ALKALOIDS OF *THALICTRUM* XXXI.[1] SYNTHESIS OF RUGOSINONE

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ABSTRACT.—Two similar pathways are described for the total synthesis of rugosinone (1), a minor alkaloid from *Thalictrum rugosum*. For both procedures the Reissert derivative of 6,7-methylenedioxyisoquinoline was used for generation of the isoquinoline portion. The benzoyl part in one pathway employed 2-benzyloxy-3,4-dimethoxybenzaldehyde with final removal of the benzyl group by trimethylsilyl iodide. For the other pathway 2,3,4-trimethoxybenzaldehyde was used instead, and final generation of the phenolic group was by selective cleavage with boron trichloride.

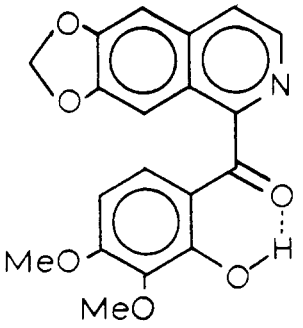
The roots of *Thalictrum rugosum* Ait. (Ranunculaceae) yielded a very small amount of a carbonyl-containing benzylisoquinoline alkaloid named rugosinone (1), $C_{19}H_{15}NO_6$. The paucity of material prevented a complete characterization of the substance, but the spectral data provide information that could be accommodated by any one of structures **1** through **5**. The data has been presented and discussed (1). Briefly, the spectral evidence suggested the following: First, from mass spectral studies, the carbonyl group must be at the α-carbon and the methylenedioxy group on the isoquinoline ring. Second, from the proton magnetic resonance spectrum, two *ortho*- and two *para*- protons are indicated. Also, the phenolic group appears strongly hydrogen bonded, suggesting a location *ortho* to the carbonyl.

To establish without doubt the structure of rugosinone, a total synthesis was undertaken. Of the five possible choices, structure **1** seemed the most likely from biogenetic considerations. The synthesis was accomplished in a straight-forward manner by two similar routes as summarized in scheme 1. Both pathways utilized the Reissert compound (2) of 6,7-methylenedioxyisoquinoline (3), namely, 2-benzoyl-1-cyano-6,7-methylenedioxy-1,2-dihydroisoquinoline (**6**) (4) for generation of the isoquinoline portion. The benzoyl part in Pathway 1 was derived from the benzyl ether (**7**, R = CH_2Ph) of 3,4-dimethoxy-2-hydroxybenzaldehyde (5) and, in Pathway 2, from 2,3,4-trimethoxybenzaldehyde (**7**, R = Me) (6). Both pathways have related intermediates **8** and **9**, where R is benzyl or methyl.

A study of the first step of Pathway 1, in which the Reissert anion was treated overnight with 2-benzyloxy-3,4-dimethoxybenzaldehyde according to a literature procedure (4), showed that two products were formed, carbinol **8** (R = CH_2Ph) and its benzoyl ester, in a ratio of about 1:5. When the reaction time was decreased to 2–3 hours, the mixture ratio was reversed. The following rationalization is put forth for this observation. The product anion **10** (scheme 2) is formed rapidly and is relatively stable. Workup with methanol causes the anion to decompose, as shown in Route A, to give the major compound **8** (R = CH_2Ph) as obtained in the 2–3 hour experiment. A longer reaction period (overnight) allows the anion **10** to decompose in a slow step via an intramolecular *N*- to *O*-acyl migration and release of cyanide ion to ester **11** (Route B).

Carbinol **8** (R = CH_2Ph), produced by the short reaction time condensation

[1]For paper XXX see W.-N. Wu, J. L. Beal and R. W. Doskotch, *J. Nat. Prod.*, **43**, 143 (1980).



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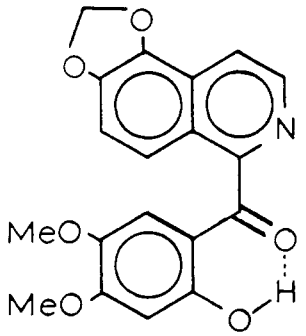

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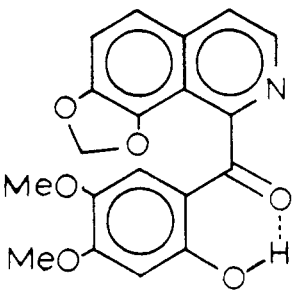

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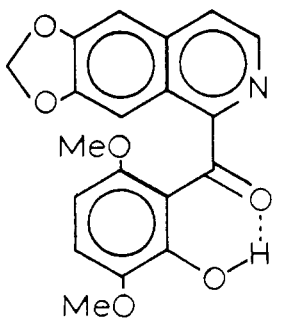

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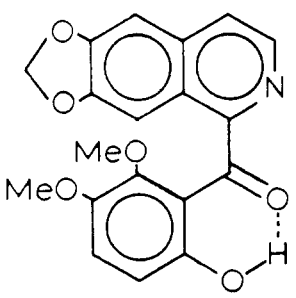

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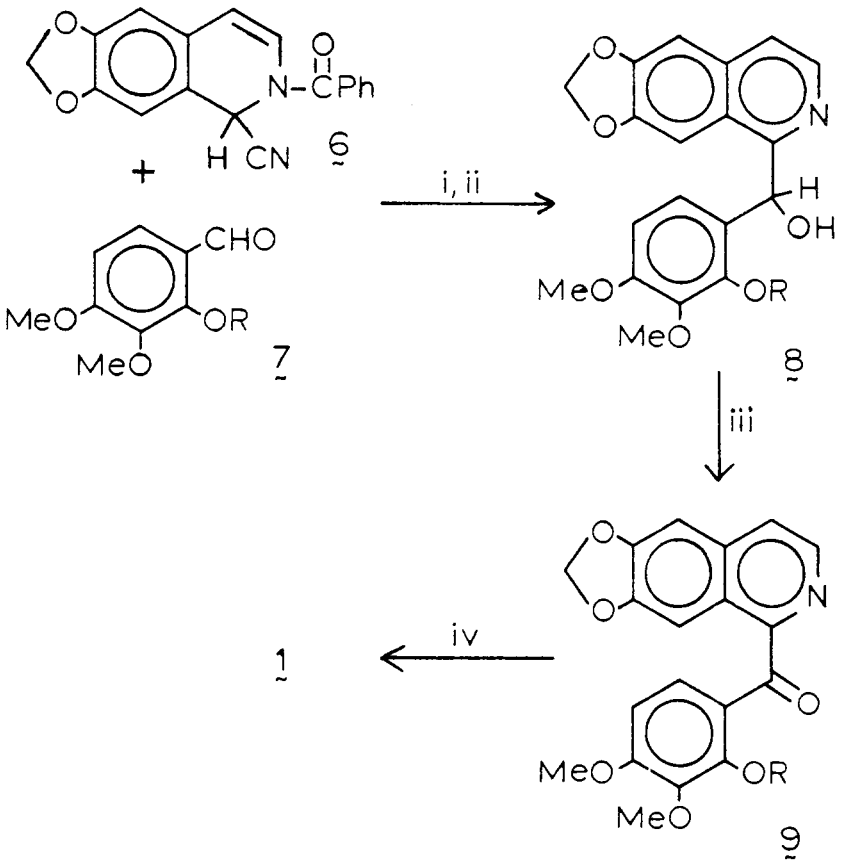
or by alkaline hydrolysis of the corresponding benzoate **11**, was oxidized to ketone **9** (R = CH_2Ph) with chromic acid. Debenzylation of ketone **9** (R = CH_2Ph) was accomplished with trimethylsilyl iodide (7) to give a product identical with natural rugosinone (**1**).



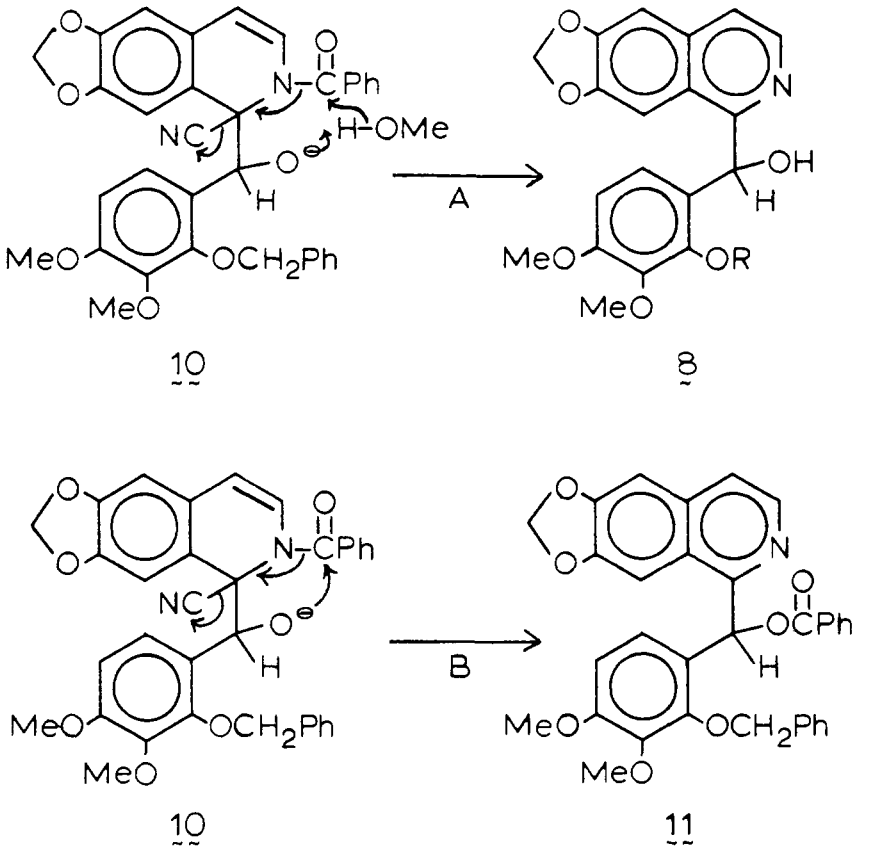
Pathway 1: R = CH_2Ph

Pathway 2: R = Me

Reagents: i, NaH-DMF; ii, KOH; iii, $Na_2Cr_2O_7$-HOAc; iv, Me_3SiI for Pathway 1 and BCl_3 for Pathway 2.

SCHEME 1. Reaction sequences for synthesis of rugosinone (**1**).

Pathway 2 was little different from the sequence of Pathway 1 except that it saved two steps in the overall procedure. These two steps, although not described in this paper, are the formation of 3,4-dimethoxy-2-hydroxybenzaldehyde from 2,3,4-trimethoxybenzaldehyde followed by benzylation to compound **7** (R = CH_2Ph). Pathway 2 utilized 2,3,4-trimethoxybenzaldehyde directly. The product with Reissert compound **6** was the trimethoxy carbinol **8** (R = Me), after alkaline hydrolysis for maximization of yield. Oxidation of the alcohol with chromic acid afforded ketone **9** (R = Me) which gave rugosinone (**1**) on selective demethylation with boron trichloride (8). It should be noted that debenzylation of ketone **9** (R = CH_2Ph) was not possible with boron trichloride.



SCHEME 2. Decomposition of Anion **10** with Methanol (Route A) and by Intramolecular Rearrangement (Route B).

EXPERIMENTAL[2]

2-BENZYLOXY-3,4-DIMETHOXYBENZALDEHYDE (7, R=CH_2Ph).—A mixture of 2-hydroxy-3,4-dimethoxybenzaldehyde (5) (3.29 g, 0.018 mole), benzyl chloride (5.26 g, 0.042 mole), and potassium carbonate (5.45 g) in dimethylformamide (90 ml) was refluxed for 2 hours. The cooled reaction mixture was filtered to remove inorganic salts, and the filtrate was distilled under vacuum. The product 7 (R=CH_2Ph) (4.48 g, 91%) was collected between bp 192–4° at 1 mmHg and exhibited the following spectral properties: nmr ($CDCl_3$, 60 MHz) δ 3.92 (s, 2 OMe), 5.21 (s, $PhCH_2$), 6.74 and 7.58 (ABq, J 8.8, H-5 and H-6), 7.36 (m, C_6H_5) and 10.1 (s, CHO); and ir νmax 1675 cm^{-1} (C=O).

REACTION OF REISSERT COMPOUND **6** WITH 2-BENZYLOXY-3,4-DIMETHOXYBENZALDEHYDE (7, R=CH_2Ph). *A*. OVERNIGHT REACTION.—Sodium hydride (50 mg, 2.1 mmole) was suspended in 8 ml dimethylformamide and Reissert compound **6** (500 mg, 1.64 mmole) in 10 ml of dimethylformamide was added over 5 minutes at −15° under nitrogen. After 10 minutes of reaction time, aldehyde 7 (R=CH_2Ph) (449 mg, 1.65 mmole) in 8 ml of dimethylformamide was added within 10 min while the temperature was maintained between −13° and −10°. The brownish solution was stirred 2 hours at 0°, then left at room temperature overnight.

[2]Melting points are uncorrected. Nuclear magnetic resonance spectra were determined in stated solvents with tetramethylsilane as internal standard on a Varian A-60A or Bruker HX-90E instrument, and with chemical shifts (δ) reported in ppm and coupling constants (J) in Hz. Infrared and ultraviolet spectra were taken in chloroform on a Beckman IR 4230 and in methanol on a Beckman UV 5260 instruments, respectively. Mass spectra were obtained on an AEI MS-9, MS-30 or DuPont 21-491 instrument by direct inlet probe at 70 eV.

Methanol was added and the solvent removed by vacuum distillation. The residue was dissolved in 40 ml of benzene, extracted with 2 x 20 ml of water and dried over anhydrous sodium sulfate. Removal of the solvent left a crude mixture of two products as observed by tlc on silica gel G with methylene chloride, R_f 0.22 and 0.12. The major product (higher R_f) crystallized from ethanol as colorless needles (580 mg, 64%), mp 123–4°, and was identified as the benzoate ester **11** of alcohol **8** (R = CH_2Ph): nmr ($CDCl_3$, 60 MHz) δ 3.81 and 3.88 (2s, 2 OMe), 5.00 and 5.15 (AB q, *J* 11.1, $PhCH_2$), 5.96 (s, OCH_2O), and 6.60–8.36 (overlapping multiplets for 16 aromatic protons and one methine); ir νmax 1717 cm^{-1} (C=O); and uv λmax 331 nm (log ϵ 3.78), 317 (3.68), 293 (3.64), 282 (3.83) and 238 (4.82).

Anal. Calcd for $C_{33}H_{27}NO_7$ (549): C, 72.12; H, 4.95; N, 2.55.
Found: C, 72.16; H, 4.97; N, 2.54%.

The minor product (lower R_f) (100 mg) was isolated by column chromatography on 21 g of silicic acid with chloroform as eluent and was identified as the carbinol **8**, data for which is reported below.

B. SHORT-TIME REACTION.—Sodium hydride (100 mg, 4.2 mmole) was suspended in 10 ml of dimethylformamide and 1.0 g (3.3 mmole) of Reissert compound **6** in 15 ml of dimethylformamide was added over 5 min. at −10° under nitrogen. After a 5 min reaction time, 2-benzyloxy-3,4-dimethoxybenzaldehyde (**7**, R = CH_2Ph) (0.92 g, 3.4 mmole) in 10 ml of dimethylformamide was added over 10 min at −10°. The mixture was stirred 2 hours at 0° then left at room temperature for 2 hours. Methanol was added, and the mixture was distilled under vacuum. The residue was taken up in 30 ml of benzene, washed with water (2 x 20 ml) and dried over anhydrous sodium sulfate. Tlc results showed the product ratio of ester to alcohol, as reported in section A, to be reversed. Hydrolysis of the product mixture by 0.2 g of potassium hydroxide in 11 ml of water and 20 ml of ethanol at reflux for 3 hours deposited on cooling, 1.0 g (69%) of carbinol **8** (R = CH_2Ph), data for which is given below.

HYDROLYSIS OF THE BENZOATE OF 2-BENZYLOXY-3,4-DIMETHOXYPHENYL-1-(6,7-METHYLENEDIOXYISOQUINOLYL)CARBINOL (**8**, R = CH_2Ph).—A solution of the benzoate of carbinol **8** (R = CH_2Ph) (200 mg, 0.36 mmole) in 8 ml of ethanol was added to a solution of potassium hydroxide (0.2 g) in 11 ml of water. The mixture was refluxed for 3 hours; on cooling, the product **8** (R = CH_2Ph) crystallized as colorless needles (140 mg), which were recrystallized from ethanol to give material with mp 153–4°: nmr (dimethylsulfoxide-d_6, 90 MHz) δ 3.78 (s, 2 OMe), 4.80 and 5.02 (AB q, *J* 10.8, $PhCH_2$), 5.94 (d, *J* 6, OH, lost with deuterium oxide), 6.50 (d, *J* 6, C*H*OH, forms a singlet with D_2O), 6.12 and 6.15 (ABq presumed but resolution not clear for *J* determination, OCH_2O), 6.75 and 6.91 (ABq, *J* 8.9, H-5' and H-6'), 7.32 (s, 6H, C_6H_5 and H-5 or H-8), 7.42 (s, H-8 or H-5), 7.57 and 8.27 (ABq, *J* 5.7, H-3 and H-4); ir νmax 3320 cm^{-1} (OH); uv λ max 328 nm (log ϵ 3.86), 315 (3.75), 290 (3.79), 276 (3.92) and 236 (4.89); and ms *m/r* 445 (0.6, M^+), 430 (0.5, M–Me), 428 (0.4, M–OH), 416 (0.7), 354 (6, M–$PhCH_2$), 338 (100, M–$PhCH_2O$), 202 (6, $C_{11}H_8NO_3$), 172 (23, $C_{10}H_6NO_2$) and 91 (52, C_7H_7).

Anal. Calcd for $C_{26}H_{23}NO_6$ (445): C, 70.10; H, 5.20; N, 3.14.
Found: C, 70.12; H, 5.21; N, 3.14%.

1-(2-BENZYLOXY-3,4-DIMETHOXYBENZOYL)-6,7-METHYLENEDIOXYISOQUINOLINE (**9**, R = CH_2Ph).—A solution of carbinol **8** (R = CH_2Ph) (500 mg, 1.12 mmole) in 5 ml of acetic acid was mixed with 357 mg (1.2 mmole) of sodium chromate in 5 ml of acetic acid. After being heated for 3 min on the steam bath, the mixture was diluted with water, basified with ammonium hydroxide, and extracted with ether (3 x 40 ml). The combined ether extract was washed with water (2 x 40 ml) and dried over anhydrous sodium sulfate. Evaporation of the ether left a residue that crystallized from aqueous ethanol as colorless rhomboids of product **9** (R = CH_2Ph) (400 mg, 80%): mp 109–110°: nmr ($CDCl_3$), 60 MHz) δ 3.76 and 3.83 (2s, 2 OMe), 4.79 (s, $PhCH_2$), 5.93 (s, OCH_2O), 6.7–7.7 (m, 9 ArH), 7.31 and 8.21 (ABq, *J* 5.5, H-3 and H-4); ir ν max 1660 cm^{-1} (C=O); and uv λ max 328 nm (log ϵ 4.26), 290 (4.45) and 236 (4.97).

Anal. Calcd for $C_{27}H_{21}NO_6$ (443): C, 70.42; H, 4.77; N, 3.16.
Found: C, 70.19; H, 4.86; N, 3.14%.

2,3,4-TRIMETHOXYPHENYL-1-(6,7-METHYLENEDIOXYISOQUINOLYL)CARBINOL (**8**, R = Me).—Sodium hydride (50 mg, 2.1 mmole) was suspended in 8 ml of dimethylformamide to which was added Reissert compound **6** (500 mg, 1.64 mmole) in 10 ml of dimethylformamide over 5 min at −15° under nitrogen. After 10 min, 325 mg (1.66 mmole) of 2,3,4-trimethoxybenzaldehyde in 10 ml of dimethylformamide was added over 10 min at −10°. The mixture was stirred at 0° for 2 hours and left at room temperature for 2 hours. Methanol was added, and the solvent was evaporated under vacuum. The residue was dissolved in 30 ml of benzene, washed with 2 x 30 ml of water, and dried over anhydrous sodium sulfate. The residue remaining after removal of the solvent was refluxed with 121 mg of potassium hydroxide in 5 ml of water and 8 ml of ethanol for 3 hours. On cooling, the reaction solution deposited carbinol **8** (R = Me) as colorless needles, 524 mg (87%). Recrystallization from ethanol gave a product with mp 163–4°: nmr ($CDCl_3$, 60 MHz) δ 3.78, 3.92 and 4.05 (3s, 3 OMe), 5.98 and 6.03 (ABq, *J* 0.9, OCH_2O), 6.51 (s, C*H*OH, sharpens with D_2O), 6.52 and 6.62 (ABq, *J* 8.7, *ortho*-ArH), 7.04 and 7.31 (2s, H-6 and H-8) and, 7.43 and 8.39 (ABq, *J* 5.7, H-3 and H-4); ir ν max 3300 cm^{-1} (assoc.

OH); uv λ max 327 (log ε 4.04), 313 (3.98), 290 (3.96), 278 (4.08) and 237 (4.95); and ms *m/e* 369 (0.8%, M^+), 353 (3), 339 (20), 338 (100, M–OMe), 322 (67), 306 (18), 277 (20), 202 (14), 197 (10), 187 (16), 181 (20), 172 (62), 149 (37) and 73 (93).

Anal. Calcd for $C_{20}H_{19}NO_6$ (369): C, 65.03; H, 5.19; N, 3.79.
Found: C, 65.08; H, 5.16; N, 3.84%.

1-(2,3,4-TRIMETHOXYBENZOYL)-6,7-METHYLENEDIOXYISOQUINOLINE (**9**, R=Me).—Carbinol **8** (R=Me) (210 mg, 0.57 mmole) in 2 ml of acetic acid was treated with 170 mg (0.57 mmole) of sodium dichromate in 2 ml of acetic acid. After being heated on a steam bath for 3 min, the mixture was diluted with 10 ml of water, basified with ammonium hydroxide, and extracted with 3 x 30 ml of ether. The interfacial solid was dissolved in 30 ml of chloroform; the organic phases were washed with water, then combined and dried over anhydrous sodium sulfate. Evaporation of the solvent left a residue which crystallized from aqueous ethanol as colorless rhombic crystals (193 mg, 93%) of ketone **9** (R=Me): mp 140.0–140.5°; nmr ($CDCl_3$, 60 MHz) δ 3.38, 3.80 and 3.93 (3s, 3 OMe), 6.10 (s, OCH_2O), 6.79 and 7.58 (ABq, *J* 8.9, *ortho*-ArH), 7.13 and 7.64 (2s, H-6 and H-8), 7.56 and 8.35 (ABq, *J* 5.5, H-3 and H-4); ir ν max 1660 cm^{-1} (C=O); and uv λ max 328 nm (log ε 4.25), 290 (4.45) and 236 (4.97).

Anal. Calcd for $C_{20}H_{17}NO_6$ (367): C, 65.39; H, 4.66; N, 3.81.
Found: C, 65.37; 4.70; N, 3.78%.

RUGOSINONE (**1**). *A.* FROM BENZYL KETONE **9** (R=CH_2Ph).—A solution of benzyl ketone **9** (R=CH_2Ph) (30 mg, 68 μmole) in 5 ml of chloroform was mixed with 0.22 ml of a 90% solution of trimethylsilyl iodide and refluxed 5 hours under nitrogen. After quenching with water, the chloroform layer was separated, washed with water (2 x 10 ml), and dried over anhydrous sodium sulfate. Removal of the solvent by evaporation and chromatography of the residue on 1.2 g of silicic acid with chloroform as solvent yielded 20 mg (84%) of rugosinone (**1**), which was crystallized from ethyl acetate as pale yellow needles, mp 223–4°, and undepressed when admixed with the natural material. Also, the nmr, ir, uv and mass spectra[3] were identical with those from natural rugosinone (1).

Anal. Calcd for $C_{19}H_{15}NO_6$ (353): C, 64.58; H, 4.28; N, 3.96.
Found: C, 64.10; H, 4.28; N, 3.96%.

B. FROM TRIMETHOXY KETONE **9** (R=Me).—A solution of the trimethoxy ketone **9** (R=Me) (100 mg, 0.27 mmole) in 20 ml of methylene chloride at −18° was treated with 1.5 ml of 1M boron trichloride in methylene chloride cooled to −70°. The reaction mixture was allowed to come to room temperature (about 5 min), then quenched with water. The organic layer was separated, washed with water (2 x 20 ml), and dried over anhydrous sodium sulfate. Evaporation of solvent and chromatography of the residue on 2 g of silicic acid with chloroform as solvent gave 70 mg (73%) of rugosinone (**1**), identical (mp, uv, ir and nmr) with the natural product (1).

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[3]The mass spectrum of rugosinone (**1**) has the reported base peak at *m/e* 294, for which no composition was suggested (1). Recently an accurate mass measurement of 294.0754 was obtained for it, which most probably corresponds with $C_{17}H_{12}NO_4$ (calculated value 294.0766) arising from loss of CO and OCH_3. It would appear that the loss is from the phenolic ring portion and that this fragmentation is of greater importance than cleavage at the carbonyl position.