distillation. The dry residue was treated with 10 ml of water, and the mixture was allowed to stand at 4° for ~20 h. The resulting precipitate was removed by filtration, washed with 5 ml of water, and vacuum dried over P_2O_5 to give 3.04 g of product (product A). The aqueous filtrate was extracted with dichloroethane (five 10-ml portions) and methylene chloride (five 10-ml portions). The combined organic solutions were washed with water (two 10-ml portions) and vacuum evaporated (near the end with the addition of two 10-ml portions of CCl_4). The residue was vacuum dried over P_2O_5 to give 0.30 g of product (product B, a semicrystalline mass; the monoether content in all of the experiments was 0.2-5.3%, while the diether content was 2.4-7.1%). All of the aqueous solutions were vacuum evaporated to dryness, and the residue was vacuum dried over P_2O_5 and extracted with methylene chloride (three 30-ml portions) by refluxing each time for 15 min. Carbon tetrachloride (two 5-ml portions) was added, and the solvents were removed completely by vacuum distillation (product C remained in the flask; the ethers and starting materials were absent in this and subsequent experiments).

* The authors thank V. S. Troitskaya for recording the IR spectra.

TABLE 2. Results of Methylation of Dihydroxycoumarins

Reaction conditions	Yields of ethers,[a] %										
	Ib	Ic	Id	overall yield, %	IIb	IIc	IId	overall yield, %	IIIb	IIIc	IIId	overall yield, %
1 mole NaOH, 1 mole $(CH_3)_2SO_4$, alcohol 20°, ~20 h	40,2	4.6	5,4	50,2	20,6	2,6	2,4	25,6	9,1	13,1	7,9	30,1
2 mole NaOH, 1 mole $(CH_3)_2SO_4$, alcohol 20°, ~20 h	6,6	36,3	13,2	56,1	6,2	31,2	13,0	50,4	7,1	13,8	21,6	42,5
CH_2N_2, DMFA + ether	10,8	0[b]	3,4	14,2	12	0[b]	2,4	14,4	8,7	6,5	1,5	16,7

[a]The yields of ethers in mixtures of A and C are presented in the experiments carried out with alkali.
[b]This compound also was not detected by paper chromatography.

PMR spectrum in pyridine–benzene (1:3),* δ, ppm: 1.9 (m, 4-CH_3),† 2.9 (s, CH_3 reference), 3.5 (s, OCH_3 IIId), 3.6 (s, 7-OCH_3 IIIb), 3.75 (s, 8-OCH_3 IIIc), 3.8 (s, OCH_3 IIId). The yields of the ethers are given in Table 2. Unchanged IIIa (56.4%) was recovered.

D) A 15-mmole sample of IIIa was methylated in the presence of 30 mmole of NaOH as in the preceding experiment. See Table 2 for the yields of ethers. Unchanged IIIa (35.6%) was recovered.

E) An ether solution of diazomethane (13.2 mmole) was added at +3° to a solution of 0.84 g (4.4 mmole) of IIIa in 4 ml of DMFA, and the mixture was held at 3° for 30 min and allowed to stand at 20° for ~16 h. It was then vacuum evaporated (near the end with two 10-ml portions of CCl_4), and the residue was vacuum dried over P_2O_5 (see Table 2). Unchanged IIIa (65.3%) was recovered.

Methylation of 4-Methyl-6,7-dihydroxycoumarin (IIa). A) A 15-mmole sample of IIa was methylated with dimethyl sulfate in alcohol in the presence of 15 mmole of NaOH in analogy with IIIa. PMR spectrum of solution 1 [pyridine–benzene (1:2)], δ, ppm: 3.6 (s, 6-OCH_3 IIc and IId), 3.45 (s, 7-OCH_3 IIb and IId). The assignment was made by means of 4-methyl-6-methoxy-7-trideuteromethoxycoumarin obtained by methylation by means of CD_3I of a genuine sample of IIc in CD_3OD solution. Pyridine (1 ml) and 0.6 ml of $C_6H_5SO_2Cl$ were added to 1 ml of a pyridine solution of products A and C, and the mixture was heated at 60–80° for 4 h (solution 2). PMR spectrum of solution 2, δ, ppm: 3.9 (unresolved OCH_3 signals IId), 3.65 (unresolved OCH_3 signals of benzene sulfonates IIb and IIc), 3.2 (s, CH_3 reference), and 2.2–2.4 (m, 4-CH_3). The yield of IId was determined by analysis of solution 2, while the yields of IIb and IIc were determined by analysis of solution 1 (Table 2). Unchanged IIa (74.3%) was recovered.

B) A 15-mmole sample of IIa was methylated in the presence of 30 mmole of NaOH in analogy with IIIa (Table 2). Unchanged IIa (34.9%) was recovered.

C) A 4.4-mmole sample of IIa was methylated with diazomethane as in the case of IIIa (Table 2). Unchanged IIa (77.0%) was recovered.

Methylation of 6,7-Dihydroxycoumarin (Ia). A) A 15-mmole sample of Ia was methylated in the presence of 15 mmole of NaOH in analogy with IIIa (Table 2).

B) A 15-mmole sample of Ia was methylated in the presence of 30 mmole of NaOH in analogy with IIIa (Table 2).

C) A 4.4-mmole sample of Ia was methylated with diazomethane as in the case of IIIa (Table 2).

Because of the systematic error in the integration, the reproducibility of the measurements was ~2%. The error in the determination of the yields of the ethers with respect to the least intense PMR signal was ~20% as compared with ~3% for the most intense signal. In experiments involving the methylation of IIa with 1 and 2 moles of NaOH, three control analyses each of genuine mixtures of the appropriate composition were made. The average deviation in the determinations in the standard mixtures were as

*Other solvents are less suitable because of the low solubilities of the investigated substances in them, and in pyridine alone the protons of all of the CH_3O groups give an unresolved signal at 4 ppm.
†The following abbreviations are used here and subsequently: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet.

follows (in percent): for IIb −0.8 and −1.4, for IIc +23 and +10, and for IId −34 and −27). An additional analysis was also made in the determination of IId in control experiments with 1 and 2 moles of NaOH. For 2.2 and 5.9% IId, IIa was taken in amounts corresponding to the percentages of monoethers and IIa in the control mixture. The deviations in the determinations were as follows (in percent): −16.7 and −6.6 in the analysis of the mixture in pyridine and −53.4 and −16.3, respectively, after benzenesulfonation (the average deviation of ~30% in the determination of IId is, consequently, a systematic error and it can be taken into account).

4-Methyl-7-benzyloxy-8-acetylcoumarin (V). A mixture of 7.64 g (35 mmole) of pure 4-methyl-7-hydorxy-8-acetylcoumarin (IV) [6] with mp 168-169°, 8.9 g (70 mmole) of benzyl chloride, and 12.09 g (88 mmole) of anhydrous K_2CO_3 in absolute acetone was refluxed for 40 h. The acetone was removed by distillation, 10% NaOH was added to the residue, and the alkaline mixture was extracted with dichloroethane. The organic layer was evaporated, and the residue was treated with petroleum ether and ether to give 5.8 g (54%; according to chromatographic data, the product did not contain impurities) of V with mp 140-141° (from alcohol). Found, %: C 73.9; H 5.4. $C_{19}H_{16}O_4$. Calculated, %: C 74.0; H 5.2.

4-Methyl-7-benzyloxy-8-hydroxycoumarin (VI). A 1.39-g sample of coumarin V was oxidized by the Dakin method [3], and the reaction mixture was acidified with hydrochloric acid and extracted with dichloroethane. The organic layer was evaporated partially, ether was added to the residue, and 0.82 g (64.6%) of VI with mp 183-184° (from alcohol) was removed by filtration. Found, %: C 72.4; H 5.0. $C_{17}H_{14}O_4$. Calculated, %: C 72.3; H 5.0.

4-Methyl-7-benzyloxy-8-methoxycoumarin (VII). A 1.13-g sample of coumarin VI was methylated with dimethyl sulfate in the presence of K_2CO_3 in absolute acetone by refluxing the mixture for 7 h. The solvent was removed by distillation, 5% NaOH was added, and the mixture was extracted with chloroform. The organic layer was evaporated to give 1.13 g (95%) of VII with mp 141-142° (from alcohol). Found, %: C 72.9; H 5.5. $C_{18}H_{16}O_4$. Calculated, %: C 73.0; H 5.4.

4-Methyl-7-hydroxy-8-methoxycoumarin (IIIc). A 0.89-g sample of VII was debenzylated in alcohol over $Pd/BaSO_4$ to give 0.58 g (94%) of IIIc with mp 162-163° (the product was treated with ether and then recrystallized from benzene); a mixture of the product with isomer IIIb (mp 160°) had mp 120-122°. Chromatography of IIIc on paper gave a spot with R_f 0.50 that fluoresces in UV light. Isomeric IIIb formed a brown spot with R_f 0.40 that did not fluoresce. The R_f values of IIIc and IIIb on Silufol were 0.63 and 0.53 (ethyl acetate), 0.50 and 0.37 [ethyl acetate–chloroform (1 : 1)], and 0.55 and 0.42 [ethyl acetate–chloroform (2 : 1)], respectively. According to the literature data, IIIc has mp 163° [4] and IIIb has mp 160-161° [3].

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