REGIONAL AND STERIC COURSE OF THERMAL REACTIONS IN SOME RHOEADINE ALKALOID N-OXIDES

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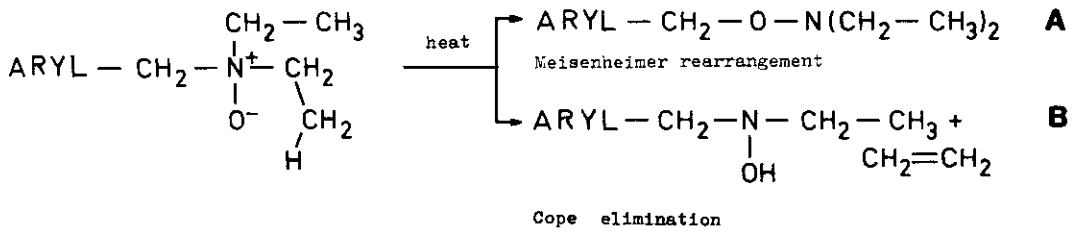
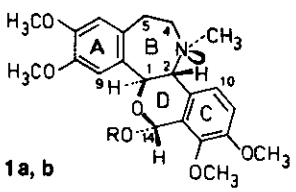
Abstract - The thermal behavior of a typical series of rhoeadine alkaloid N-oxides, 2a, 2b, 6b, and 7b, derived from alpinigenine (1a) or its B/D-cis analog 5a is greatly dominated by the Meisenheimer-type of rearrangement with the regiospecific formation of the benzoxazocine congeners 3a, 3b, and 8 of these alkaloids. Alternatively, Cope elimination has been possible under more extreme reaction conditions when the side product 4 was isolated in addition to 3a. In each case of rearrangement there was full retention of configuration. The N-epimeric O-methyl-cis-alpinigenine N-oxides A (6b) and B (7b) serving as starting materials, as well as the hemiacetals corresponding them, have been discussed in terms of their chirality at nitrogen and C-14.

The Meisenheimer rearrangement and the Cope elimination are two types of reaction that could take place when tertiary amine oxides are heated at temperatures ranging in general between 80 and 200°C. The Cope elimination[1,2] is always bound with the presence of hydrogen on a ß-carbon, while the Meisenheimer rearrangement[3] constitutes an intramolecular N⟶O migration of certain groups which are essentially confined to allyl, benzyl and a few others, Scheme I. The O-substituted hydroxylamines A resulting from this rearrangement are now considered to be formed through a homolytic cleavage-recombination pathway[5]. Stereochemical studies done in a few cases[6,7] have shown that retention of configuration was always combined with racemization varying to a considerable degree.
Among the isoquinoline family of alkaloids, the thermal behavior of N-oxides has been examined in the protopine[8], phthalideisoquinoline[9], and 1-benzyltetrahy-

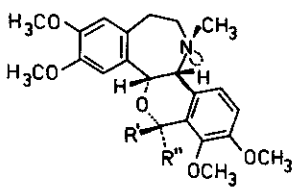
droisoquinoline[10] groups. In this paper, pyrolysis of the four N-oxides 2a, 2b, 6b, and 7b related to the rhoeadine alkaloid[11] alpinigenine[12,13](1a) was found to follow the Meisenheimer mode, which in this case included both full regiospecificity and retention of configuration at the central carbon, C-2. A side product tentatively assigned structure 4 was probably due to Cope elimination occuring at temperatures higher than those required for the rearrangement. The results are depicted in the formulae.



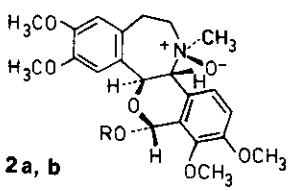
SCHEME 1



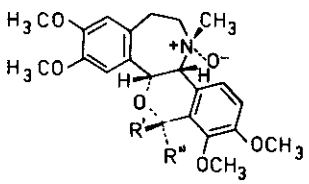
1a, b



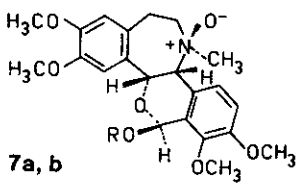
5a R'=H, R"= OH; **5b** R'= OCH_3, R"=H



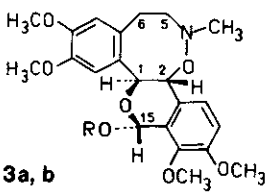
2a, b



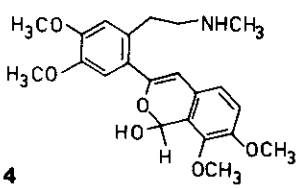
6a R'=H, R"=OH; **6b** R'= OCH_3, R"= H



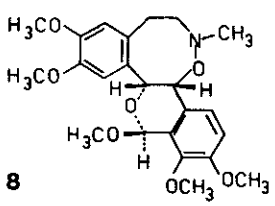
7a, b



3a, b



4



8

1, 2, 3, 7: a R = H, **b** R = CH_3

The starting N-oxides were either known from our previous work as the B/D-trans fused ones, viz. alpinigenine N-oxide[12] (2a) and epialpinine N-oxide[13] (2b), or were prepared from the known[13] N,C(14)-stereoisomeric cis-alpinigenine N-oxides A (6a) or B (7a) using acid-catalyzed acetalization in methanol at ambient temperature to form the N-epimeric O-methyl-cis-alpinigenine N-oxides A (6b) or B (7b), respectively. The latter was also formed as the only reaction product by direct N-oxidation of 5b using perbenzoic acid at 0°C or boiling ethanolic hydrogen peroxide.

As to the thermal reaction of the acetal N-oxides, Meisenheimer rearrangement was found to occur when 2b, 6b or 7b were heated at ca. 130°C under reduced pressure and the stable benzoxazocine derivatives 3b and 8 were isolated in yields ranging between 55 and 75 %. A higher temperature of at least 160°C was required for the transformation of the hemiacetal 2a into 3a.

The routine mass spectra of these oxygen-expanded rhoeadine-type molecules were very complex and the low-intensity molecular ions always lost 60 or 59 mass units which were due to the expulsion of $CH_2{=}N^+(OH)CH_3$ and thus analogous to other 1,2-oxaza-ring systems[14], see Experimental. By the way, the mass spectra of N-oxides were almost identical with those of Meisenheimer products, meaning that thermal rearrangement inside the spectrometer may compete with ionization. On the other hand, the presence of a small M-16 peak was indicative of oxygen abstraction from the N-oxide molecular ion[15].

The regiospecific insertion of an oxygen atom between nitrogen and benzylic C-2 rather than C-4 with formation of the ring B-enlarged 1,2-oxaza-compounds 3a, 3b, and 8 was predicted from the general course of Meisenheimer rearrangement[5]. Conclusive evidence of this was gained from the nmr data. In the ^{13}C spectra of all ring-enlarged compounds, the particular ring carbon that becomes directly attached to oxygen should exhibit a downfield shift of maximum size, owing to the high electronegativity of oxygen. As shown in Table 1, carbon 2 in the benzoxazocines 3a, 3b or 8 encounters a downfield shift as high as $\Delta\delta$ = +17.0 to +19.0 ppm when compared to carbon 2 in the alkaloids derived from, i. e. 1a, 1b or 5b. On the contrary, C-5 in the ring-enlarged compounds compared to C-4 in the parent alkaloids was much less affected.

Such a high degree of deshielding as observed for C-2 is due to an oxygen α-substituent effect, which is similar to that found in 6-membered heterocycles[18]. As to the ß-carbon relative to ring B oxygen, it should be mentioned that C-5 in

each benzoxazocine was shifted downfield by some 6 to 8 ppm. A shift of similar degree was observed for C-1 in the B/D-*trans* benzoxazocines, both 3a and 3b, while this was significantly smaller in the B/D-*cis* compound 8.

Table 1.- Carbon-13 chemical shifts[a] (ppm) of ring B carbons[b] of the benzazepine alkaloids 1a, 1b, and 5b and of their Meisenheimer rearrangement products 3a, 3b, and 8

Carbon[c]	1a	1b	5b	Carbon[d]	3a	3b	8
C-1	63.0	62.8	76.7	C-1	68.8	68.7	75.3
C-2	61.6	61.6	59.6	C-2	80.4	80.6	76.6
$N-CH_3$	33.6	33.4	40.2	$N-CH_3$	45.6	46.6	46.7
C-4	55.9	55.9	54.5	C-5	62.0	62.0	62.4
C-5	31.2	31.2	32.6	C-6	30.8	30.9	31.2
C-5a	131.5	131.5	134.5	C-6a	129.8	129.6	133.1
C-9a	135.3	135.3	129.5	C-10a	132.8	133.0	130.5

a) Chemical shift values were measured from the central solvent line of $CDCl_3$ and calculated to TMS ($\delta_{TMS} = \delta_{CDCl_3} + 77.0$ ppm).

b) Identification of carbons was performed using single frequency off-resonance (SFORD) spectra, selective ^{13}C $\{^1H\}$ decoupling experiments, and selective ^{13}C $\{^1H\}$ NOE measurements. For 1a an assignment was already reported in the literature[16], which was confirmed in every detail by our investigation. A comprehensive discussion of ^1H and ^{13}C nmr spectra for alpinigenine and its congeners will be published[17].

c) Benzazepine numbering.

d) Benzoxazocine numbering.

The two γ-carbons located in ring B, i. e., C-6 and C-10a, show little or no response which in general is upfield, except for C-10a of 8. This diversity may result from the fact that β- and γ-substituent effects are less dependent on the electronegativity of the substituent in question, rather than a consequence from the complexity of steric and/or electronic interactions in the 7- or the 8-membered ring systems involved. In the proton nmr spectra of the benzoxazocines 3a, 3b, and 8 the downfield shifts associated with 2-H ($\Delta\delta$ = +0.5 to +0.8 ppm)

also reflect the site of oxygen insertion, see Table 2.

Rhoeadine alkaloids fall into two main groups[11], the B/D-trans compounds with a trans diaxial arrangement and a large vicinal coupling for 1-H and 2-H, $^3J_{1,2} \sim$ 7.5 to 9.5 Hz, or the thermodynamically more stable B/D-cis series showing ~1.0 to 2.5 Hz. As to stereochemistry, Meisenheimer rearrangement in both the B/D-trans N-oxides 2a and 2b as well as the cis-compounds 6b and 7b has been found to proceed with full retention of configuration at C-2. Evidence of this was provided by the fact that vicinal couplings indicative of the mode of ring B/D-conjunction have not changed in the benzoxazocines 3a, 3b, or 8, cf. Table 2. Accordingly, all benzoxazocine derivatives resemble the alkaloids derived from in having an optical rotation of positive sign.

No products of side reactions were isolated, except the singular case that alpinigenine N-oxide (2a) was heated at 180°C, a temperature higher than that required normally. Under these conditions the Meisenheimer product 3a was accompanied by a small amount of the optically inactive hydroxylamine 4, the tentative structure of which mainly rests upon its UV-spectrum (λ_{max} 215, 328 nm) which indicates the occurrence of two aromatic chromophores connected by a double bond.

The thermal reactions of a typical triad of rhoeadine alkaloid N-oxides are distinguished for their high degree of specificity in both regional and stereochemical terms. Retention of configuration at C-2 is in accord with a homolytic dissociation recombination mechanism occurring in a solvent cage[5,6]. Retention had already been observed in the pyrolysis of simpler N-oxides, but a considerable amount of racemization was always present[7]. Even in more recent studies dealing with isoquinoline N-oxides, stereochemical aspects were neglected[9,10].

The stereochemistry of the four N-oxides as 6a, 6b, 7a, and 7b related to cis-alpinigenine (5a) requires a comprehensive discussion based on the principles summarized in a recent review article[11]. As reported previously[13], N-oxidation of 5a gave rise to the two isomeric N-oxides A (6a) and B (7a) which differ in their chirality not only at the quaternary nitrogen but also at the anomeric carbon, C-14. The slightly dominating isomer A similar to 5a has an equatorial N-methyl group (δ = 3.28 ppm) and consequently, no interaction between the axial rearside N-oxide oxygen atom and the aromatic proton at C-10 is obvious from the proton nmr spectrum of 6a when compared to that of 5a, Table 2. On the other hand, the axial N-methyl group of N-oxide B (7a) shows a much more up-field signal (δ = 2.77 ppm, $\Delta\delta$ = -0.51 ppm), while its equatorial oxygen approximates

10-H, thus producing a very pronounced down-field shift in the latter (δ = 7.84, $\Delta\delta$ = +0.93 ppm relative to 5a).

Table 2.- Selected proton nmr data[a] of benzazepine alkaloids, N-oxides and Meisenheimer products

Compound	aromatic				benzylic			C(14)-OCH_3	NCH_3
	6-H	9-H	10-H	11-H	1-H	2-H	14-H		
benzazepine alkaloids									
1a	6.68	7.24	7.23 (8.9)	6.94 (8.9)	5.80 (9.4)	4.03 (9.4)	6.40	-	2.34
1b	6.66	7.30	7.18 (8.6)	6.90 (8.6)	5.54 (9.3)	3.99 (9.3)	5.81	3.54	2.29
5a	6.69	6.69	6.91 (8.3)	6.85 (8.3)	4.59 (1.0)	3.15 (1.0)	6.34	-	2.20
5b	6.60	6.76	6.96 (8.4)	6.87 (8.4)	5.07 (2.2)	3.68 (2.2)	5.74	3.53	2.22
N-oxides									
6a	6.71[b]	6.73[b]	6.97 (8.3)	6.91 (8.3)	4.79 (1.4)	4.30 (1.4)	6.49	-	3.28
7a	6.62	6.83	7.84 (8.6)	7.00 (8.6)	5.43 br.	4.53 br.	6.33	-	2.77
6b	6.72	6.72	7.09 (8.5)	6.95 (8.5)	5.35 br.	4.40 br.	5.83	3.76	3.55
7b	6.67	6.79	7.76 (8.6)	7.01 (8.6)	5.39 br.	4.51 br.	5.79	3.68	2.77
Meisenheimer products									
	aromatic				benzylic			C(15)-OCH_3	NCH_3
	7-H	10-H	11-H	12-H	1-H	2-H	15-H		
3a	6.71	7.25	7.27 (8.8)	6.97 (8.8)	5.43 (9.3)	4.59 (9.3)	6.38	-	2.70
3b	6.72	7.31	7.25 (8.6)	6.95 (8.6)	5.26 (9.3)	4.57 (9.3)	5.82	3.51	2.69
8	6.76	6.76	7.07 (8.4)	6.98 (8.4)	5.11 br.	4.64 br.	5.81	3.52	2.65

a) Chemical shifts (δ) with vicinal coupling constants $^3J_{H,H}$ (Hz) in parentheses. b) Assignment may be interchanged. br.: Broadened singlet.

Stable N-epimeric couples of N-oxide alkaloids are now well established and in several cases an equatorial N-methyl group of a corresponding cyclic tertiary

amine N-oxide in proton nmr was found to show the more down-field signal among the two epimeric counterparts, for example, $\Delta\delta$= +0.34 ppm[16] or $\Delta\delta$= +0.25 ppm[17]. There are examples of N-epimeric N-oxide couples, however, that disclose no significant difference in their N-methyl resonances[10]. An alternative approach to the chirality of alkaloid N-oxides was *via* nmr nuclear Overhauser difference studies[21].

The stereochemistry at anomeric carbon is opposite in the two hemiacetal N-oxides 6a and 7a, but it is identical in the methyl acetals 6b and 7b. The latter two alike hemiacetal 7a have (14S)-chirality which is mirrored in their proton nmr spectra by a strong down-field shift for 1-H ($\Delta\delta \sim$+0.6 ppm) due to 1,3-diaxial interaction with an axial oxygen substituent at C-14. Such an interaction is absent in N-oxide A (6a) ($\delta_{1\text{-H}}$ = 4.79 ppm) showing that 6a has adopted the same chirality at C-14 and nitrogen as the starting 5a. N-oxide A is a stable compound that neither shows mutarotation nor is liable to rearrange into its apparently more stable isomer B (7a). In the methyl acetal N-oxides, 6b and 7b, additional evidence for the chiral uniformity at the anomeric carbon was gained from reductive retransformation of the two into O-methyl-*cis*-alpinigenine (5b) using lithium aluminium hydride.

EXPERIMENTAL

All melting points (mp) were taken on a microscope hot stage apparatus and are corrected. Optical rotations were determined in methanol solution using a "Polamat A" from Zeiss/Jena. Ultraviolet spectra (uv) were recorded in 95 % ethanol on an "Ultrascan" spectrophotometer from Hilger & Watts. Nuclear magnetic resonance (nmr) spectra were measured in $CDCl_3$ on a Bruker WP-200 at 200.13 MHz and 50.33 MHz for ^1H or ^{13}C, respectively; chemical shift (δ) values are ppm downfield from standard tetramethylsilane and coupling constants (J) are in Hertz. Mass spectra (ms) were run on an Ardenne (Dresden) low-energy ionizing instrument with the sample evaporator heated to approximately 100°C.

O-Methyl-*cis*-alpinigenine N-Oxide A (6b).- A solution of *cis*-alpinigenine N-oxide A[13] (6a) (160 mg, 0.384 mM) in 15 ml of dry 0.1 N methanolic HCl was kept at room temperature in the dark overnight and then evaporated to dryness ensuring temperatures below 40°C. The residue was dissolved in CH_2Cl_2 and stirred with dry K_2CO_3 (1 g) for 15 min and the mixture filtered and evaporated *in vacuo*. The crude product was crystallized from methanol avoiding temperatures above 40°C

and using a stream of nitrogen for concentrating the solution to give crystals sensitive to light (116 mg, 65 % yield), mp 220-224°C (dec.), $[\alpha]_D^{24}$ +242.5° (c = 0.8).- Anal. calcd for $C_{23}H_{29}NO_7 + 2H_2O$ (467.5): C, 59.08; H, 7.12; N, 3.00 %. Found: C, 59.10; H, 6.84; N, 2.79.- uv: $\lambda_{max}(log\,\varepsilon)$ = 211(4.62), 238(4.23), 284 nm (3.67).- ms: m/z = 431(0.5 %, M^+), 415(10 %, - O), 413(10 %), 399(100 %), 371(16 %, - $CH_2{=}N^+(CH_3)OH$), 340(65 %), 209(81 %), 206(40 %),193(40 %), 179 (40 %).

O-Methyl-cis-alpinigenine N-Oxide B (7b).- a) A mixture of 5 ml of methanol and 2.5 ml of aqueous H_2O_2 (30 %) containing O-methyl-cis-alpinigenine[13] (5b) (415mg, 1.00 mM) was refluxed for 4.5 h, another portion of oxidant (2 ml) being added after 3 h. Evaporation of the solvent under reduced pressure (t < 40°C) gave a product which in benzene solution was transferred to a column of alumina (40 g, H_2O content 5 %) prepared in benzene. Less polar substances were removed using the same solvent and addition of 2 % of Et_2O to the eluant yielded 7b (400 mg) uniform on tlc. No yield can be specified, since the amorphous substance by analogy to other N-oxides should incorporate an unknown number of structurally bound water molecules resisting usual drying procedures, $[\alpha]_D^{25}$ +150.4° (c = 0.8).- uv: $\lambda_{max}(log\,\varepsilon)$ = 211(4.59), 237(4.23), 284 nm (3.69).- ms: m/z = 431(10 %, M^+), 415(43 %, - O), 399(90 %), 371(39 %, - $CH_2{=}N^+(CH_3)OH$), 356(44 %), 340(78 %), 222(52 %), 209(100 %), 194(84 %), 179(82 %).

b) A solution of 5b (124.5 mg, 0.300 mM) in 4 ml of $CHCl_3$ was treated with perbenzoic acid (55 mg, 0.400 mM) dissolved in 2 ml of $CHCl_3$ at 5°C for 18 h. The reaction mixture was diluted with $CHCl_3$, neutralized with aqueous K_2CO_3, dried and evaporated in vacuo (t < 40°C). The product was shown by tlc to contain a minute amount of the isomeric N-oxide, 6b, which was separated by chromatography on alumina as described in the preceding paragraph. The yield of 7b was 110 mg.

c) cis-Alpinigenine N-oxide B monohydrate[13] (7a) (70 mg, 0.16 mM) was treated with 4 ml of 0.1 N methanolic HCl and worked up as shown in the preparation of 6b (65 % yield).

Deoxygenation of the N-Oxides 6b and 7b Using $LiAlH_4$.- The N-oxides 6b and 7b (200 mg each) were reduced in tetrahydrofuran with 100 mg of $LiAlH_4$ at boiling temperature for 3 h and the products isolated were found to be identical by mp, ir, and tlc with both each other and O-methyl-cis-alpinigenine (5b).

Thermal Rearrangement of N-Oxides 2a, 2b, 6b, and 7b: (1S, 2R, 15R)-8,9,13,14,15-Pentamethoxy-4-methyl-1,2,5,6-tetrahydro-4H-isochromano [3,4-a] benz [c] oxazocine (3b).- Epialpinine N-oxide trihydrate[13] (2b) (280 mg, 0.577 mM) was heated at 125-135°C under reduced pressure (1 Torr) for 45 min. The material was crystallized using methanol to give 3b (184 mg, 74 %), mp 200-202°C, $[\alpha]_D^{22}$ +246.5° (c = 0.16).- Anal. calcd for $C_{23}H_{29}NO_7$ (431.5): C, 64.02; H, 6.77; N, 3.25 %. Found: C, 64.30; H, 7.05; N, 3.47 %.- uv: λ_{max}(log ε) = 231(277), 282 nm (3.07).- ms: m/z = 431(6 %, M^+), 415(10 %), 399(100 %), 371(43 %, - $CH_2=N^+(CH_3)OH$), 356(50 %), 340 (81 %), 222(50 %), 209(50 %), 206(67 %), 194(63 %), 178(55 %), 165(50 %), 147 (70 %).

(1R, 2R, 15S)-8,9,13,14,15-Pentamethoxy-4-methyl-1,2,5,6-tetrahydro-4H-isochromano [3,4-a] benz [c] oxazocine (8).- a) O-Methyl-cis-alpinigenine N-oxide B x nH_2O (7b) (260 mg) was thermolyzed in the way specified above and the crude product (222 mg) was separated over a column of alumina (14 g, H_2O content 5 %). Benzene/Et_2O = 4:1 as the eluant provided 8 (127 mg), mp 164-166°C from methanol, $[\alpha]_D^{26}$ +197.3° (c = 0.6).- Anal. calcd for $C_{23}H_{29}NO_7$ (431.5): C, 64.02; H, 6.77; N, 3.25 %. Found: C, 64.37; H, 6.74; N, 3.35 %. - uv: λ_{max}(log ε) = 210(4.36), 233 (3.92), 283 nm (3.65).- ms: m/z = 431(26 %, M^+), 399(100 %), 371(84 %, - $CH_2=N^+(CH_3)OH$), 356(90 %), 340(67 %), 222(56 %), 209(89 %), 194(79 %), 179(86 %).
b) Analogously, 6b (93.6 mg, 0.200 mM) gave 40 mg of 8, mp 162-164°C, $[\alpha]_D^{23}$ +196.1° (c = 0.5), identical by ir, ms, and tlc with the benzoxazocine 8 prepared above from 7b.

(1S, 2R, 15R)-15-Hydroxy-8,9,13,14-tetramethoxy-4-methyl-1,2,5,6-tetrahydro-4H-isochromano [3,4-a] benz [c] oxazocine (3a).- Alpinigenine N-oxide monohydrate[12] (2a) (400 mg, 0.919 mM) was heated at 160°C under reduced pressure (1 Torr) for 70 min. Crystallization from methanol gave pure 3a (240 mg, 62.6 %), mp 187-188°C, $[\alpha]_D^{21}$ +258.1° (c = 0.7).- Anal. calcd for $C_{22}H_{27}NO_7$ (417.5): C, 63.29; H, 6.52; N, 3.36 %. Found: C, 63.29; H, 6.60; N, 3.27 %.- ir (nujol): 3200 (broad), 3374 cm^{-1} (OH).- uv: λ_{max}(log ε) = 210(4.62), 233(4.27), 284 nm (3.74).- ms: m/z = 417 (6 %, M^+), 399 (100 %), 371 (35 %), 358(42 %), 340(69 %), 206(62 %), 179(94 %).

1-Hydroxy-7,8-dimethoxy-3-[4,5-dimethoxy-2-(N-hydroxy-ß-methylaminoethyl)-phenyl]-isochromene (4).- Compound 2a (300 mg, 0.690 mM) was heated at 180°C under reduced pressure (1 Torr) for 30 min. The material containing the hydroxylamine 4 in addition to the benzoxazocine 3a was chromatographed on alumina (20 g, 5 % H_2O) using methylene chloride as solvent and eluent to yield a small fraction of

4. After addition of 3 % of methanol to the solvent, 108 mg of impure 3a were eluted. Compound 4 was crystallized from Et_2O and 15 mg of crystals (5.2 %) were obtained, mp 186-189°C, optically inactive.- ir($CHCl_3$): 1639 (C=C), 3603 cm^{-1} (OH).- uv: λ_{max} (log ε) = 215(4.43), 328 nm (4.33). - ms: m/z = 399(100 %), 382 (16 %), 370(12 %), 356(48 %), 340(92 %), 325(68 %), 309(57 %), 297(50 %), 281 (57 %), 178(80 %), 151(62 %).

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