92184-53-7; **3f**, 92184-54-8; **3g**, 92184-55-9; **3h**, 80351-01-5; **3i**, 92184-56-0; **3j**, 92184-57-1; **4a**, 89773-80-8; **4b**, 79559-06-1; **4c**, 92184-58-2; **4d**, 92184-59-3; **4e**, 92184-60-6; **4f**, 92184-61-7; **5e**, 92184-62-8; **5f**, 80351-04-8; **5g**, 92184-63-9; **5h**, 80351-05-9; **5i**, 89773-81-9; **5j**, 92184-64-0; **6f**, 80351-06-0; **6h**, 80351-07-1; (*R**,*R**)-**7a**, 92184-72-0; (*R**,*S**)-**7a**, 92184-65-1; **7b**, 92184-66-2; **8**, 92184-67-3; $ClCOCHClCH_2CH_3$, 7623-11-2; $(C_6H_5)_2C{=}NNH_2$, 5350-57-2; $(C_6H_5)_2C{=}NNHCOCHClCH_2CH_3$, 92184-68-4; $C_6H_5CH{=}CHCHO$, 104-55-2; $C_6H_5CH{=}CHCOCH_3$, 122-57-6; CH_3I, 74-88-4; CH_3CH_2I, 75-03-6; CH_3CHO, 75-07-0; $(CH_3)_2CO$, 67-64-1.

Synthesis of [1]Benzopyrano[3,4-*d*]isoxazol-4-ones from 2-Substituted Chromone-3-carboxylic Esters. A Reinvestigation of the Reaction of 3-Acyl-4-hydroxycoumarins with Hydroxylamine. Synthesis of 4-(2-Hydroxybenzoyl)isoxazol-5-ones

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A convenient method for the synthesis of ethyl 2-substituted chromone-3-carboxylates by the condensation of *o*-acetoxyaroyl chlorides with β-keto esters is described. These chromones are converted into the corresponding 4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-ones (**7**) by treatment with hydroxylamine. The previously reported synthesis of the fused isoxazole **7b** from 3-acetyl-4-hydroxycoumarin with the same reagent is shown to be in error. Instead of the reported compound **7b**, the products obtained appear to be a mixture of 4-(2-hydroxybenzoyl)-3-methylisoxazol-5(4*H*)-one (**11a**) as the main product and 4-methyl-3*H*-[1]benzopyrano[4,3-*c*]isoxazol-3-one (**12a**). Chemical evidence is presented in support of their structures. The **11a**:**12a** ratio can be affected by varying the reaction conditions. By using a 1/1.2/2 molar ratio of 3-acyl-4-hydroxycoumarins (**9**), hydroxylamine hydrochloride, and potassium acetate, respectively, a series of compounds **11** was obtained in good yields.

The use of chromone derivatives to synthesize heterocyclic systems via a ring opening and ring closure sequence with appropriate nucleophiles is well-known.[1-6] There have been however only few applications using 4-oxo-4*H*-[1]benzopyran-3-carboxylic acids (**1**) or their esters (**2**).[7-9] Recently, we reported their conversion to 4-oxo-1*H*-[1]benzopyrano[4,3-*c*]pyrazoles with phenylhydrazine.[10,11] Reaction of chromone-3-carboxylic acid (**1a**) with hydroxylamine hydrochloride, in refluxing petroleum ether, has been described as yielding the oxazepine (**3**) via a Beckmann rearrangement (Scheme I).[12]

However, structure **3** was not established with certainty and remained open to question, since we noted the lack of molecular ion $C_{10}H_7NO_4$ (205.2) and a surprising fragmentation pattern in the mass spectrum: *m/e* 161 ($M - CO_2$), 134, 121, 105, 93. It seemed more logical to us that the nucleophile nitrogen would attack at the C-2 position of the chromone rather than at the C-4. We therefore synthesized a series of ethyl 4-oxo-4*H*-[1]benzopyran-3-carboxylate derivatives (**2**) with a view to obtaining fused isoxazole derivatives by reacting with hydroxylamine. We also prepared the known acids **1a**,**b** in order to see whether the 3-ethoxycarbonyl or 3-carboxy substituent have an influence on the structure of the reaction products.

Scheme I

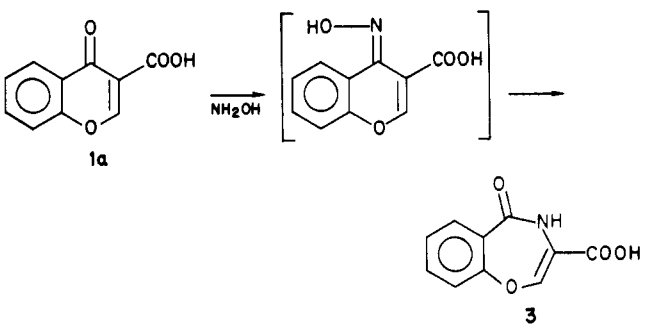


Table I. Ethyl 4-Oxo-4*H*-[1]benzopyran-3-carboxylates 2

compd	% yield	mp, °C (solvent), or bp (mmHg)	mol form or lit. mp, °C
2b	84	68 (EtOAc)	63–65[15,16]
2c	75	157–167 (0.1)	oil[16]
2d	66	86–87 (EtOAc/hexane 3:7)	88–91[16]
2e	60	102–103 (EtOH)	$C_{13}H_{11}ClO_4$
2f	60	93–94 (EtOAc/hexane 1:9)	$C_{14}H_{14}O_4$

A. Reaction of Hydroxylamine with Chromone-3-carboxylic Acids (1). Treatment of **1a**,**b** with hydroxylamine gave the isoxazoles (**4a**,**b**). The reaction proceeded by nucleophilic attack at the C-2 position of the chromone followed by decarboxylation and isoxazole cyclization

(1) Elkaschef, M. A. F.; Abdel-Megeid, F. M. E.; Mokhtar, K. E. M.; Elbarnashawi, M. F. *Indian J. Chem.* **1973**, *11*, 860.
(2) Beugelmans, R.; Morin, C. *J. Org. Chem.* **1977**, *42*, 1356.
(3) Morin, C.; Beugelmans, R. *Tetrahedron* **1977**, *33*, 3183.
(4) Szabo, V.; Borbely, J.; Theisz, E.; Janzso, G. *Tetrahedron Lett.* **1982**, *23*, 5347.
(5) Petersen, U.; Heitzer, H. *Liebigs Ann. Chem.* **1976**, 1663.
(6) Haas, G.; Stanton, J. L.; Winkler, T. *J. Heterocycl. Chem.* **1981**, *18*, 619.
(7) Klutchko, S.; Shavel, J., Jr.; von Strandtmann, M. *J. Org. Chem.* **1974**, *39*, 2436.
(8) Sato, K.; Inoue, S.; Ohasi, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1289.
(9) Okumara, K.; Kondo, K.; Oine, J.; Inoue, I. *Chem. Pharm. Bull.* **1974**, *2*, 33.
(10) Chantegrel, B.; Nadi, A. I.; Gelin, S. *Tetrahedron Lett.* **1983**, *24*, 381.
(11) By reaction with phenylhydrazine chromone-3-carboxylic acids **1a**,**b** afforded the same fused pyrazoles as their corresponding ethyl esters **2a**,**b**.
(12) Ghosh, C. K.; Mukhopadhyay, K. K. *Synthesis* **1978**, 779.

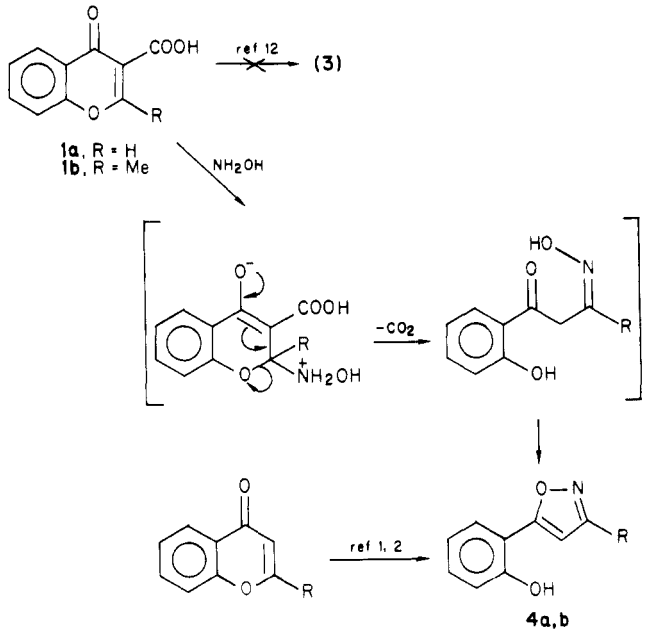
0022-3263/84/1949-4419$01.50/0

Table II. 4*H*-[1]Benzopyrano[3,4-*d*]isoxazol-4-ones 7

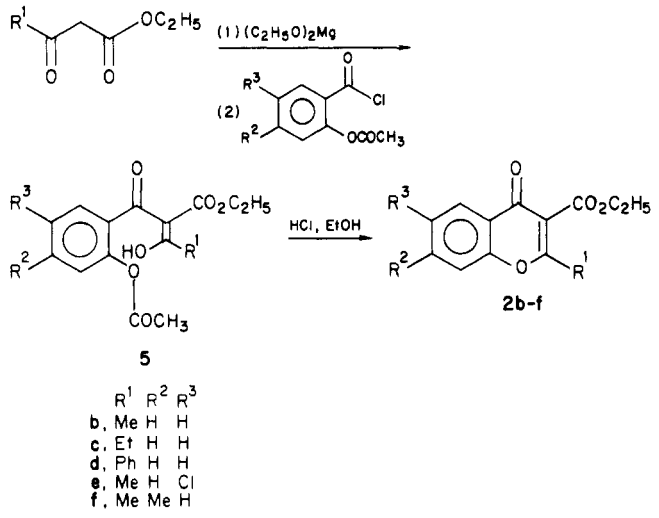
product	% yield	mol form[a]	mp, °C	IR, $\nu_{C=O}$ ($CHCl_3$), cm^{-1}	UV, λ_{max} (ϵ 10^{-3}) (EtOH), nm
7b	65	$C_{11}H_7NO_3$	175–176	1760	306 (7.2), 272 (13.1), 265 (12.1)
7c	51	$C_{12}H_9NO_3$	129–130	1755	306 (7.2), 272 (12.9), 266 (11.8)
7d	70	$C_{16}H_9NO_3$	199–200	1760	306 (8.9), 264 (15.9)
7e	68	$C_{11}H_6ClNO_3$	173–174	1755	315 (6.5), 278 (12.0), 266 (12.0)
7f	79	$C_{12}H_9NO_3$	190–191	1755	318 (8.7), 306 (10.2), 280 (14.0), 270 (11.7)

[a] Satisfactory analytical values (–0.29% for C, H, N, and Cl) were reported for all compounds in the table.

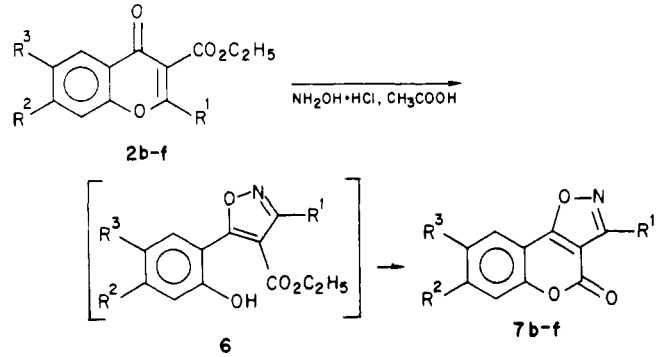
Scheme II



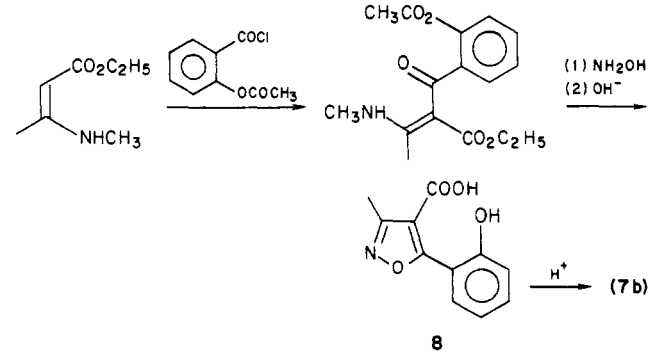
Scheme III



Scheme IV



Scheme V



(Scheme II). The structure of compounds **4a,b** was deduced from their identical spectral and physical properties with those of the authentic compounds previously obtained from chromone[2] and 2-methylchromone[1] with hydroxylamine. Further evidence for structure **4a** was supported by its mass spectrum which exhibited strong peaks at *m/e* 161 (molecular ion), (M^+ calcd 161), 121 (2 – HO – C_6H_4 – $C{\equiv}O^+$), 93 (2 – HO – $C_6H_4^+$) typical of the spectral fragmentation pattern of isoxazoles.[2,13,14] Therefore, based on the similarities between the mass spectral data of **4a** with those reported for **3**,[12] it is clearly evident that the structure **3** should be revised to **4a**.

B. Reaction of Hydroxylamine with Ethyl Chromone-3-carboxylates (2). Synthetic methods for 2-substituted chromone-3-carboxylic esters involve the basic cyclization of methyl [*o*-(acyloxy)benzoyl]acetates[7] or acylation of β-keto esters by salicyloyl chloride[15] or *o*-fluorobenzoyl chloride.[16] We have found a facile entry to the chromones (**2**) by acid-catalyzed cyclization of the condensation products **5** of 2-acetoxybenzoyl chlorides with the ethoxymagnesio enolates of β-keto esters (Scheme III, Table I).

Treatment of the chromones **2b–f** with hydroxylamine hydrochloride in refluxing acetic acid afforded the expected fused isoxazoles **7b–f**. The formation of these compounds results from nucleophilic attack at the C-2 position of the chromone ring, isoxazole cyclization, and subsequent lactonization in acid medium (Scheme IV). The intermediate isoxazole **6b** was isolated when the reaction was carried out in pyridine. Under the same conditions, ethyl chromone-3-carboxylate (**2a**) ($R^1 = R^2 = R^3 = H$) yielded only intractable material.

The structure of the compounds **7** was consistent with the ^1H NMR, IR data, and elemental analyses (Table II). Moreover, the structure of **7b** was unambiguously established by comparison with an independently synthesized sample. This was accomplished by the series of transformations presented in the Scheme V by a method reported for 3-methyl-5-phenylisoxazole-4-carboxylic acid.[17]

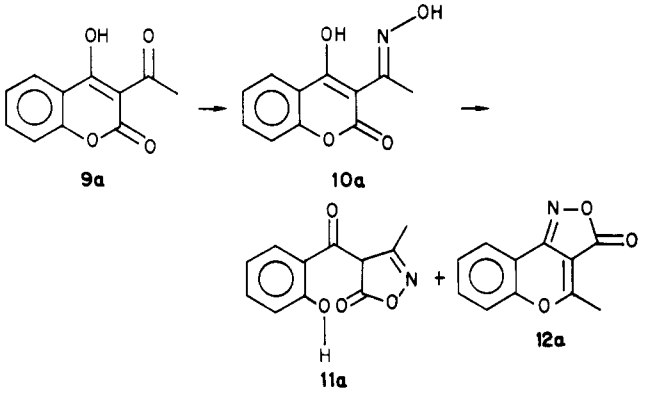
(13) Nonhebel, D. *Org. Mass Spectrom.* **1971**, *3*, 1519.
(14) Beam, C.; Dyer, M.; Schwarz, R.; Hauser, C. *J. Org. Chem.* **1970**, *35*, 1806.
(15) Charlton, J. L.; Lypka, G.; Sayeed, V. J. *Heterocycl. Chem.* **1980**, *17*, 593.
(16) Coppola, G. M.; Dodsworth, R. W. *Synthesis* **1981**, 523.

Table III. Yields of 11a and 12a in the Reaction of 9a with NH_2OH in Various Experimental Conditions

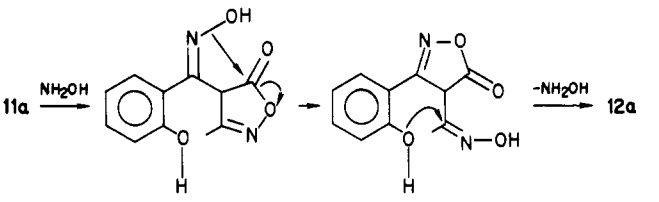
molar ratio 9a/NH_2OH·HCl/$KOCOCH_3$	solvent, mL[a] (ethanol/water)	products, % yield[b] 11a	12a	total yield, %
1:3.8:2.7[c]	20:8	57	19	76
1:3.8:2.98[d]	40:0	32	20	52
1:1:2	40:10	74	~0	74
1:1.2:2	40:16	84	~3	87
1:3:3	40:16	56	23	79

[a] For 10 mmol of **9a**, at reflux for 2 h. [b] Isolated yield. [c] Klosa's conditions: ref 20. [d] Desai's conditions using sodium acetate: ref 21.

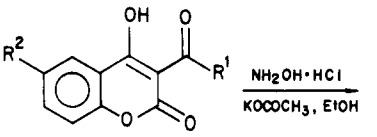
Scheme VI



Scheme VII

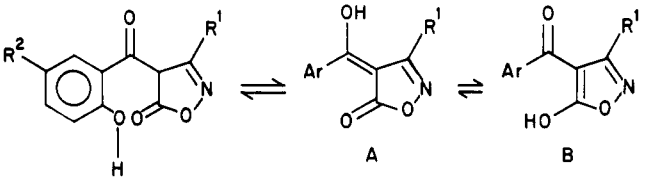


Scheme VIII



9a–e

	R^1	R^2
a,	Me	H
b,	Et	H
c,	Ph	H
d,	Me	Cl
e,	Me	Me



11a–e

A series of 4*H*-benzopyrano[3,4-*d*]isoxazol-4-ones **7** (R^1 = H) have been described from reaction of hydroxylamine with 4-chloro-3-formylcoumarins.[18,19] We question the identity of these products, since we have previously shown that their 4-chloro-3-formylcoumarin precursors were not in fact prepared.[10]

C. Reaction of 3-Acyl-4-hydroxycoumarins with Hydroxylamine. Review of the literature reveals some confusion and uncertainty about the assignment of the structure of the reaction products of 3-acyl-4-hydroxycoumarins (**9**) with hydroxylamine. In 1955, Klosa[20] reported that **9a** and **9b** gave crystalline oximes on treatment with an excess of hydroxylamine hydrochloride and potassium acetate in refluxing ethanol. More recently, Desai and Usgaonkar[21] have suggested that the "oximes" of Klosa were the 4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-ones **7**. They found that the oximes of **9** can be obtained only at room temperature and reported that they did not undergo Beckmann rearrangement but readily cyclodehydrated to **7**. Recently,[22] the formation of the isoxazole **7b** from 3-acetyl-4-hydroxycoumarin (**9a**) was also reported, under basic conditions at room temperature. The fused isoxazole structure could be ruled out since the physical properties given by these authors were different from our findings (see part B). In order to clarify this discrepancy, we repeated Klosa's work and found that the reaction of **9a** with hydroxylamine under his conditions, afforded a mixture of 4-(2-hydroxybenzoyl)-3-methylisoxazol-5(4*H*)-one (**11a**) as the main product accompanied by 4-methyl-3*H*-[1]-benzopyrano[4,3-*c*]isoxazol-3-one (**12a**)(Scheme VI). The yields of **11a** and **12a** were found to be dependent of the reaction conditions (Table III). The formation of **11a** involves the oxime **10a** as intermediate and a nucleophilic attack at the C-2 lactone carbonyl by the hydroxyimino group with ring opening. Such a cleavage of the lactone ring has been recently observed by us in 3-acyl-4-hydroxycoumarin phenylhydrazones.[23]

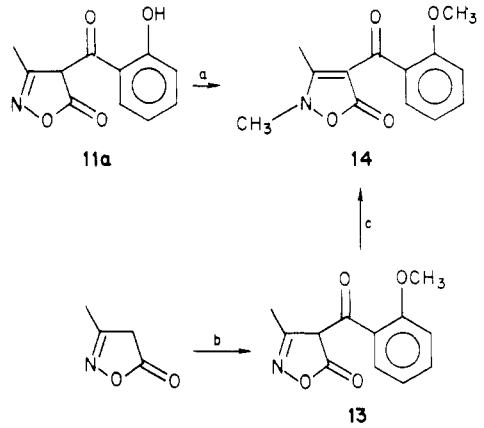
Treatment of the pure compound **11a** with an excess of hydroxylamine led to a 11:1 molar ratio mixture of **11a** and **12a**. The reaction sequence in the Scheme VII could thus be considered as a plausible mechanism for the formation of **12a** when the reaction is carried out with an excess of hydroxylamine. In the alkaline conditions of Makkay,[22] we have only isolated the oxime **10a** but not the fused isoxazole **7b**.

From the results of Table III, we have found that 4-(2-hydroxybenzoyl)isoxazol-5(4*H*)-one derivatives (**11a–e**) could be obtained, in good yields, by simply treating 3-acyl-4-hydroxycoumarins (**9a–e**) with 1.2 equiv of hydroxylamine hydrochloride and 2 equiv of potassium acetate and thus provide a useful route to a series of hitherto unknown compounds **11** (Scheme VIII).

The structure of compounds **11** was demonstrated by the analytical and spectral data. Their IR and NMR spectra were in close analogies with previous findings concerning the 4-acyl-5-isoxazolone derivatives.[24–26]

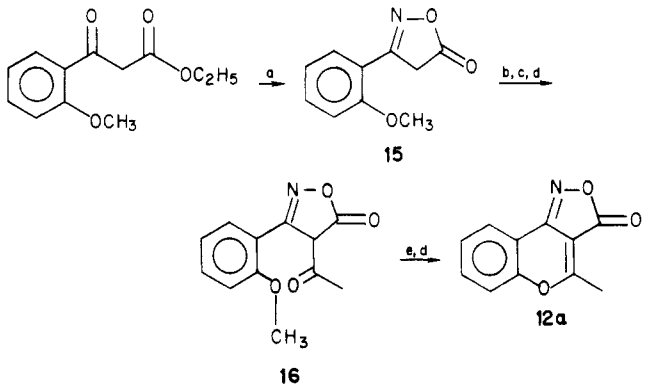
(17) Benary, E. *Chem. Ber.* **1909**, *42*, 3912.
(18) Moorty, S. R.; Sundaramurthy, V.; Subba Rao, N. V. *Indian J. Chem.* **1973**, *11*, 854.
(19) Darbarwar, M.; Sundaramurthy, V. *Synthesis* **1982**, 337.
(20) Klosa, J. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1955**, *288*, 356.
(21) Desai, M. K.; Usgaonkar, R. N. *Indian J. Chem.* **1977**, *15* (B), 379.
(22) Makkay, C.; Makkay, M. *Stud. Univ. Babes-Bolyai Chem.* **1979**, 28.
(23) Chantegrel, B.; Nadi, A. I.; Gelin, S. *Synthesis* **1983**, 214.
(24) Korte, F.; Storiko, K. *Chem. Ber.* **1961**, *94*, 1956.
(25) Müller, W.; Kraatz, U.; Korte, F. *Tetrahedron* **1973**, *29*, 4291.
(26) Maquestiau, A.; Van Haverbeke, Y.; Muller, R. N. *J. Heterocycl. Chem.* **1975**, *12*, 85.

Scheme IX[a]



[a] (a) Me_2SO_4, NaOH 1 N; (b) *o*-methoxybenzoic anhydride, sodium *o*-methoxybenzoate; (c) CH_3I, K_2CO_3, acetone.

Scheme X[a]



[a] (a) $NH_2OH \cdot HCl$, CH_3COOH; (b) triethyl orthoacetate; (c) KOH 3%; (d) HCl 10%; (e) $AlCl_3$, benzene.

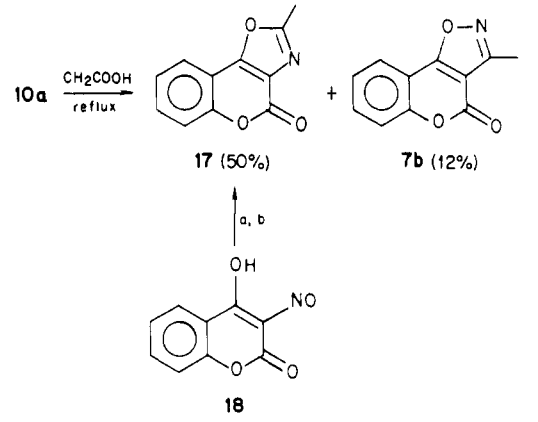
Compounds **11** exist in the enol structure A or B as evidenced by their ^1H NMR spectra which displayed a broad signal from two OH protons at rather lowfield. It is known that the shift of the enol proton of 4-acyl-5-isoxazolones was concentration dependent.[26] In the IR spectra, they showed a broad OH absorption band between 3200–2100 cm^{-1} and a carbonyl stretching band at 1670–1700 cm^{-1}. Among the two enolic forms of 4-acyl-5-isoxazolones, 4-(1-hydroxyalkylidene) (type A) or 5-hydroxy (type B), the former has been proposed.[25,26]

The structure of **11a** was confirmed by an alternate synthesis of its N-methylated derivative **14**. Acylation of 3-methyl-5-isoxazolone by 2-methoxybenzoic anhydride according to Korte's method[24] and subsequent methylation afforded a compound which was identical in all respects with that obtained by methylation of **11a**[27] (Scheme IX).

We have also prepared compound **12a** by C-acylation of 3-(2-methoxyphenyl)-5-isoxazolone (**15**) followed by cleavage of the methoxy group by aluminium chloride in benzene (Scheme X).

Finally, we have found that contrary to the published results[21] the oxime **10a** undergoes a Beckmann rearrangement with thionyl chloride. By simply refluxing **10a** in acetic acid, the oxazole **17** was obtained as the main product accompanied by a small amount of the isoxazole **7b** (molar ratio 5:1). The structure of **17** was confirmed

Scheme XI[a]



[a] (a) H_2, Pd/C, $(CH_3CO)_2O$; (b) $(CH_3CO)_2O$, reflux.

with a sample prepared from 3-nitroso-4-hydroxycoumarin **18**[28] (Scheme XI).

Experimental Section

All melting points were determined on a Kofler block. Infrared and ultraviolet spectra were obtained with Beckman Model Acculab 2 and DB spectrometers. ^1H NMR spectra were recorded on a Brucker WP 80 spectrometer and are expressed in parts per million from Me_4Si as internal standard. Elemental analyses were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

Ethyl 4-Oxo-4*H*-[1]benzopyran-3-carboxylates (2b–f). To a solution of β-keto ester (0.1 mol) in dry toluene (100 mL) was added magnesium ethylate (11.4 g, 0.1 mol). The mixture was stirred and refluxed for 2 h. After cooling to 0–5 °C, a solution of 2-acetoxyaroyl chloride (0.11 mol) in acetonitrile (50 mL) was added dropwise with stirring. The reaction mixture was allowed to stand at room temperature for 3 h and then poured into cold 10% hydrochloric acid (100 mL). The organic layer was separated and the aqueous layer was extracted with ether (50 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in ethanolic hydrogen chloride solution prepared from absolute ethanol (120 mL) and acetyl chloride (2 mL) and then refluxed for 1 h. The solvent was evaporated and the residue was dissolved in methylene chloride, washed with 10% $NaHCO_3$ (twice) and water, and dried (Na_2SO_4). Removal of the solvent gave the chromones **2b–f** (Table I).

Reaction of Chromone-3-carboxylic Acids 1a,b with Hydroxylamine. 5-(2-Hydroxyphenyl)isoxazole (4a) and 5-(2-Hydroxyphenyl)-3-methylisoxazole (4b). To a mixture of **1a**[29] or **1b**[7] (5 mmol) and potassium acetate (0.5 g, 5 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (0.7 g, 10 mmol) in water (8 mL). After refluxing for 2 h, the solvent was evaporated and the residue was triturated with water (20 mL), filtered, and recrystallized from ethanol/water (1:1). **4a**: 0.6 g (75%); mp 183–184 °C (lit.[2] mp 181 °C); IR ($CHCl_3$) 3260 (OH), 1620 (C=N) cm^{-1}; ^1H NMR (MeSO-d_6) δ 6.9 (d, 1 H, J = 2 Hz), 6.9–7.5 (m, 3 H), 7.7–7.9 (m, 1 H), 8.60 (d, 1 H, J = 2 Hz), 10.5 (s, 1 H); mass spectrum (70 eV) m/e (relative intensity) 161 (M^+, 100), 134 (10), 121 (66), 105 (21), 93 (18) **4b**: 0.8 g (90%); 216–218 °C (lit.[1] mp 220 °C); IR ($CHCl_3$) 3230 (OH), 1625 (C=N) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.33 (s, 3 H), 6.84 (s, 1 H), 6.9–7.5 (m, 3 H), 7.7–7.9 (m, 1 H), 10.5 (s, 1 H).

Ethyl 5-(2-Hydroxyphenyl)-3-methylisoxazole-4-carboxylate (6b). A mixture of chromone **2b** (2.32 g, 10 mmol) and hydroxylamine hydrochloride (1 g, 14 mmol) in pyridine (50 mL) was refluxed for 1 h. Pyridine was then evaporated in vacuo and the residue was dissolved in methylene chloride (100 mL), washed with 5% hydrochloric acid (3 × 50 mL), and dried (Na_2SO_4). The solvent was evaporated to give a crude mixture of **7b** and **6b** which was separated by chromatography on silica

(27) Identification of the N-methylated compound was based upon our work on the alkylation of 4-acyl-5-isoxazolones which will be reported in a forthcoming publication.

(28) Arndt, F.; Loewe, L.; Un, R.; Ayca, E. *Chem. Ber.* **1951**, *84*, 319.
(29) Klutchko, S.; Cohen, M. P.; Shavel, J., Jr.; von Strandtmann, M. *J. Heterocycl. Chem.* **1974**, *11*, 183.

Table IV. 4-(2-Hydroxybenzoyl)isoxazol-5(4*H*)-ones (11)

product	% yield	mol form[a]	mp, °C	UV (EtOH) λ max, nm (ε 10^{-3})	IR (KBr), cm^{-1} ν OH	IR (KBr), cm^{-1} ν CO
11a	84	$C_{11}H_9NO_4$	175–176 dec	344 (7.9)	3440, 3200–2100	1670
11b	74	$C_{12}H_{11}NO_4$	130–131	342 (8.8)	3440, 3200–2100	1700
11c	72	$C_{16}H_{11}NO_4$	86–87	346 (7.7), 252 (10.2)	3400, 3200–2100	1670
11d	67	$C_{11}H_8ClNO_4$	204–205	347 (8.4)	3440, 3200–2100	1700
11e	43	$C_{12}H_{11}NO_4$	146–147	344 (8.0)	3440, 3200–2100	1700

[a] Satisfactory analytical values (–0.34% for C, H, N, and Cl) were reported for all compounds in the table.

gel with methylene chloride as eluent. The minor compound **7b** was first eluted (0.1 g, 5%) and then **6b** (1.2 g, 48%). An analytical sample of **6b** was obtained by recrystallization from ethyl acetate/hexane (1:4): mp 109–110 °C; IR ($CHCl_3$) 3180 (OH), 1715 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 7 Hz), 2.53 (s, 3 H), 4.41 (q, 2 H, J = 7 Hz), 7.0–7.3 (m, 2 H), 7.4–7.8 (m, 2 H), 8.0 (br s, 1 H). Anal. ($C_{13}H_{13}NO_4$) C, H, N.

Preparation of 4*H*-[1]Benzopyrano[3,4-*d*]isoxazol-4-ones (7b–f). General Procedure. A mixture of chromone **2b–f** (10 mmol) and hydroxylamine hydrochloride (1.39 g, 20 mmol) in acetic acid (50 mL) was refluxed for 4 h. After evaporation of the solvent, the residue was extracted with methylene chloride (50 mL). The organic phase was washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to give **7b–f** which were recrystallized from ethanol (except **7d** from ethyl acetate).

5-(2-Hydroxyphenyl)-3-methylisoxazole-4-carboxylic Acid (8). To a solution of ethyl 3-(methylamino)-2-butenoate (7.15 g, 50 mmol) in toluene (10 mL) was added pyridine (4.35 g, 55 mmol) followed by dropwise addition, at room temperature, of 2-acetoxybenzoyl chloride (9.93 g, 50 mmol) in toluene (10 mL). The mixture was then heated to reflux for 2 h. After addition of water (60 mL) and acidification with 10% hydrochloric acid, the mixture was extracted with ether. Drying and concentration under reduced pressure afforded the crude ethyl 2-(2-acetoxybenzoyl)-3-(methylamino)-2-butenoate which was directly used in the subsequent reaction. Ethanol (45 mL) and hydroxylamine hydrochloride (4.5 g, 65 mmol) were added to the remaining material and the mixture was refluxed for 1 h. The solvent was removed and water (75 mL) was added. After extraction with ether, the combined organic layer was washed twice with 10% aqueous potassium carbonate and water. After evaporation of the solvent the ester groups of the remaining isoxazole were hydrolyzed by refluxing for 1 h with 10% aqueous potassium hydroxide (100 mL). The clear solution was acidified with concentrated hydrochloric acid. The formed precipitate was filtered to give 4.16 g of the title compound (38%). The analytical sample was obtained by recrystallization from ethanol: mp 247–248 °C; IR ($CHCl_3$) 3180 (OH), 1690 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.41 (s, 3 H), 6.7–7.0 (m, 2 H), 7.2–7.5 (m, 2 H), 10.9 (br s, 2 H). Anal. ($C_{11}H_9NO_4$) C, H, N.

Cyclodehydration of 8 to 7b. A mixture of **8** (2.4 g, 11 mmol) and acetic acid (30 mL) was refluxed for 2 h. Evaporation of acetic acid gives **7b** in a quantitative yield. Recrystallization from ethanol gives 1.7 g (77%) of analytical sample. This compound was identical with that described above (identity established by comparison of infrared and NMR spectra) (Table II).

Reaction of 3-Acetyl-4-hydroxycoumarin (9a) with Hydroxylamine. 4-(2-Hydroxybenzoyl)-3-methylisoxazol-5(4*H*)-one (11a) and 4-Methyl-3*H*[1]benzopyrano[4,3-*c*]isoxazol-3-one (12a). A mixture of **9a** (20 mmol), hydroxylamine hydrochloride, water, potassium acetate, and ethanol (for the various amounts of reagents see Table III) was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in water (80 mL). The aqueous solution was filtered and then acidified to pH 1 with concentrated hydrochloric acid. The reaction mixture was allowed to stand for 1 h, cooled, and filtered to give **11a** and **12a** as a solid mixture. After drying, **12a** was extracted with methylene chloride (50 mL) and the insoluble compound **11a** was collected by filtration. The methylene chloride solution was evaporated to leave crude **12a** which was recrystallized from ethanol (for the yields of **11a** and **12a** see Table III).

11a: physical and spectral data are given in Table IV. **12a**: mp 208–209 °C; IR ($CHCl_3$) 1780 sh, 1755 (C=O), 1670 (C=N) cm^{-1}; UV (ethanol) nm (log ε) 320 (3.74), 304 (3.70), 252 (3.84); ^1H NMR ($CDCl_3$) δ 2.80 (s, 3 H), 7.5–7.9 (m, 3 H), 8.1–8.4 (m, 1 H); MS, m/e (relative intensity) 201 (M^+, 100), 172 (12), 156 (11), 143 (50), 115 (45). Anal. ($C_{11}H_7NO_3$) C, H, N.

Preparation of 4-(2-Hydroxybenzoyl)isoxazol-5(4*H*)-ones (11a–e). General Procedure. A mixture of **9a–e** (20 mmol), hydroxylamine hydrochloride (1.67 g, 24 mmol) in water (33 mL), potassium acetate (3.92 g, 40 mmol), and ethanol (80 mL) was refluxed for 2 h. The reaction mixture was worked up as above to afford compounds **11a–e** which were recrystallized from acetonitrile. In the case of **11c** which is soluble in methylene chloride, the crude compound was directly recrystallized (Table IV).

4-(2-Methoxybenzoyl)-3-methylisoxazol-5(4*H*)-one (13). This compound was prepared according to Korte's method.[24] A mixture of 3-methylisoxazol-5-one[30] (4.5 g, 45.5 mmol), sodium 2-methoxybenzoate (9 g, 52 mmol), and 2-methoxybenzoic anhydride (46 g, 0.16 mol) was heated at 100 °C for 7 h in an oil bath. After addition of water (300 mL) and stirring, the solution was filtered and extracted with ether (3 × 100 mL). The aqueous phase was then acidified with concentrated hydrochloric acid. The formed precipitate was collected and purified by chromatography on silica gel with ethyl acetate/acetic acid (95:5) as eluent to give **13** (4 g, 42%). The analytical sample was obtained by recrystallization from acetonitrile: mp 260 °C dec.; IR ($CHCl_3$) 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 1.81 (s, 3 H), 3.88 (s, 3 H), 6.9–7.8 (m, 5 H). The product was directly used in the subsequent reaction.

2,3-Dimethyl-4-(2-methoxybenzoyl)isoxazol-5(2*H*)-one (14). A. From 13. To a mixture of **13** (1 g, 4.3 mmol) and potassium carbonate (0.6 g, 4.3 mmol) in acetone (10 mL) was added methyl iodide (1.3 mL, 20 mmol). The mixture was stirred and refluxed for 8 h and then evaporated. The residue was triturated with water (50 mL) and extracted with methylene chloride (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The resulting solid was recrystallized from ethanol to give **14**: 0.7 g (66%); mp 139–140 °C; IR ($CHCl_3$) 1755, 1630 (C=O) cm^{-1}; UV (ethanol) nm (log ε) 294 (4.17), 244 (3.94); ^1H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 3.63 (s, 3 H), 3.85 (s, 3 H), 6.9–7.2 (m, 2 H), 7.3–7.7 (m, 2 H). Anal. ($C_{13}H_{13}NO_4$) C, H, N.

B. From 11a. To a stirred solution of **11a** (2.19 g, 10 mmol) in 1 N NaOH (30 mL) was added dimethyl sulfate (3 mL, 32 mmol) dropwise. The mixture was then allowed to stand at room temperature for 3 h, basified, and stirred again for 30 min. The reaction mixture was diluted with water (100 mL) and extracted with methylene chloride (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was recrystallized from ethanol to give **14**: 1 g (40%); identical (melting point, IR, ^1H NMR) with the sample obtained from **13**.

3-(2-Methoxyphenyl)isoxazol-5(4*H*)-one (15). A mixture of ethyl (2-methoxybenzoyl)acetate[31] (8.88 g, 40 mmol) and hydroxylamine hydrochloride (2.9 g, 42 mmol) in acetic acid (120 mL) was refluxed for 1 h. The solvent was evaporated in vacuo and the residue was recrystallized from ethanol to afford **15**: 4.5 g (59%); mp 107–108 °C; IR ($CHCl_3$) 1805 (C=O) cm^{-1}; UV (ethanol) nm (log ε) 300 (4.18), 252 (4.25); ^1H NMR ($CDCl_3$) δ 3.93 (s, 3 H), 3.96 (s, 2 H), 6.9–7.2 (m, 2 H), 7.4–7.7 (m, 1 H), 7.8–9.0 (m, 1 H). Anal. ($C_{10}H_9NO_3$) C, H, N.

4-Acetyl-3-(2-methoxyphenyl)isoxazol-5(4*H*)-one (16). This compound was prepared from **15** (3.82 g, 20 mmol) and triethyl orthoacetate (4.3 g, 40 mmol) by the literature method[24] and recrystallized from ethyl acetate/hexane (1:4) 3 g (64%); mp

(30) Hydorn, A. E.; McGinn, F. A.; Moetz, J. R.; Schwartz, J. *J. Org. Chem.* **1962**, *27*, 4305.
(31) Tahara, Y. *Chem. Ber.* **1892**, *25*, 1306.

105–106 °C; IR ($CHCl_3$) 1705 (C=O), 1635 (C=N) cm^{-1}; UV (ethanol) nm (log ϵ) 282 (4.13); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3 H), 3.85 (s, 3 H), 6.9–7.2 (m, 2 H), 7.3–7.7 (m, 2 H), 12.0 (s, 1 H). Anal. ($C_{12}H_{11}NO_4$) C, H, N.

Preparation of 12a from 16. A mixture of **16** (1 g, 4.3 mmol) in anhydrous benzene (50 mL) and aluminium chloride (1.33 g, 10 mmol) was refluxed for 2 h. The reaction mixture was then poured into cold 10% hydrochloric acid (200 mL), the organic layer was separated, and the aqueous layer was extracted with benzene (50 mL). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was recrystallized from ethanol to give **12a**: 0.23 g (27%); identical (melting point, IR, ^1H NMR) with the sample obtained from **9a**.

2-Methyl-4*H*-[1]benzopyrano[3,4-*d*]oxazol-4-one (17). A. From Beckmann Rearrangement of the Oxime 10a. In Thionyl Chloride. To a suspension of **10a** (2.19 g, 10 mmol) in anhydrous chloroform (100 mL) was added thionyl chloride (4.4 mL, 60 mmol). The mixture was refluxed for 4 h and then poured into cold water. The organic layer was washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), concentrated, and chromatographed over silica gel (methylene chloride as eluent) to give the oxazole **17**: 0.8 g (79%); mp 196–197 °C (ethanol) (lit.[32] mp 195–196 °C).

In Acetic Acid. A mixture of **10a** (2.19 g, 10 mmol) in acetic acid (100 mL) was refluxed for 4 h. After removal of acetic acid, the residue was dissolved in methylene chloride (50 mL), washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), concentrated, and chromatographed over silica gel (methylene chloride as eluent) to give first the isoxazole **7b** (0.25 g, 12%) and then the oxazole **17** (1 g, 50%): mp 194–195 °C (ethanol).

The spectral properties of **17** (IR, ^1H NMR) were the same as for an authentic sample prepared by the following procedure.

B. From 4-Hydroxy-3-nitrosocoumarin (18). A modification of the literature method[33] was used. A solution of **18**[28] (1.15 g, 6 mmol) in acetic anhydride (50 mL) was hydrogenated (ca. 1 atm) over 0.5 g of 10% Pd/C until 2 equiv of hydrogen have been taken up. The mixture was then refluxed for 30 min, filtered to remove the catalyst, and evaporated in vacuo. The residue was recrystallized from ethanol to give the oxazole **17**: 0.7 g (58%); mp 194–195 °C.

Registry No. 1a, 39079-62-4; **1b**, 51751-37-2; **2a**, 51085-94-0; **2b**, 74555-98-9; **2c**, 79388-03-7; **2d**, 77037-46-8; **2e**, 92397-11-0; **2f**, 92397-12-1; **3**, 68723-84-2; **4a**, 61348-47-8; **4b**, 51138-49-9; **5b**, 92397-13-2; **5c**, 92397-14-3; **5d**, 92397-15-4; **5e**, 92397-16-5; **5f**, 92397-17-6; **6b**, 92397-18-7; **6c**, 92397-19-8; **6d**, 92397-20-1; **6e**, 92397-21-2; **6f**, 92397-22-3; **7b**, 64547-88-2; **7c**, 64517-77-7; **7d**, 64517-78-8; **7e**, 92397-23-4; **7f**, 92397-24-5; **8**, 92397-25-6; **9a**, 2555-37-5; **10a**, 32321-82-7; **11a**, 92397-26-7; **12a**, 92397-27-8; $CH_3C(O)CH_2C(O)OEt$, 141-97-9; $EtC(O)CH_2C(O)OEt$, 4949-44-4; $PhC(O)CH_2C(O)OEt$, 94-02-0; $CH_3C(O)O$-*o*-$C_6H_4C(O)Cl$, 5538-51-2; $CH_3NHC(CH_3)=CHC(O)OEt$, 870-85-9; AcO-*o*-$C_6H_4C(O)C(C(O)OEt)=C(CH_3)NHCH_3$, 92397-28-9; NH_2OH, 7803-53-4; 2-acetoxy-5-chlorobenzoyl chloride, 5538-53-4; 2-acetoxy-4-methylbenzoyl chloride, 57148-35-3.

Supplementary Material Available: Analytical data for all new compounds **2e–f**, **7b–f**, **6b**, **8**, **11a–e**, **12a**, **14–16**; ^1H NMR for compounds **2e–f**, **7b–f**, **11a–e** (2 pages). Ordering information is given on any current masthead page.

(32) Stammer, C. H. *J. Org. Chem.* **1960**, *25*, 460.

(33) Huebner, C. F.; Link, K. P. *J. Am. Chem. Soc.* **1945**, *67*, 99.

Condensation of Crotonic and Tiglic Acid Dianions with Aldehydes and Ketones

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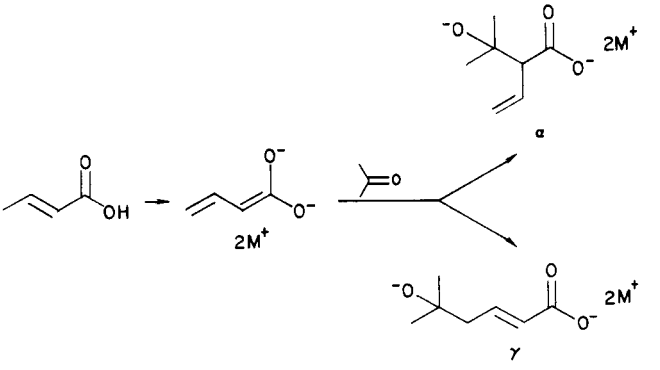
The lithium dianions of crotonic and tiglic acids reacted with *n*-heptanal, benzaldehyde, isobutyraldehyde, 2,2-dimethyl-3,3-dimethoxypropionaldehyde, acetone, and cyclopentanone at −78 °C, room temperature, and 65 °C to give α- and γ-condensation products. The kinetically controlled pathway gives largely or entirely the β-hydroxy acid from condensation at the α-carbon, but at higher temperature the reaction is reversible leading to the more stable δ-hydroxy α,β-unsaturated acid. In addition to the reaction temperature, steric effects associated with both the carbonyl electrophile and the acid dianion were found to influence the α:γ ratio of condensation products.

Deprotonation of the carboxylate salt of an α,β-unsaturated acid to give a dianion affords a practical means for introducing substitution at either the α- or γ-carbon of the acid. This chemistry, generalized in Scheme I, has been explored by Casinos and Mestres for the reaction of crotonate and senecioate (3,3-dimethylacrylate) dianions with aldehydes and ketones.[1] It was shown by these authors that the ratio of α- to γ-products was dependent on the structure of the acid, the structure of the carbonyl electrophile and, especially, on the temperature of the reaction.

The finding that both α- and γ-isomers can be obtained from the reaction of crotonate dianion with ketones supports the results of an earlier investigation of Pfeffer et al.[2] The latter attributed Watanabe's claim[3] of exclusive formation of the γ-product of crotonate dianion with cyclohexanone to the failure of the more hindered α-substituted acid to undergo esterification, which resulted in this isomer escaping detection. In their study of the reaction of senecioate dianion with benzaldehyde, Cardillo

Scheme I



(1) Casinos, I.; Mestres, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1651.
(2) Pfeffer, P.; Silbert, L.; Kensel, E. *Tetrahedron Lett.* **1973**, 1163.
(3) Suga, K.; Watanabe, S.; Fujita, T. *Aust. J. Chem.* **1972**, *25*, 2393.

0022-3263/84/1949-4424$01.50/0