Acknowledgment.—We wish to thank the Research Committee of Washington State University for partial support of this work, as well as the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant 2403-A1, 4.

Peracid Oxidation of Ene–Lactams. A Synthesis of Macrocyclic Imides

JEHAN F. BAGLI AND HANS IMMER

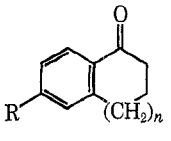
Department of Chemistry, Ayerst Research Laboratories, Montreal, Quebec, Canada

Received March 18, 1970

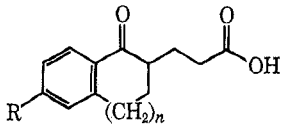
The substituted propionic acids **2a–c** prepared by conventional procedures were converted to the amides **3a–d**, which were ring closed in presence of *p*-toluenesulfonic acid to the unsaturated lactams **4a–d**. On peracid oxidation of **4a**, the ketone **5** was obtained. The oxidation of **4b–d** yielded with oxygen insertion the products **7a–c**. The structures of these compounds were proven by alkaline degradation. The mechanism of the peracid oxidation is discussed.

In our earlier work on the synthesis of medium-ring benzoic acid lactones,[1] we oxidized cyclic enol ethers with an excess of *m*-chloroperbenzoic acid. In some instances we observed a deviation from the normal reaction pathway leading to cyclic carbonates instead of the expected lactones. A mechanism for this insertion of an extra oxygen atom was proposed. The present paper deals with the peracid oxidation of ene–lactams which provides a synthetic approach to a novel class of macrocyclic imides.

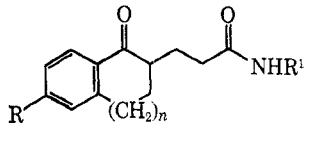
Ketones **1a–c** were converted into the corresponding formyl derivatives with ethyl formate in the usual manner. These compounds were reacted with ethyl acrylate in the presence of triethylamine to generate propionic acid esters which were transformed to the acids **2a–c**. These were converted to the amides **3a–d** which in turn were cyclized with *p*-toluenesulfonic acid in boiling toluene to yield the cyclic ene–lactams **4a–d**.



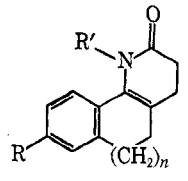
1a, R = H; $n = 2$
b, R = H; $n = 1$
c, R = OCH_3; $n = 1$



2a, R = H; $n = 2$
b, R = H; $n = 1$
c, R = OCH_3; $n = 1$

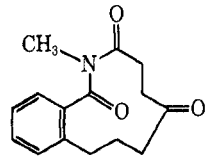


3a, R = H; $R^1 = CH_3$; $n = 2$
b, R = R^1 = H; $n = 1$
c, R = H; $R^1 = CH_3$; $n = 1$
d, R = OCH_3; $R^1 = CH_3$; $n = 1$

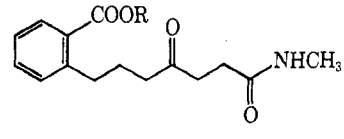


4a, R = H; $R^1 = CH_3$; $n = 2$
b, R = R^1 = H; $n = 1$
c, R = H; $R^1 = CH_3$; $n = 1$
d, R = OCH_3; $R^1 = CH_3$; $n = 1$

Oxidation of the ene–lactam **4a** with an excess of *m*-chloroperbenzoic acid led, in good yield, to a product whose analytical and spectral data corroborated with structure **5**. On alkaline treatment of this ketone, the benzoic acid **6a** was obtained, which was characterized as its methyl ester **6b**.

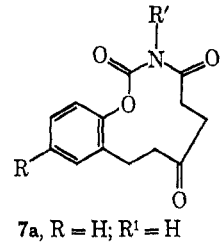


5



6a, R = H
b, R = CH_3

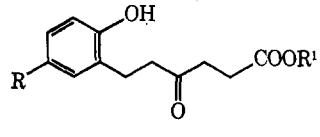
In contrast, the oxidation of the ene–lactam **4b** under the same conditions led to a compound containing an extra oxygen (molecular ion at *m/e* 247). Its elemental analysis confirmed the formula $C_{13}H_{13}NO_4$. The infrared, ultraviolet, and nmr spectra were in complete agreement with the assigned structure **7a**. Similar oxidation of the lactams **4c** and **d** led to the isolation of the macrocyclic imides **7b** and **c**, respectively.



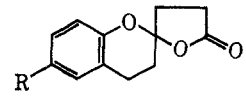
7a, R = H; R^1 = H
b, R = H; $R^1 = CH_3$
c, R = OCH_3; $R^1 = CH_3$

The structures of these compounds were proven by alkaline degradation.

Treatment of the ketones **7a** and **b** with aqueous methanolic sodium hydroxide yielded the phenolic acid **8a**. The compound **7c**, under identical conditions, led to **8b**.



8a, R = H; R^1 = H
b, R = OCH_3; R^1 = H
c, R = OCH_3; $R^1 = CH_3$



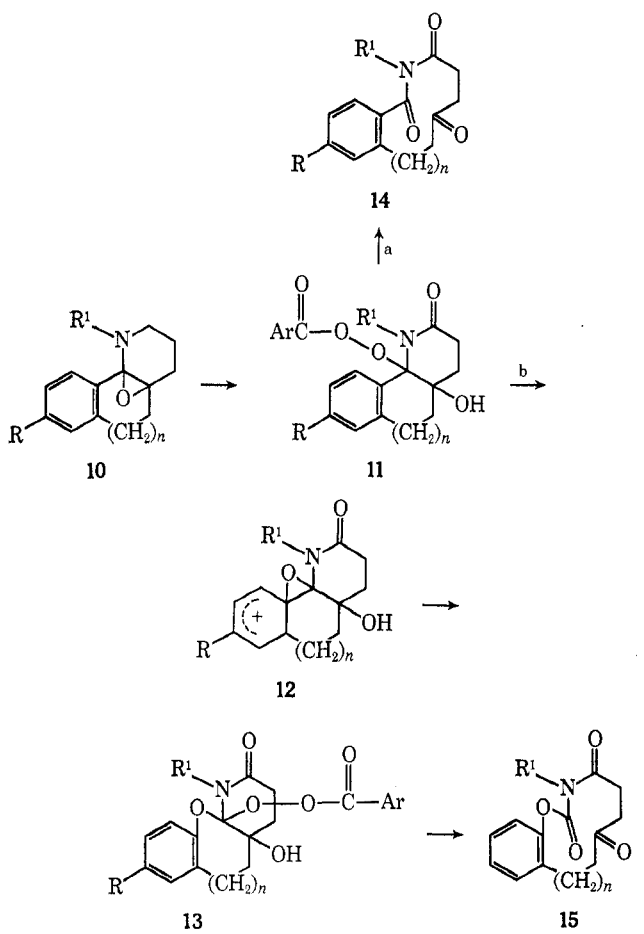
9a, R = H
b, R = OCH_3

(1) (a) H. Immer and J. F. Bagli, *J. Org. Chem.*, **33**, 2457 (1968); (b) J. F. Bagli and H. Immer, *Can. J. Chem.*, **46**, 3115 (1968).

The acid **8a** was dehydrated on treatment with acetic anhydride to a product, which showed in its infrared spectrum a carbonyl band at 1780 cm^{-1}. The ultraviolet spectrum was characteristic for an isolated benzene ring. The mass spectral data and the elemental analysis were in agreement with structure **9a**. Analogous reaction of the methoxy derivative **8b** yielded **9b**. The acid **8a** was readily synthesized by an aldol condensation of O-hydroxybenzaldehyde and levulinic acid,[2] followed by hydrogenation of the resulting unsaturated acid.

Discussion

The results obtained can best be accommodated by the mechanism proposed for the oxidation of enol ethers.[1]



The initially formed epoxide **10** is opened by *m*-chloroperbenzoic acid.[3] The electron deficiency at the benzylic oxygen atom in the perester **11** causes: (a) fragmentation to form the product **14** (n = 2), and (b) formation of the phenonium ion **12** (n = 1), which is attacked by another mole of peracid to form **13**. This perester leads through fragmentation to the product **15**.

The substrates **4b–d** react exclusively *via* pathway b, regardless of the presence of an electron donating group (as in **4d**), stabilizing the phenonium ion.[4] The substitution at the nitrogen does not change the course of the reaction (compare **4b** and **4d**). The substrate **4a**, on the other hand, leads through pathway a to **6**. Everything else being equal, but the size of the central ring the conformational differences must account for the different reaction pathways.[5] Similar results were already obtained in the oxidation of enol ethers.[1] The cases presented here, however, show a much higher degree of specificity and provide a striking example of the very subtle steric demands for phenonium-ion participation.

Experimental Section[6]

Ketopropionic Acids. 1,2,3,4-Tetrahydro-1-oxo-2-naphthalenepropionic acid (2b) was prepared *via* the formyl compound followed by condensation with ethyl acrylate and base hydrolysis, mp 108–110° (lit.[7] 108–110°).

1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthalenepropionic acid (2c) was prepared using the above procedure and had mp 134–135° (lit.[8] 128–130°). **2,3,4,5-Tetrahydro-1-oxo-1H-benzocycloheptene-2-propionic acid (2a)** was synthesized when 2,3,4,5-tetrahydro-1-oxo-1H-benzocycloheptene (8 g) in dry benzene (200 ml) and ethyl formate (20 ml) were cooled in ice. Sodium hydride (6 g) was added gradually and the mixture stirred at room temperature for 3 days under nitrogen. The acidic **2,3,4,-5-tetrahydro-2-hydroxymethylene-1H-benzocycloheptene-1-one** (9.8 g) was isolated in the usual manner. The crude formyl ketone (4.23 g) was stirred with ethyl acrylate (5.6 ml) in methanol (20 ml) in presence of triethylamine (0.93 ml) at 40° for 4 days. The mixture was diluted with ether, washed with sodium carbonate (5%), then with saturated sodium chloride, the ether was extract dried, and the solvent was removed. The residue was distilled to yield (91%) the ethyl ester of the acid **2a** (4.75 g): bp 140–145° (0.2 mm); $\nu_{max}^{CHCl_3}$ 1727, 1665 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_3$ (260): C, 73.82; H, 7.74. Found: C, 73.35; H, 7.56.

Hydrolysis in aqueous methanolic potassium hydroxide gave the acid **2a**, in quantitative yield: mp 82–83°; $\nu_{max}^{CHCl_3}$ 1700, 1675, and 1600 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}O_3$ (232): C, 72.39; H, 6.94. Found: C, 72.64; H, 6.89.

Preparation of Acid Amides. A. From Acid Chlorides.—To a suspension of the sodium salt of acid **2b** (11 g) in benzene (150 ml) containing a few drops of pyridine, oxalyl chloride (18 ml) was added dropwise under ice cooling. The mixture was allowed to reach room temperature and stirred for 45 min. After filtration, the solvent was removed to yield the corresponding acid chloride (checked by infrared).

The above acid chloride was dissolved in dry benzene (55 ml) and methyl amine passed for 30 min. The clear solution was diluted with benzene, washed with water, dried, and the solvent was removed to yield (77.5%) **1,2,3,4-tetrahydro-N-methyl-1-oxo-2-naphthalenepropionamide (3c)** (8.2 g). A sample crystallized from methanol–ether: mp 93–94°; $\nu_{max}^{CHCl_3}$ 3470, 3355, 1672, and 1605 cm^{-1}; λ_{max} 246 mμ (13,700); nmr δ 8.0 (*ortho* aromatic proton[9]), 7.33 (3 H, aromatic), δ 2.82 (3 H, N-methyl doublet).

Anal. Calcd for $C_{14}H_{17}O_2N$ (231): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.93; H, 7.3; N, 5.93.

1,2,3,4-Tetrahydro-1-oxo-2-naphthalenepropionamide (3b) was obtained in a similar manner using ammonia in place of methyl amine: mp 147–148°, $\nu_{max}^{CHCl_3}$ 34 00, 3500, 1676, and 1600 cm^{-1}; λ_{max} 247 mμ (10,550); nmr δ 8.0 (*ortho* aromatic proton), 7.32 (3 H, aromatic).

(2) S. H. Zaheer, I. K. Kacker, and N. S. Rao, *Chem. Ber.*, **89**, 351 (1956).

(3) The occurrence of this opening under the prevailing mild conditions can be explained by invoking participation of phenonium ion. For examples, see R. Huisgen, *Angew. Chem.*, **69**, 341 (1957).

(4) These results are in contrast to those obtained upon oxidation of enol ethers (see ref 1a). A comparison on rigid mechanistic ground is invalidated by the functional and conformational differences in the heterocyclic ring.

(5) The same tendency is reflected in the formolysis of 1,2-benzylcyclenyl-3-methyl tosylates of different ring size (see ref 3).

(6) All experimental conditions were the same as described in ref 14 of our earlier communication (see ref 1a), except that silica gel (0.05–0.2 mm Merck) was employed for column chromatography. Nmr were recorded in deuteriochloroform.

(7) W. E. Bachmann and G. D. Johnson, *J. Amer. Chem. Soc.*, **71**, 3463 (1949).

(8) A. A. Akhrem and I. G. Zavelskaya, *Izv. Akad. Nauk SSSR*, 1637 (1960).

(9) "*ortho* proton" refers to the proton *ortho* to the carbonyl substituent.

Anal. Calcd for $C_{13}H_{15}O_2N$ (217): C, 71.87; H, 6.96; N, 6.45. Found: C, 71.97; H, 6.75; N, 6.85.

1,2,3,4-Tetrahydro-6-methoxy-N-methyl-1-oxo-2-naphthalenepropionamide (3d) prepared in the same way had mp 139–140°; $\nu_{max}^{CHCl_3}$ 3450, 3330, 1715, and 1600 cm^{-1}; λ_{max} 224 (12,200), 272 mμ (15,650); nmr δ 7.98 (*ortho* aromatic proton), 6.79 (3 H, aromatic), 3.83 (3 H, O-methyl), 2.82 (3 H, N-methyl doublet).

Anal. Calcd for $C_{15}H_{19}O_3N$ (261.3): C, 68.94; H, 7.33. Found: C, 68.93; H, 7.12.

B.—Another procedure used for amides is examplified in the preparation of **2,3,4,5-tetrahydro-N-methyl-1-oxo-1H-benzocycloheptene-2-propionamide (3a)**. To a solution of carbonyldiimidazole (2.32 g) in tetrahydrofuran (18 ml) was added a solution of acid **2a** (2.52 g) and the mixture stirred for 2 min, monomethylamine was bubbled through for 30 min, the reaction mixture was diluted with ether, washed with water, dried and the solvent was removed. The crude product was passed through silica gel (300 g) and was eluted with ethyl acetate–benzene 4:1, to yield (75.5%) crystals (2.05 g). Crystallization from methylene chloride–ether gave a sample with mp 72–73°; ν_{max}^{Nujol} 3260, 1672, 1635, and 1595 cm^{-1}; λ_{max} 246 mμ (7400); nmr δ 7.8–7.1 (4 H, aromatic), 2.78 (3 H, N-methyl, doublet).

Anal. Calcd for $C_{15}H_{19}O_2N$ (245): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.77; H, 7.65; N, 5.76.

Preparation of Lactams.—The lactams were generally prepared in 80–90% yield by refluxing the toluene solution of the acid amide in presence of *p*-toluene sulfonic acid over a period of 2–4 hr, using a Dean-Stark, water separator. **3,4,5,6-Tetrahydro-1-methylbenzo[*h*]quinolin-2(1H)-one (4c)** had mp 113–115°; $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}; λ_{max} 281 mμ (8450); nmr δ 7.19 (4 H aromatic), 3.2 (3 H, N-methyl singlet).

Anal. Calcd for $C_{14}H_{15}ON$ (213.2): C, 78.84; H, 7.09; N, 6.57. Found: C, 78.93; H, 6.96; N, 6.51.

3,4,5,6-Tetrahydrobenzo[*h*]quinolin-2(1H)-one (4b) crystallized from chloroform–ether and had mp 181–183°; $\nu_{max}^{CHCl_3}$ 3400, 1674 cm^{-1}; λ_{max} 292 mμ (5700).

Anal. Calcd for $C_{13}H_{13}ON$ (199): C, 78.36; H, 6.58; N, 7.03. Found: C, 78.07; H, 6.58; N, 7.14.

3,4,5,6-Tetrahydro-8-methoxy-1-methylbenzo[*h*]quinolin-2(1H)-one (4d) had mp 78–80°; $\nu_{max}^{CHCl_3}$ 1650, 1600 cm^{-1}; λ_{max} 231 (19,300), 287 (13,200); nmr δ 7.2–6.6 (3 H, aromatic), 3.83 (3 H, O-methyl) 3.18 (3 H, N-methyl).

Anal. Calcd for $C_{15}H_{17}O_2N$ (243.3): C, 74.05; H, 7.04; N, 5.76. Found: C, 73.75; H, 6.94; N, 5.58.

1,3,4,5,6,7-Hexahydro-1-methyl-2H-benzo[6,7]cyclohepta-[1,2-*b*]pyridine-2-one (4a) crystallized from ether–petroleum ether had mp 100–101°; ν_{max}^{Nujol} 1660 cm^{-1}; λ_{max} 252 (6400); nmr δ 7.2 (4 H, aromatic, multiplet), 2.9 (3 H, N-methyl, singlet).

Anal. Calcd for $C_{15}H_{17}ON$ (227): C, 79.26; H, 7.50; N, 6.16. Found: C, 79.23; H, 7.68; N, 6.30.

Peracid Oxidation.—A typical oxidation procedure was as follows. To a suspension of *m*-chloroperbenzoic acid (9.5 g) in methylene chloride (40 ml) was added a solution of lactam (3.9 g) in methylene chloride so as to maintain gentle reflux. The mixture was stirred for 1 hr (the time varied from one to 4 hr for different substrates). The reaction mixture was cooled in an ice bath, and was filtered. The residue was crystallized from benzene to yield (62.4%) the **5,6,8,9-tetrahydro-1,3-benzoxazecycloundecane-2,4,7(3H)-trione (7a)**: 3 g; mp 137–138°; $\nu_{max}^{CHCl_3}$ 1762, 1705 cm^{-1}; λ_{max} 262 mμ (620); nmr δ 7.1 (4 H, aromatic).

Anal. Calcd for $C_{13}H_{13}O_4N$ (247): C, 63.15; H, 5.30; N, 5.66. Found: C, 63.34; H, 5.23; N, 5.50.

5,6,8,9-Tetrahydro-3-methyl-1,3-benzoxazecycloundecane-2,-4,7(3H)-trione (7b) yielded 47% and was crystallized from methanol–ether: mp 139–140°, $\nu_{max}^{CHCl_3}$ 1748, 1710, and 1675 cm^{-1}; λ_{max} 257 mμ (430); nmr δ 7.18 (4 H, aromatic). The mass spectrum showed *m/e* 261 (M^+), 248 ($M - 18$)$^+$.

Anal. Calcd for $C_{14}H_{15}O_4N$ (261): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.30; H, 5.80; N, 5.33.

5,6,8,9-Tetrahydro-11-methoxy-3-methyl-1,3-benzoxazecycloundecane-2,4,7(3H)-trione (7c) yielded 37.2% and was crystallized from chloroform–hexane: mp 169–171°; $\nu_{max}^{CHCl_3}$ 1748, 1712, and 1675 cm^{-1}; λ_{max} 275 (2180); 282 mμ (2050); nmr δ 6.87 (3 H, aromatic), 3.78 (3 H, O-methyl) and 3.28 (3 H, N-methyl). The mass spectrum showed *m/e* 291 (M^+), 273 ($M - 18^+$).

Anal. Calcd for $C_{15}H_{17}O_5N$ (291): C, 61.85; H, 5.88; N, 4.81. Found: C, 61.73; H, 5.57; N, 4.62.

4,5,8,9-Tetrahydro-2-methyl-1H-2-benzazacycloundecane-1,-3,6(2H,7H)-trione (5) yielded 63.5% and was crystallized from acetone–isopropyl ether to give crystals: mp 107–108°; ν_{max}^{Nujol} 1700, 1670 cm^{-1}; λ_{max} 225 mμ (10,500); nmr δ 7.3 (4 H, aromatic), 3.1 (3 H, N-methyl, singlet)

Anal. Calcd for $C_{15}H_{17}O_3N$ (259): C, 69.48; H, 6.61; N, 5.4. Found: C, 69.50; H, 6.49; N, 5.33.

O-(6-Carboxy-4-oxohex-5-enyl)benzoic Acid (8a). A.—To a suspension of ketone **7a** (0.52 g) in methanol (6 ml) was added a solution of sodium hydroxide (0.24 g) in water (1.5 ml). The reaction mixture was stirred for 45 min at room temperature. The mixture was then diluted with ether and extracted with water. The water layer acidified and reextracted with ether. After the usual work up the crude product was crystallized from methanol–ether to give in 72.5% yield the acid **8a**: mp 120–121°; ν_{max}^{Nujol} 3200 1700, 1580 cm^{-1}; λ_{max} 275 (2420) neutral, and 295 mμ (3700) alkaline; nmr δ 6.8 (4 H, aromatic). The mass spectrum showed *m/e* 204 ($M - 18^+$).

Anal. Calcd for $C_{12}H_{14}O_4$ (222): C, 64.85; H, 6.35. Found: C, 64.76; H, 6.76.

B.—The above acid was synthesized by hydrogenation of O-(6-carboxy-4-oxohex-5-enyl)benzoic acid[2] (2.9 g) in methanol in presence of 5% palladium on charcoal (0.2 g). The product obtained from hydrogenation was identical in all respects with that synthesized by procedure A.

O-[6-(N-methylcarbamido)-4-oxohexyl]benzoic Acid Methyl Ester (6b).—To a solution of ketone (**5**) 0.25 g in methanol (4 ml), was added a solution of sodium hydroxide (3 ml, 10%) and the mixture was stirred for 10 min. The methanol was removed, and the residue was diluted with water. The aqueous solution was washed with chloroform, and acidified with 10% hydrochloric acid. Reextraction with chloroform yielded after work up an acid (0.256 g). The acid was directly esterified with diazomethane. The resulting crude ester was purified by passing through a column of silica gel and eluting with 60% ethyl acetate–benzene. The ester had mp 84–85°; $\nu_{max}^{CHCl_3}$ 3440, 1730, 1710, 1675 cm^{-1}; λ_{max} 267 mμ (362); nmr 7.25 (4 H, aromatic), 2.97 (3 H, N-methyl doublet).

Anal. Calcd for $C_{16}H_{21}O_4N$ (291): C, 65.96; H, 7.27; N, 4.56. Found: C, 65.82; H, 7.30; N, 4.87.

3,4-Dihydro-2-hydroxy-2H-benzopyran-2-propionic Acid γ-Lactone (9a).—To a solution of acid **8a** (0.2 g) in acetic anhydride (3 ml) sodium acetate (5 mg) was added. The solution was stirred for 5 min. The mixture was diluted with methanol, and the solvent was evaporated. The residue taken in ether, and worked up as usual to yield 0.18 g of product, crystallized from chloroform–hexane to yield **9a**: mp 102–104°; $\nu_{max}^{CHCl_3}$ 1780, 1600 cm^{-1}; λ_{max} 270 (1490) 276 mμ (1530); nmr δ 7.01 (4 H, aromatic). The mass spectrum showed *m/e* 204 $(M)^+$, 160 $(M - 44)^+$.

Anal. Calcd for $C_{12}H_{12}O_3$ (204): C, 70.58; H, 5.92. Found: C, 70.91; H, 5.66.

3,4-Dihydro-2-hydroxy-6-methoxy-2H-benzopyran-2-propionic Acid γ-Lactone (9b).—To a suspension of ketone **7c** (0.4 g) in methanol (5 ml) was added a solution of sodium hydroxide (0.15 g) in water (1.5 ml). The reaction mixture was stirred for 30 min under nitrogen. It was then diluted with ether and the aqueous layer was acidified. The acid **8b** was isolated and characterized by infrared spectrum. The above acid (0.35 g) was directly treated with acetic anhydride (3 ml) and stirred for 1 hr. The product (0.25 g) was isolated as described in the above experiment. Crystallization from chloroform–hexane gave 0.18 g of compound **9b**: mp 103–104°, $\nu_{max}^{CHCl_3}$ 1775, 1600 cm^{-1}; λ_{max} 290 mμ (2820); nmr δ 6.75 (3 H, aromatic), 3.78 (3 H, O-methyl); 2.55 (8 H, multiplet).

Anal. Calcd for $C_{13}H_{14}O_4$ (234): C, 66.66; H, 6.02. Found: C, 66.76; H, 5.81.

Registry No.—**2a**, 25743-83-3; **2a** (ethyl ester), 25661-99-8; **3a**, 25662-00-4; **3b**, 25662-01-5; **3c**, 25662-02-6; **3d**, 25662-03-7; **4a**, 25662-04-8; **4b**, 25662-05-9; **4c**, 25662-06-0; **4d**, 25662-07-1; **5**, 25662-08-2; **6b**, 25662-09-3; **7a**, 25662-10-6; **7b**, 25662-11-7; **7c**, 25662-12-8; **8a**, 25665-48-9; **9a**, 3243-89-8; **9b**, 25665-49-0.

Acknowledgment.—We gratefully acknowledge the technical assistance of Miss G. Sumariwalla. We thank Dr. G. Schilling and his associates for analytical and spectral data and Dr. M. Götz for his helpful comments.