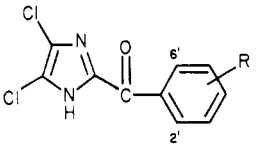
Table I



no.[a]	R	method	mp, °C (dec)	formula	(M_r)
2	2′,6′-OH_2	A, B	239–241	$C_{10}H_6Cl_2N_2O_3$	(273)
16	2′,6′-OH_2, 3′-Me	A	193–195	$C_{11}H_8Cl_2N_2O_3$	(287)
17	2′,6′-OH_2, 3′-*n*-Pr	A, B	153–155	$C_{13}H_{12}Cl_2N_2O_3$	(315)
18	2′,6′-OH_2, 4′-*n*-Pr	A	125–128	$C_{13}H_{12}Cl_2N_2O_3$	(315)
19	2′,6′-OH_2, 3′,5′-Me_2	A	198–200	$C_{12}H_{10}Cl_2N_2O_3$	(301)
20	2′,3′-OH_2	B	247–248	$C_{10}H_6Cl_2N_2O_3$	(273)
21	2′,5′-OH_2	B	238–240	$C_{10}H_6Cl_2N_2O_3$	(273)
22	3′,4′-OH_2	B	256–258	$C_{10}H_6Cl_2N_2O_3$	(273)

[a] The compounds listed had spectral properties and mass spectral data for the molecular ion fully compatible with the assigned structures. The C, H, and N analyses were within ±0.3% of the calculated values.

mixture was allowed to stir at room temperature for 2.5 h, 300 mL of 1 N sulfuric acid was added, and the mixture was extracted with ethyl acetate. Removal of solvent in vacuo yielded a solid, which after trituration with ether gave **12** as a white solid: yield 10.0 g (70%); mp 157–158 °C; NMR (Me_2SO-d_6) δ 3.65 (6, s, OCH_3), 5.55 (1, br s, OH), 6.00 (1, m, CH), 6.55 (2, d, $H_{3'}$ and $H_{5'}$), 7.20 (1, d of d, $H_{4'}$); mass spectrum, *m/e* 306, 304, 302 (M^+). Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_3$: C, 47.57; H, 3.99, N, 9.25. Found: C, 47.54; H, 3.98; N, 9.31.

2′,6′-Dimethoxyphenyl 4,5-Dichloroimidazol-2-yl Ketone (13). To a solution of 2′,6′-dimethylphenyl-4,5-dichloroimidazolylcarbinol (**12**; 8.7 g, 29 mmol) in acetone (75 mL) at 5 °C was added dropwise 2.7 M Jones reagent[18] (11 mL; the standard solution was prepared by dissolving 26.7 g of chromic trioxide in 23 mL of concentrated sufuric acid diluted with water to a volume of 100 mL). The mixture was allowed to stir at room temperature for 1.5 h and then 2-propanol (2 mL) was added. The solvent layer was separated from a green gum by filtration. The solvent was evaporated in vacuo, and the resulting solid was triturated with water and then dried to afford **13**: yield 6.4 g (74%); mp 201–202 °C dec; NMR (Me_2SO-d_6) δ 3.62 (6, s, OCH_3), 6.70 (2, d, $H_{3'}$, $H_{5'}$), 7.35 (1, d of d, $H_{4'}$); IR (KBr) 1681 (C=O) cm^{-1}; mass spectrum, *m/e* 304, 302, 300 (M^+).

2′,6′-Dihydroxyphenyl 4,5-Dichloroimidazol-2-yl Ketone (2). To a solution of ketone **13** (2.23 g, 7.4 mmol) in dry benzene (400 mL) at room temperature was added aluminum bromide (7.9 g, 29.6 mmol, 99.9% pure) all at once. The mixture, under a nitrogen atmosphere, was allowed to stir vigorously for 1.5 h and was then poured into cold water and extracted with diethyl ether. The combined ether extract was dried over anhydrous $MgSO_4$ and evaporated in vacuo to give a red solid. The solid was recrystallized from aqueous methanol to afford **2** as red crystals: yield 1.18 g (58%); mp 239–241 °C; NMR (Me_2SO-d_6) δ 6.35 (2, d, $H_{3'}$, $H_{5'}$), 7.05 (1, m, $H_{4'}$); IR (KBr) 1640 (C=O) cm^{-1}; mass spectrum, *m/e* 276, 274, 272 (M^+). Anal. Calcd for $C_{10}H_6Cl_2N_2O_3$: C, 44.00; H, 2.22; N, 10.26. Found: C, 44.08; H, 2.31; N, 10.05.[19]

2′,6′-Dihydroxyphenyl 4,5-Dichloroimidazol-2-yl Ketone *O,O*-Diacetate (8). The reaction of **2** (0.50 g, 1.8 mmol), acetic anhydride (1.4 g, 14 mmol), and 4-(dimethylamino)pyridine (10 mg) in benzene (15 mL) under reflux for 2.5 h gave **8** as a white crystalline material: yield 0.44 g (69%); mp 229–230 °C; NMR (Me_2SO-d_6) δ 2.03 (6, s, $OCOCH_3$), 7.20 (2 H, m, $H_{3'}$, $H_{5'}$), 7.60 (1 H, d of d, $H_{4'}$); IR (KBr) 1770, 1680 (C=O) cm^{-1}; mass spectrum, *m/e* 360, 358, 356 (M^+).

2′,3′-Dimethoxyphenyl-4,5-dichloroimidazol-2-ylcarbinol (15). Method B. To a solution of 2-bromo-4,5-dichloroimidazole[15] (4.5 g, 21 mmol) in tetrahydrofuran (75 mL) at −70 °C was added dropwise 2.4 M *n*-butyllithium in hexane (17.3 mL, 42 mmol) over 1 h. To this mixture was added dropwise a solution of 2,3-dimethoxybenzaldehyde (3.44 g, 21 mmol) in tetrahydrofuran (30 mL) while the temperature was maintained at −70 °C. The mixture was then allowed to warm to room temperature and was poured into ice-cold 1 N sulfuric acid solution. The aqueous mixture was extracted with ethyl acetate. The combined extracts were dried and evaporated to afford a residue, which was then triturated with diethyl ether to give **15**: yield 2.73 (44%); mp 269–270 °C dec; NMR (Me_2SO-d_6) δ 3.70 (3, s, OCH_3), 3.85 (3, s, OCH_3), 5.97 (1, d, J = 5 Hz, CH), 6.18 (1, d, J = 5 Hz, OH), 7.10 (3, m, $H_{4'-6'}$); mass spectrum, *m/e* 306, 304, 302 (M^+). Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_3$: C, 47.57; H, 3.99; N, 9.25. Found: C, 47.73; H, 3.71; N, 9.16.

Acknowledgment. We thank Drs. B. W. Cue, Jr., and L. J. Czuba for their helpful discussions and suggestions during our collaboration in the area of pyoluteorin research and Dr. A. E. Girard for providing antibacterial testing results on the compounds listed in Table I.

Registry No. 2, 81293-92-7; **3**, 31709-80-5; **4**·HCl, 81293-93-8; **5**, 81293-94-9; **6**, 81293-95-0; **7**, 81293-96-1; **8**, 81315-58-4; **9**, 13750-84-0; **10**, 81315-59-5; **11**, 81293-97-2; **12**, 81293-98-3; **13**, 81293-99-4; **14**, 16076-27-0; **15**, 81294-00-0; **16**, 81294-01-1; **17**, 81294-02-2; **18**, 81294-03-3; **19**, 81294-04-4; **20**, 81294-05-5; **21**, 81294-06-6; **22**, 81294-07-7; (2,6-dimethoxyphenyl)lithium, 2785-97-9; 2,3-dimethoxybenzaldehyde, 86-51-1; *N*-(2,2-diethoxyethyl)-2,2-diethoxyacetamidine hydrochloride, 53981-62-7.

(18) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.
(19) The demethylation of **13** was also accomplished, albeit in lower (47%) yield, by heating an intimate mixture of **13** and 10 equiv of freshly purified pyridine hydrochloride at 210 °C for 3 h.

Concerning the Preparation of Optically Pure *N*-(Thiocarboxy)-L-aspartic Anhydride

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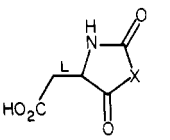
Central Research, Chemical Process Research, Pfizer Inc., Groton, Connecticut 06340

Received November 24, 1981

In the course of work directed toward a new synthesis of the dipeptide sweetener, aspartame, we wished to prepare *N*-thiocarboxy-L-aspartic anhydride **1** (L-Asp-NTA).[1]



1, X = S
2, X = O

(1) Dewey, R. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J., Jr.; Schwam, H.; Barkemeyer, H.; Arison, B. H.; Veber, D. F.; Strachan, R. G.; Milkowski, J.; Denkewalter, R. G.; Hirschmann, R. *J. Org. Chem.* **1971**, *36*, 49. This paper provides an elegant and definitive account of the use of NTA's in peptide synthesis.

0022-3263/82/1947-2199$01.25/0

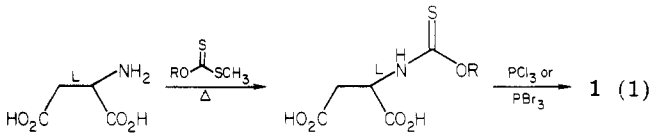
Table I

expt	starting matl	reagent	solvent	% yield of 1[a]	% ee
1	4a	PBr_3	EtOAc	95	100
2	4a	PCl_3	EtOAc	100	65
3	4a	PCl_3/HBr	EtOAc	79	72
4	4a	AcBr	EtOAc	25	95
5	4a	PBr_3/imidazole[b]	Et_2O	57	94
6	4a	PCl_3/imidazole[b]	Et_2O	29	61
7	4b	PBr_3	EtOAc	87	94
8	4b	AcBr	EtOAc	18	97
9	4b	PCl_3	EtOAc	23	3

[a] Isolated yield. [b] Added nucleophile.

Although the existence of **1** has been alluded to in the patent literature,[2] its preparation and properties have not been described. The analogous Leuchs' anhydride, **2**, has been synthesized from L-aspartic acid (**3**), although only in 20–25% yield.[3] This compound was reported as being difficult to isolate in crystalline form by a reproducible procedure. In our hands, **2** proved to be extremely hygroscopic and was not amenable toward bulk preparation and prolonged storage.

We therefore turned our attention to the synthesis of **1** and are now pleased to report that, in contrast to **2**, **1** is a readily available, stable, highly crystalline substance. The reaction scheme[1,4] employed is shown in eq 1.



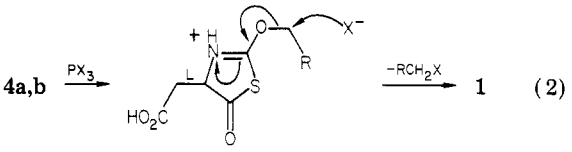
3 **4a**, R = CH_3; **b**, R = C_2H_5 (1)

Compound **3** was reacted with either dimethyl or methyl ethyl xanthate[5] in aqueous methanolic sodium hydroxide to afford the corresponding thionourethane derivative (**4a,b**). When the thionourethane was cyclized with PBr_3 or PCl_3 in ethyl acetate, pure **1** precipitated from solution in high yield. Reaction of **4a** and PBr_3 gave **1** with an optical rotation of −109° (*c* 1, THF); this value was unchanged after three crystallizations from THF/ether.[6] However, the use of PCl_3 led to **1**, whose optical rotation was only −71° (65% ee).

This unexpected difference in optical purity prompted us to study the cyclization reaction in greater detail. Our results are summarized in Table I.

Two conclusions can be reached on the basis of the above data, namely: (1) bromine-containing cyclization reagents (PBr_3, AcBr) led to markedly higher enantiomeric excesses (ee's) than the chloride-containing reagents tested; (2) the steric bulk of the *O*-alkyl group in **4a,b** has a pronounced effect on the ee when PCl_3 is used.

These observations are interesting in terms of the presumed reaction mechanism[1] (vide infra, eq 2).

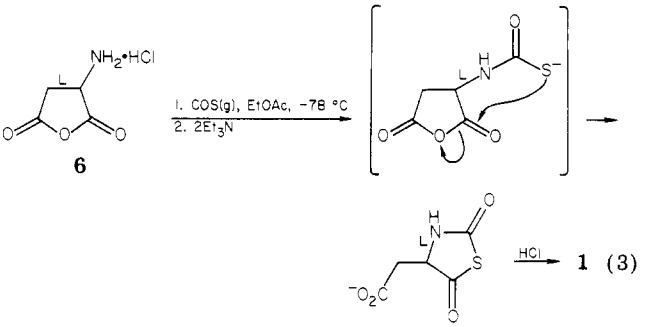


4a,b → **5** → **1** (2)

R = H, CH_3; X = Cl, Br

It was previously pointed out[1] that an intermediate such as **5** is structurally analogous to an azlactone and, hence, appreciably vulnerable to racemization. One might reasonably expect that the extent of racemization would be dependent on the relative rates of O-dealkylation with X^- and enolization.[7] Our results are consistent with the assumption that Br^- is a better nucleophile/weaker base than Cl^-; dealkylation to give RCH_2Br is very rapid relative to enolization. The comparison between Cl^- and Br^- shows that the magnitude of this effect can be dramatic. In particular, when **4a** (R = CH_3) was cyclized with PCl_3 in ethyl acetate (expt 2, Table I), a quantitative yield of **1** with 65% ee was obtained; however, in the case of the more sterically demanding **4b** (R = C_2H_5), PCl_3 gave very poor results (expt 9, 23% yield of **1**, 3% ee). PBr_3 was virtually insensitive to this steric factor: reaction with **4b** afforded an 87% yield of **1** (expt 7, 94% ee).

We also investigated a novel alternative synthesis of **1** which is depicted in the reaction scheme shown in eq 3.



6 → **1** (3)

(2) U.S. Patent 3 846 398, 1974.

(3) Hirschmann, R.; Schwam, H.; Strachan, R. G.; Schoenewaldt, E. F.; Barkemeyer, H.; Miller, S. M.; Conn, J. B.; Garsky, V.; Veber, D. F.; Denkewalter, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 2746.

(4) NTA's are conveniently prepared from amino acid thionourethanes: (a) Dewey, R. S.; Schoenewaldt, E. F.; Joshua, H.; Paleveda, W. J., Jr.; Schwam, H.; Barkemeyer, H.; Arison, B. H.; Veber, D. F.; Denkewalter, R. G.; Hirschmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 3254. (b) Khorana, H. G. *Chem. Ind. (London)* **1951**, 129. (c) Aubert, P.; Knott, E. B. *Nature (London)* **1950**, *166*, 1039. (d) Bailey, J. *J. Chem. Soc.* **1950**, 3461. (e) Aubert, P.; Jeffreys, R. A.; Knott, E. B. *Ibid.* **1951**, 2195. (f) Kricheldorf, H. R.; Bösinger, K. *Makromol. Chem.* **1976**, *177*, 1243.

(5) Other xanthate esters were also investigated: methyl isopropyl xanthate gave only a 12% yield of the *O*-isopropylthionourethane; allyl amyl xanthate (American Cyanamid, Aero 3302) and methyl *tert*-butyl xanthate failed to afford any of the desired product.

(6) As pointed out by a referee, recrystallization of the NTA to constant rotation does not ensure that the compound is 100% optically pure. When *N*-(thiocarboxy)-L-aspartic acid anhydride **1** was reacted with L-phenylalanine methyl ester, D-aspartyl-L-phenylalanine methyl ester was formed to the extent of 6–8% (determined by HPLC analysis of the crude reaction mixture). This product arises from optically impure NTA, racemization during the reaction, or a combination of these two possibilities. However, it is therefore reasonable to assume that 6–8% represents an upper limit for the amount of *optical impurity* in the NTA reagent. If the coupling reaction were carried out in tritiated water, the resulting D,L product would serve to differentiate racemization from optically impure NTA.

(7) X^- may function as a weak base which is capable of enolizing, and thereby racemizing, the thiazolone intermediate **5**.

L-Aspartic anhydride hydrochloride[8] (6) was suspended in ethyl acetate saturated with carbonyl sulfide gas at −78 °C. Triethylamine (2 equiv) was added, and, after a 4.5-h reaction period, the mixture was quenched with excess aqueous hydrochloric acid at low temperature. A standard workup afforded a 51% yield of white, crystalline, optically pure 1. Although 6 is known to react with nucleophiles to give regioisomeric ring-opened products,[9] its reaction at the amino group with an electrophilic species, e.g., COS, is unprecedented.

In summary, we have found that 1 is a synthetically accessible, potentially valuable derivative of L-aspartic acid; the optimum conditions for its preparation in optically pure form have been determined. The use of 1 in a superior synthesis of aspartame will be reported in the near future.[10]

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer. NMR spectra were obtained with a Varian XL-100 or EM-360L spectrometer with Me_4Si as an internal standard. Optical rotations were determined by using a Perkin-Elmer 141 polarimeter. Microanalyses were performed by the Pfizer Analytical Department.

General Procedure for the Preparation of *N*-(Alkoxythiocarbonyl)-L-aspartic Acid Derivatives 4a,b. L-Aspartic acid (0.150 mol) was suspended in 15 mL of water 0 °C, and 50% aqueous sodium hydroxide solution (0.300 mol) was added dropwise. The appropriate xanthate ester (0.165 mol) in 15 mL of methanol was added in one portion. The mixture was heated at 45 °C for 2 h, cooled to room temperature, and washed with two 30-mL portions of CH_2Cl_2. The CH_2Cl_2 extracts were discarded, and the aqueous phase was acidified with 12 N HCl at 0 °C. The solution was saturated with solid sodium chloride and extracted with two 100-mL portions of ethyl acetate. The organic extracts were dried ($MgSO_4$) and evaporated to give white crystalline product.

***N*-(Methoxythiocarbonyl)-L-aspartic acid (4a)** was prepared from dimethyl xanthate[11] according to the above procedure: 87%; mp 127–128 °C dec; $[\alpha]^{25}_D$ + 70.5° (*c* 1, THF); ^1H NMR (Me_2SO-d_6) δ 2.73 (d, 2 H, *J* = 6 Hz), 3.63 (s, 3 H), 4.43 (dt, 1 H, *J* = 6 Hz, 8 Hz), 6.63 (d, 1 H, *J* = 8 Hz); IR (KBr) 1715, 1515 cm^{-1}.

An analytical sample was crystallized from ether/hexane. Anal. Calcd for $C_6H_9NO_5S$: C, 34.81; H, 4.35; N, 6.76; S, 15.46. Found: C, 34.80; H, 4.33; N, 6.75; S, 15.66.

***N*-(Ethoxythiocarbonyl)-L-aspartic acid (4b)** was similarly prepared from methyl ethyl xanthate:[11] 89%; mp 133 °C dec; $[\alpha]^{25}_D$ + 57.1° (*c* 1, THF); ^1H NMR (Me_2SO-d_6) δ 1.23 (t, 3 H, *J* = 7 Hz), 2.67 (d, 2 H, *J* = 6 Hz), 4.37 (q, 2 H, *J* = 7 Hz), 4.93 (dt, 1 H, *J* = 6 Hz, 8 Hz), 9.26 (d, 1 H, *J* = 8 Hz); IR (KBr) 1739, 1724, 1515 cm^{-1}.

An analytical sample was recrystallized from ether/hexane. Anal. Calcd for $C_7H_{11}NO_5S$: C, 38.00; H, 5.01; N, 6.33; S, 14.50. Found: C, 38.39; H, 4.99; N, 6.19; S, 14.24.

General Procedure for the Preparation of *N*-(Thiocarboxy)-L-aspartic Anhydride 1 from 4a,b. The *N*-(alkoxythiocarbonyl)-L-aspartic acid derivative (**4a** or **4b**, 1.00 mol) was dissolved in 1200 mL of ethyl acetate at 0 °C, and phosphorous tribromide (0.50 mol) was added in one portion. The cooling bath was removed and the temperature allowed to rise spontaneously to 35–40 °C. The solution was stirred for 10 min, after which time a granular white precipitate had formed. The reaction mixture was cooled to 0–5 °C, and the product was collected by filtration, washed with a small volume of ether, and dried. The material thus obtained was analytically pure.

***N*-(Methoxythiocarbonyl)-L-aspartic acid (4a)** was cyclized according to the above procedure to give a 95% yield of **1**: mp 200–205 °C dec; $[\alpha]^{25}_D$ −109° (*c* 1, THF); ^1H NMR (Me_2SO-d_6) δ 2.83 (d, 2 H, *J* = 5 Hz), 4.70 (t, 1 H, *J* = 5 Hz), 9.23 (br s, 2 H, exchangeable); IR (KBr) 3225, 1739, 1724, 1653, 1399 cm^{-1}. Anal. Calcd for $C_5H_5NO_4S$: C, 34.28; H, 2.88; N, 8.00; S, 18.31. Found: C, 34.36; H, 3.03; N, 7.84; S, 18.19.

Preparation of *N*-(Thiocarboxy)-L-aspartic Acid Anhydride 1 from L-Aspartic Anhydride Hydrochloride and COS. L-Aspartic anhydride hydrochloride[8] (6; 3.02 g, 20 mmol) was suspended in 150 mL of ethyl acetate at −78 °C; carbonyl sulfide gas[12] was then bubbled into the solution over a period of 10 min. Triethylamine (5.6 mL, 40 mmol) was added in one portion at −78 °C. Carbonyl sulfide addition was continued for 30 min, and then the reaction mixture was stirred for 4 h at −78 °C. The cold solution was quenched with 50 mL of 1 N HCl and allowed to warm to room temperature. The layers were separated, and the aqueous phase was extracted with 100 mL of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated. The white crystalline residue was digested in ether, collected by filtration, and dried. Compound **1** was obtained in 51% yield; this material was identical (melting point, $[\alpha]^{25}_D$, NMR) with samples of **1** prepared from **4a,b**.

Registry No. 1, 77217-04-0; 3, 56-84-8; 4a, 77217-03-9; 4b, 78255-92-2; 6, 34029-31-7; MeOC(S)SMe, 19708-81-7; EtOC(S)SMe, 623-54-1.

(8) L-Aspartic anhydride hydrochloride was prepared by the action of $POCl_3$ on L-aspartic acid: Ariyoshi, Y.; Yamatani, T.; Uchiyama, N.; Sato, N. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2208.

(9) Ariyoshi, Y.; Yamatani, T.; Uchiyama, N.; Adachi, Y.; Sato, N. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1893.

(10) Manuscript in preparation.

(11) The required xanthate esters were easily prepared in high yield by S-alkylation of sodium ethyl xanthate or potassium methyl xanthate with dimethyl sulfate in water.

(12) Carbonyl sulfide is commercially available from Matheson Co., Inc.

Synthesis of 3,2′:5′,3″-Terthiophene and Other Terthiophenes by the Thiophenecarboxaldehyde → Ethynylthiophene → Dithienylbutadiyne Route

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Out of 14 possible terthiophene isomers, only 4 have been described in the literature to date. The best known is α-terthienyl (2,2′:5′,2″-terthiophene, **5a**), first obtained as a byproduct in the synthesis of bithienyl[1] and later characterized in the flowers of the common Marigold (*Tagetes erecta*),[2] as well as in other plants belonging to the family Compositae,[3] which frequently also contain related thiophene components.[4] Natural and synthetic α-terthienyls have interesting nematocidal activity,[5] and recently the ultraviolet light mediated antibiotic activity of α-terthienyl[6] and its enhanced nematocidal activity in

(1) Steinkopf, W.; Leitsmann, R.; Hofmann, K. H. *Justus Liebigs Ann. Chem.* **1941**, *546*, 180.

(2) Zeichmeister, L.; Sandoval, A. *Arch. Biochem.* **1945**, *8*, 425.

(3) Gommers, F. J.; Voor in'tHolt, D. J. M. *Neth. J. Plant Pathol.* **1976**, *82*, 1.

(4) (a) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1970**, *103*, 834. (b) Bohlmann, F.; Zdero, C. *Ibid.* **1976**, *109*, 901. (c) Krishnaswamy, N. R.; Seshadri, T. R.; Sharma, B. R. *Curr. Sci.* **1966**, *35*, 542. (d) Krishnaswamy, N. R.; Seshadri, T. R.; Sharma, B. R. *Tetrahedron Lett.* **1966**, 4227.

(5) (a) N. V. Philips' Gloeilampenfabrieken, British Patent 880 801, 1961; *Chem. Abstr.* **1962**, *56*, 106244. (b) Takano, T.; Iwata, T.; Atarashi, S.; Okado, S. *Yakugaku-Kenkyu* **1965**, *36*, 132; *Chem. Abstr.* **1966**, *64*, 7299*b*.

0022-3263/82/1947-2201$01.25/0