served after 1 min. After an additional 15 min the solvent was evaporated under reduced pressure. To the resulting oil was added 2 mL of acetic anhydride and the mixture was stirred at 40 °C for 20 min. The mixture was cooled to room temperature, 1 mL of pyridine was added, and the mixture was stirred overnight. Standard workup resulted in 6.0 mg of a yellow oil which was chromatographed on a 2 × 0.9 cm silica column (Bond Elut Si, Analytichem International) with 5 mL of CH_2Cl_2 followed by 10 mL of EtOAc. The EtOAc fraction was further purified by HPLC on a Whatman 4.6 mm × 25 cm Partisil 5 column using 60:40 EtOAc/CH_2Cl_2 as eluant. At a flow of 1.2 mL/min the major fraction eluted at 20 min which gave, after evaporation, 3.5 mg of pure lactone 4. TLC analysis on silica gel with 19:1 EtOAc/EtOH showed a single spot, R_f 0.43.

Compound 4 had the following properties: EIMS (70 eV), m/z (relative intensity) 359 (8.7, M - HOAc), 300 (6.4, M - HOAc - CH_3CONH_2), 286 (12.2), 244 (17.7), 240 (6.7, M - HOAc - CH_3CONH_2 - HOAc), 130 (67.5), 91 (46.5, $PhCH_2^+$), 43 (100); ^1H NMR ($CDCl_3$) δ 5.09 (d, J = 11.2 Hz, H2), 4.40 (m, H3), 1.65 (q, J = 12.4 Hz, H_{ax}-4), 2.35 (dt, J = -13.8 and 4.0 Hz, H_{eq}-4), 4.41 (m, H5), 1.31-1.60 (br m, 6 H on C6, C7, and C8), 5.03 (pentet, J = 6.1 Hz, H9), 2.85 (dd, J = -13.8 and 6.5 Hz, H10), 2.77 (dd, J = -13.8 and 6.0 Hz, H10'), 7.16 (dt, J = 7.2 and 1.6 Hz, H2'' and H6''), 7.27 (tt, J = 7.2 and 1.6 Hz, H3'' and H5''), 7.22 (tt, J = 7.2 and 1.6, H4''), 5.58 (br d, J = 7.4 Hz, NH), 2.17 (s, Ac), 1.98 (s, Ac), 1.95 (s, Ac).

Derivatization of Amino Acids with Marfey's Reagent. To a 1-mL vial containing 2 μmol of pure amino acid standard in 40 μL of H_2O was added 2.8 μmol of 2-[(5-fluoro-2,4-dinitrophenyl)amino]propanamide (FDAA)[20] in 80 μL of acetone followed by 20 μL of 1 N $NaHCO_3$. The mixture was heated for 1 h at 40 °C. After cooling to room temperature, 10 μL of 2 N HCl was added and the resulting solution was filtered through a 4.5 μm filter and stored in the dark until HPLC analysis.

To prepare FDAA derivatives of the amino acids in the scytonemin A hydrolyzate, a 40-μL aliquot containing 0.3 mg of the amino acid mixture was reacted with 4.2 μmol of FDAA in 115 μL of acetone as described above. A 5-μL aliquot of the resulting mixture of FDAA derivatives was analyzed by HPLC using a 4.6 mm × 10 cm C-18 column (Brownlee) fitted with a 4.6 mm × 1.5 cm precolumn. A linear gradient of (A) 90% triethylammonium phosphate (50 mM, pH 3.0)/10% MeCN and (B) MeCN with 0% B at the start → 40% B over 40 min (flow rate 2 mL/min) was used to separate the FDAA derivatives which were detected by UV absorption at 340 nm. Each peak in the chromatographic trace was identified by comparing the retention time with that of the FDAA derivative of the pure amino acid standard. One fraction, which contained Ala, Ser, Gly, and Hse, showed peaks at 8.5, 9.6, and 11.2 (broad with shoulder at 11.3); another fraction, which contained mainly Leu, showed a peak at 27.0 min. The amino acid standards gave the following retention times in minutes: Hse, 8.5 for L; Ser, 7.6 for L and 9.6 for D; Ala, 11.2 for L and 15.3 for D; Gly, 11.3; Leu, 21.0 for L and 26.6 for D. In all cases a peak at 16.5 min was observed which was attributed to 2-[(1-hydroxy-2,4-dinitrophenyl)amino]propanamide.

Derivatization of Amino Acids with Fluorescamine for CD Analysis. The procedure described by Toome et al.[22a] was used to make the chiroptically active derivatives in situ. The CD spectra of the derivatives were recorded immediately.

Acknowledgment. This research was supported by NSF Grant CHE83-03996. Work at the Midwest Center for Mass Spectrometry, a National Science Foundation regional instrumentation facility, was supported by NSF Grant CHE82-11164. The 600-MHz proton NMR spectra were recorded at the Carnegie-Mellon Magnetic Resonance Laboratory (A. A. Bothner-By, director). We thank Dr. R. J. Greathead (Kratos Analytical Instruments) for the linked scan mass spectrum shown in Figure 2b, Dr. K. Yasanobu (University of Hawaii) for the amino acid analysis, and Susan Chu for technical assistance. Biological testing was carried out at the Lilly Research Laboratories, Indianapolis, IN; we thank Dr. J. S. Mynderse for making the arrangements.

Registry No. 1, 112793-66-5.

Supplementary Material Available: Symmetrized 2D homonuclear J-resolved spectrum of compound **2a** and the positive ion FAB mass spectrum of compound **9** (4 pages). Ordering information is given on any current masthead page.

Notes

Easy Approach to *N*-(Aminoacyl)taurine Derivatives

Maria Altamura* and Giovanni Agnês

Istituto "G. Donegani" S.p.A., via Fauser 4, 28100 Novara, Italy

Received July 10, 1987

It has been recently reported[1] that a derivative of taurine, L-(-)-ornityltaurine hydrochloride (**5a**), possesses a salty taste greater than that of sodium chloride.

More recently, Huynh-ba and Philippossian[2] questioned the organoleptic properties of the peptide, suggesting that the previously claimed saltiness resulted from NaCl present as a not easily removable artifact.

These facts prompted us to report a new synthetic pathway suitable for a wide range of *N*-acyl derivatives of taurine. The present method in fact excludes any contamination with inorganic salts and allows the preparation of otherwise hardly accessible compounds.

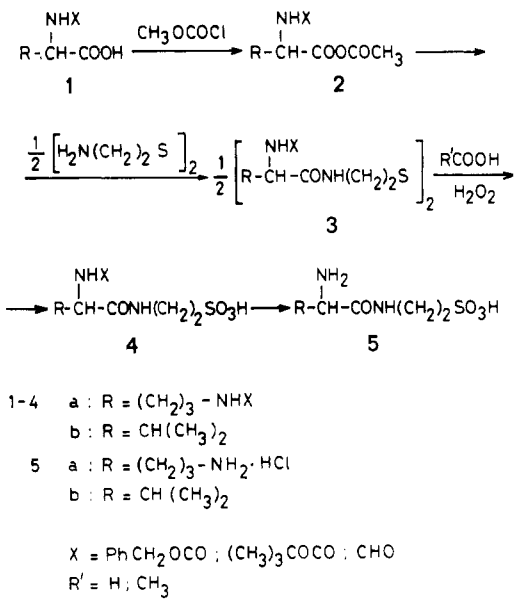
Though it is well-known that in biological systems[3,4] taurinamido derivatives can form from taurine when specific enzymes are used and that taurine or taurine sodium salt can be acylated (though in low yield) by acetic[5] or butyric[6] anhydrides or lactones,[6] any attempt to condense taurine with anhydrides, mixed anhydrides, chlorides, and activated esters (e.g., succinimide derivative) of N-protected amino acids led to negligible yields of the expected product. This is probably due to the fact that taurine is largely present in betainic form, $^+NH_3CH_2CH_2SO_3^-$, in which the nucleophilic character of the amino group is strongly reduced.

The use of taurine sodium salt did not give better results.

(1) Tada, M.; Shinoda, I.; Okai, H. *J. Agric. Food Chem.* **1984**, *32*, 992.
(2) Huynh-ba, T.; Philippossian, G. *J. Agric. Food Chem.* **1987**, *35*, 165.
(3) Siperstein, M. D.; Murray, A. W. *Science (Washington, D.C.)* **1955**, *123*, 377.
(4) Tahara, Y.; Shinmoto, K.; Yamada, Y.; Kondo, K. *Agric. Biol. Chem.* **1978**, *42*, 205.
(5) Teroaka, M. *Z. Hoppe-Seyler's Physiol. Chem.* **1925**, *145*, 238.
(6) Winterbottom, R.; Clapp, J. W.; Miller, W. H.; English, J. P.; Roblin, R. O. *J. Am. Chem. Soc.* **1947**, *69*, 1393.

0022-3263/88/1953-1307$01.50/0

Scheme I



The method reported in the present paper (Scheme I) overcomes the above difficulties and can in principle be applied to the synthesis of a wide range of taurine derivatives.

The N-protected amino acid **1**, obtained according to conventional methods,[7] is converted to the mixed anhydride **2** by methyl chloroformate and condensed with the stoichiometric amount of cystamine to form the diamide **3**. The oxidation **3** → **4** can be performed by chlorine, bromine, or organic peroxy acids. The last can be formed in situ by mixing 30% H_2O_2 (100 volumes of O_2) with an organic acid. The excess of the oxidizing agent is then removed, e.g., by sodium bisulfite, dimethyl sulfide, or 10% Pd/C.

Finally the amino group is deprotected. This can be done by catalytic hydrogenation (X = $PhCH_2OCO$), by mild acid hydrolysis (X = $(CH_3)_3COCO$), or by oxidation with H_2O_2 (X = CHO).

In the above procedure, cysteamine can be used instead of cystamine. In this case the initially formed RCH(NHX)$CONHCH_2CH_2SH$ is transformed into **3**, immediately by the oxidizing agent or slowly by exposure to the air.

Experimental Section

General Procedure. All melting points were determined on a Tottoli apparatus and are uncorrected. Optical rotation was measured with a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer and ^1H NMR spectra on a Bruker AM 300 instrument.

Mass spectra were recorded on a Finnigan MAT 8000 instrument (FAB, matrix, glycerol; fast atoms, Xe, 9.5 kV; DCI, chemical ionization source; positive and negative ions; reagent gas, isobutane).

For TLC, Merck silica plates UV 254 F were used. All solvents were RPE Carlo Erba and distilled before use. All reagents were obtained from Fluka.

***N,N'*-Bis[*N,N'*-bis(benzyloxycarbonyl)ornithyl]cystamine (3a; X = $PhCH_2OCO$).** To a solution of *N,N'*-bis(benzyloxycarbonyl)-L-ornithine (**1a**) (X = $PhCH_2OCO$) (10 g, 25 mmol) in THF (50 mL) were added *N*-methylmorpholine (2.8 mL, 25 mmol) and methyl chloroformate (2 mL, 26 mmol) under nitrogen, and the mixture was stirred for 15 min at −5 °C. A solution of cystamine dihydrochloride (2.9 g, 13 mmol) and triethylamine (3.6 mL, 26 mmol) in water (50 mL) was added to the mixture, its temperature being kept between −5 and +5 °C during the addition and then at room temperature overnight. The solid thus formed was filtered, washed with distilled water and then with diethyl ether, and dried to give 11.4 g (100% yield) of *N,N'*-bis[*N,N'*-bis(benzyloxycarbonyl)ornithyl]cystamine (**3a**; X = $PhCH_2OCO$): mp 159–161 °C; IR $\nu_{C=O}$ 1690 and 1650 cm^{-1}; ^1H NMR ($CDCl_3$, ref TMS) δ 7.3 (m, 20 H), 6.0 (br, 2 H), 5.25 (bbr, 2 H), 5.0 (m, 8 H), 4.35 (br, 1 H), 3.3 (br, 8 H), 2.7 (m, 4 H); MS (DCI) 917 $(M - H)^+$, 883, 349.

***N*-[*N,N'*-Bis(benzyloxycarbonyl)-L-ornithyl]taurine (4a; X = $PhCH_2OCO$).** To 100 mL of 98% formic acid was added 10 mL of 30% H_2O_2 (0.1 mol), and the solution was stirred for 1 h.

To the above solution, stirred and cooled at 0 °C, was added 7.6 g of *N,N'*-bis[*N,N'*-bis(benzyloxycarbonyl)ornithyl]cystamine (**3a**; X = $PhCH_2OCO$) (8.29 mmol). The temperature was then raised to 20 °C with further stirring (5 h), and the excess of oxidant was destroyed by addition of dimethyl sulfide (5 mL, 68 mmol).

The solution was evaporated in vacuo to give 7 g of crude *N*-[*N,N'*-bis(benzyloxycarbonyl)-L-ornithyl]taurine (**4a**; X = $PhCH_2OCO$), which was crystallized to give an analytical sample having mp 167 °C: ^1H NMR (DMSO-d_6) δ 7.4 (m, 10 H), 5.05 (s, 2 H), 5.03 (s, 2 H), 3.9 (m, 1 H), 3.37 (m, 2 H), 3.0 (m, 2 H), 2.63 (m, 2 H); MS (FAB) 506 $(M - H)^+$, 416, 372, 238.

***N,N'*-Bis[*N,N'*-bis(*tert*-butyloxycarbonyl)ornithyl]cystamine (3a; X = $(CH_3)_3COCO$).** *N,N'*-Bis(*tert*-butyloxycarbonyl)-L-ornithine (**1a**; X = $(CH_3)_3COCO$) (4.23 g, 12.7 mmol) was condensed with cystamine as described for the synthesis of *N,N'*-bis[*N,N'*-bis(benzyloxycarbonyl)ornithyl]cystamine (**3a**; X = $PhCH_2OCO$). The THF was then removed under reduced pressure, the residue was dissolved in ethyl acetate (200 mL), and the solution was washed with H_2O (40 mL), HCl (5% in water, 40 mL), $NaHCO_3$ (5% in water, 40 mL), and water (40 mL) and dried (Na_2SO_4).

Evaporation of the solvent and crystallization from diethyl ether gave *N,N'*-bis[*N,N'*-bis(*tert*-butyloxycarbonyl)ornithyl]cystamine (**3a**; X = $(CH_3)_3COCO$) (3.63 g, 79% yield) as a crystalline solid: mp 105–107 °C; IR $\nu_{C=O}$ 1690 and 1660 cm^{-1}; ^1H NMR ($CDCl_3$, ref TMS) (main signals) δ 7.45, 5.70, 5.05 (br, 1 H, NH), 4.3 (br, 1 H, CHCO), 2.8 (m, 2 H, CH_2S); MS (DCI) 781 $(M + H)^+$, 525 $[(M + H) - (t\text{-}BuOCO)_2NC_3H_4]^+$; 392 $[(M - H) - (M/2 - H)]^+$.

L-Ornithyltaurine Hydrochloride (5a). Method A. Crude *N*-[*N,N'*-bis(benzyloxycarbonyl)-L-ornithyl]taurine (**4a**; X = $PhCH_2OCO$) (7 g) was hydrogenated in acetic acid (70 ml), over 10% Pd/charcoal (0.5 g), with stirring at atmospheric pressure and room temperature for 2 h. After filtration and evaporation of the solvent, the crude residue, on treatment with methanol and 5.6 M HCl/dioxane (3 mL, 16.8 mmol), formed a white, hygroscopic crystalline powder. This was filtered under nitrogen, washed with ethyl ether, and dried in vacuo to give 2.97 g of pure ornithyltaurine hydrochloride (**5a**) (65% yield on **3**): $[\alpha]^{20}_D$ +7° (*c* 1, H_2O); ^1H NMR (DMSO-d_6) δ 3.77 (m, 1 H), 3.4 (m, 2 H), 2.81 (m, 2 H), 2.77 (t, 2 H), 1.5–1.8 (m, 4 H); MS (FAB) 240 $[M - Cl]^+$.

Method B. *N,N'*-Bis[*N,N'*-bis(*tert*-butyloxycarbonyl)ornithyl]cystamine (**3a**; X = $(CH_3)_3COCO$) was oxidized as described for *N,N'*-bis[*N,N'*-bis(benzyloxycarbonyl)ornithyl]cystamine (**3a**; X = $PhCH_2OCO$). The protecting group was removed by HCl/dioxane to give crystalline L-ornithyltaurine hydrochloride (**5a**) in 85% yield.

***N,N'*-Bis(*N*-formylvalyl)cystamine (3b; X = CHO).** *N*-formyl-L-valine (**1b**; X = CHO) (2 g, 13.7 mmol) was dissolved in THF (30 mL) and *N*-methylmorpholine (1.5 mL, 13.6 mmol). Methyl chloroformate (1.1 mL, 14.3 mmol) was added at −5 °C under nitrogen, and the mixture was stirred at the same temperature for 15 min. A solution of cystamine dihydrochloride (1.55 g, 6.9 mmol) and triethylamine (2 mL, 14.3 mmol) in water (30 mL) was added at 0–10 °C. The mixture was stirred at 0 °C for 30 min and at room temperature overnight. The solvent was evaporated in vacuo and the crystalline residue washed on a filter several times with water and diethyl ether: yield, 2.1 g (75%); mp 150–152 °C; IR $\nu_{C=O}$ 1665 and 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.2 (m, 1 H, NCHCO), 2.75 (t, 2 H, CH_2S), 1.95 (m, 1 H, $CH(CH_3)_2$), 0.8 (m, 6 H, CH_2).

(7) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961.

L-Valyltaurine (5b). To 60 mL of 98% formic acid was added 6 mL of 30% H_2O_2 (60 mmol), and the solution was stirred for 1 h at 0 °C. Crude *N,N'*-bis(*N*-formylvalyl)cystamine (**3b**; X = CHO) (2.1 g, 5.1 mmol), dissolved in 98% formic acid (15 mL), was added at the same temperature and the solution stirred overnight at room temperature. The excess of the oxidant was removed by addition of dimethyl sulfide (3 mL, 41 mmol). The solution was evaporated in vacuo, to give 1.83 g (71%) of L-valyltaurine (**5b**): IR $\nu_{C=O}$ 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.2 (m, 1 H, NCHCO), 3.2 (m, 2 H), 2.8 (t, 2 H), 1.95 (m, 1 H), 0.9 (m, 6 H); MS (FAB) 673 $[(M + H) + 2 M]^+$, 449 $[(M + H) + M]^+$, 225 $[M + H]^+$.

Acknowledgment. The present research has been supported by Farmitalia Carlo Erba.

Registry No. **1a** (X = CBz), 2274-58-0; **1a** (X = BOC), 57133-29-6; **1b** (X = CHO), 4289-97-8; **3a** (X = CBz), 112042-52-1; **3a** (X = BOC), 112042-53-2; **3b** (X = CHO), 112042-54-3; **4a** (X = CBz), 90990-60-6; **5a**, 90970-64-2; **5b**, 53329-38-7; cystamine dihydrochloride, 56-17-7; cystamine, 51-85-4.

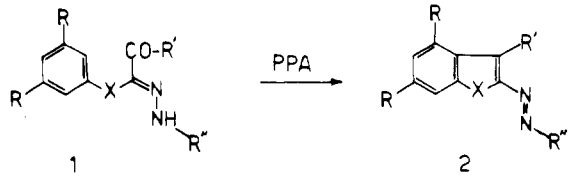
New Access to 2-(Arylazo)-, 2-(Arylhydrazo)-, and 2-Aminoindoles, -benzofurans, and -thianaphthenes

Tiziana Benincori and Franco Sannicolò*

Dipartimento di Chimica Organica e Industriale dell'Università, CNR, Centro di Studio per la Sintesi e Stereochimica di Speciali Sistemi Organici, Via C. Golgi, 19, 20133 Milano, Italy

Received June 9, 1987

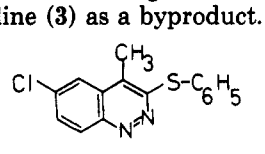
In this paper we describe the reaction of a few α-arylamino, -aryloxy, and -arylthio acyl hydrazones having general structure **1** with polyphosphoric acid (PPA). The reaction affords 2-(arylazo)indoles, -benzofurans, and -thianaphthenes **2**, respectively, in fairly good yields; the reaction is applicable to a rather wide range of substrates.



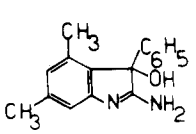
1 2

	X	R	R'	R''
a	NH	H	CH_3	C_6H_5
b	NH	CH_3	CH_3	C_6H_5
c	NH	H	CH_3	4-Cl-C_6H_4
d	NH	CH_3	C_6H_5	C_6H_5
e	O	H	CH_3	C_6H_5
f	O	CH_3	CH_3	C_6H_5
g	S	CH_3	CH_3	C_6H_5
h	S	H	CH_3	4-Cl-C_6H_4

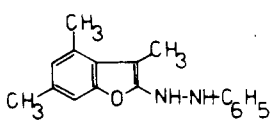
In the case of **1h**, a concurrent cyclization course was observed affording 6-chloro-4-methyl-3-(phenylthio)-cinnoline (**3**) as a byproduct.



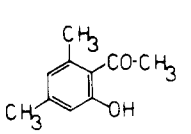
3



4



5



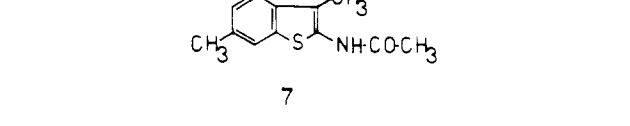
6

The structural assignment to the reaction products **2** was based on the spectral and analytical data as well as on the results of the high-pressure catalytic hydrogenation performed in one case for each class of compounds, namely, **2d**, **2f**, and **2g**.

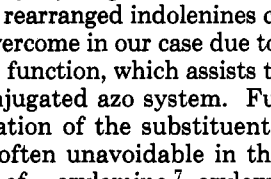
In the case of **2d**, 2-amino-4,6-dimethyl-3-phenyl-3-hydroxyindolenine (**4**) and aniline were formed. This result is in accordance with literature data reporting the easy oxidation in air of 2-aminoindoles.[1]

In the case of **2f**, a more complicated reaction course was observed affording *N*-phenyl-*N'*-[2-(3,4,6-trimethylbenzofuranyl)]hydrazine (**5**), 2,4-dimethyl-6-hydroxyacetophenone (**6**), and aniline. The hydrazo compound **5** could alternatively be prepared in better yields by controlled reduction of **2f** with zinc dust and ammonium chloride in water–acetone solution.

The formation of **6** can be interpreted through a mechanism similar to that producing **4**: the 2-aminobenzofuran derivative initially formed should undergo, like the corresponding indole compound, an easy oxidation by air. Ring opening would give a cyanohydrin as the logical precursor of **6**.



The hydrogenation of **2g** was carried out in the presence of acetic anhydride; 2-acetamido-3,4,6-trimethylthianaphthene (**7**) and acetanilide were the main reaction products.



7

The general reaction scheme leading to **2** from **1** is basically a cyclodehydration,[2] which is a known means for producing benzocondensed five-membered heterocycles from α-arylamino,[3] -aryloxy,[4] and -arylthio ketones.[5] The scope of this synthetic scheme is strongly limited when the carbon atom adjacent to the condensing carbonyl group does not carry any hydrogen atom allowing the water elimination (only rearranged indolenines can be formed[5]): this problem is overcome in our case due to the peculiarity of the hydrazonic function, which assists the loss of water on forming a conjugated azo system. Furthermore, the formal 3–2 migration of the substituent bonded to the carbonyl group, often unavoidable in the course of the cyclodehydration of α-arylamino,[7] -aryloxy,[8] and -arylthio

(1) Golubeva, G. A.; Portnov, Y. N.; Kost, A. N. *Khim. Geterotsikl. Soedin.* **1973**, *9*, 471. Kost, A. N.; Golubeva, G. A.; Zabrodnyayor, V. G.; Portnov, Y. N. *Khim. Geterotsikl. Soedin.* **1975**, *11*, 1383. Kost, A. N.; Portnov, Y. N.; Golubeva, G. A. U.S.S.R. Pat. 334 218; *Chem. Abstr.* **1972**, *77*, 48505*k*.

(2) Bradsher, C. K. *Chem. Rev.* **1946**, *38*, 447.

(3) Crowther, A. F.; Mann, F. G.; Purdie, D. *J. Chem. Soc.* **1953**, 58. Julian, P. L.; Meyer, E. W.; Magnani, A.; Cole, W. *J. Am. Chem. Soc.* **1945**, *67*, 1203. Brown, F.; Mann, G. F. *J. Chem. Soc.* **1948**, 847 and 858.

(4) Cagniant, P.; Cagniant, D. *Recent Advances in the Chemistry of Benzo[b]furan and its Derivatives*; Katritzky, A. R., Ed.; Academic: New York, 1975; Vol. 18, p 364.

(5) (a) Iddon, B.; Scrowston, R. M. *Recent Advances in the Chemistry of Benzo[b]thiophenes*; Katritzky, A. K., Boulton, A. J., Eds.; Academic: New York, 1970; Vol. 11, p 220. (b) Scrowston, R. M. *Chemistry of Benzo[b]thiophenes*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1981; Vol. 29, p 220.

(6) Garry, M. *Ann. Chim. (Paris)* **1942**, *17*, 5.

0022-3263/88/1953-1309$01.50/0