Department of Pharmaceutical Chemistry, The University of Mississippi

Thiaindanones III. Beckmann Rearrangement of Oximes (1)

K. Aparajithan, A. C. Thompson and Joseph Sam

The Beckmann rearrangement of 5-methylthiaindan-4-one oximes (I) and thiaindan-6-one oximes (IV) proceeds with the migration of the alkyl group to yield dihydrothienopyridones (II and V, respectively). In two instances, the corresponding lactones (VIIa and VIIb) also were isolated. None of the isomeric lactams (X and XI) were isolated from the Beckmann rearrangement reactions. Supporting evidence for the proposed structures is provided.

The preparations of some thiaindanones of biological interest have been described in earlier publications (2,3). In a continuation of our interest in the chemistry and biological properties of novel thiophene derivatives we have investigated the Beckmann rearrangement of I and IV.

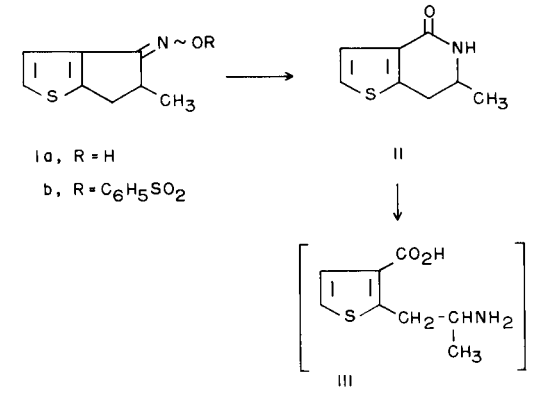
In contrast to the course of rearrangement of 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one oxime (VIII) to IX reported by Fabrichnyi *et al.* (4), I and IV proceeded via the alternate course to II and V, respectively.

The hydrolysis of IX followed by diazotization and coupling with β-naphthol gave a positive test indicating the presence of an aromatic amine; however, the hydrolysis of II and V, followed by diazotization and coupling with β-naphthol gave negative tests indicating the absence of aromatic amino groups. Ultraviolet spectral data of the hydrolysis products of II and V provided additional evidence for the course of the Beckmann rearrangements. Acid and base solutions of the products of the hydrolysis of either II or V provided similar ultraviolet spectra whereas acid and base solutions of the product of hydrolysis of IX were different. The former results are consistent with absorption spectra of aralkyl amines similar to structures III and VI. Dissimilar spectra would be expected of hydrolysis products of the isomeric lactams with the amino group attached directly to the thiophene ring such as was obtained with acid and base solutions of the product of hydrolysis of IX.

The ultraviolet spectra of the products of hydrolysis of Va and Vb were similar to the spectrum of 2-thiophenecarboxylic acid and that of Vc was similar to the spectrum of 5-chloro-2-thiophenecarboxylic acid. These similarities in spectra provide additional evidence for structures VIa, VIb, and VIc as the hydrolysis products and consequently structures Va, Vb, and Vc for the Beckmann rearrangement products. Table I summarizes the ultraviolet data of the compounds described above.

The nuclear magnetic resonance (n.m.r.) spectra of II, Vc and also of XIX are consistent with the structures assigned to them on the basis of chemical and UV spectral studies. The n.m.r. data (τ values in p.p.m.) are given at the appropriate place in the experimental.

Although the yields of the Beckmann rearrangement products (II and V) were only in the neighbor-

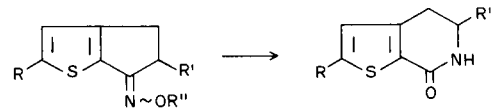


Ia, R = H

b, R = $C_6H_5SO_2$

II

III



IVa, R = R' = R" = H

b, R = R" = H, R' = CH_3

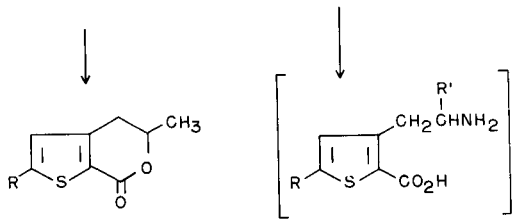
c, R = Cl, R' = CH_3, R" = H

d, R = H, R' = CH_3, R" = $C_6H_5SO_2$

Va, R = R' = H

b, R = H, R' = CH_3

c, R = Cl, R' = CH_3



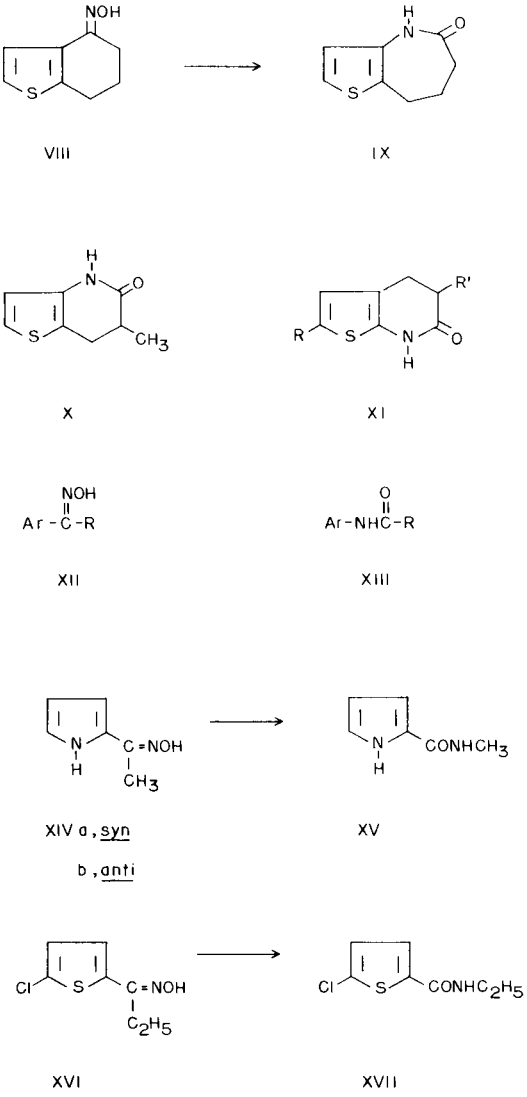
VIIa, R = H

b, R = Cl

VIa, R = R' = H

b, R = H, R' = CH_3

c, R = Cl, R' = CH_3



hood of 50%, none of the isomeric lactams (X and XI) were isolated. Only in the case of IVb and IVc was an effort made to account for all of the starting material. In the latter reactions we also isolated the corresponding lactones (VIIa and VIIb) in approximately 35% yields. The lactones along with the lactams accounted for 85-95% of the starting materials. None of the other possible rearrangement products (XI) were isolated. The lactones (VIIa and VIIb) were identified by elemental analysis and infrared and nuclear magnetic resonance spectra.

The Beckmann rearrangement of *anti*-aryl systems (XII) to the amides (XIII) with the nitrogen attached to the aryl ring is documented in the literature (5). Our results with the oximes, I and IV, suggest either that the oximes have a *syn*-aryl configuration or isomerization of the oximes from *anti* to *syn* had occurred in the reaction media.

Both the *syn* (XIVa) and *anti* (XIVb) oximes of 2-acetylpyrrole were reported to give only *N*-methyl-2-pyrrolecarboxamide (XV) (6). We also obtained only *N*-ethyl-5-chloro-2-thiophenecarboxamide (XVII), although in low yield, by the rearrangement of the oxime (XVI) of 5-chloro-2-propionylthiophene. Craig and Naik (7) obtained 2-acetamidothiophene and *N*-methyl-2-thiophenecarboxamide by the rearrangement of isomeric ketoximes, respectively. No mention, however, was made of the configuration of the oximes.

EXPERIMENTAL (8)

5-Chloro-2-propionylthiophene.

The procedure described by Hartough (9) for the preparation of 2-acetyl-5-chlorothiophene was followed. From 237 g. (2.0 moles) of 2-chlorothiophene, 325 g. (2.5 moles) of propionic anhydride and 30 g. of orthophosphoric acid (85%) there was obtained 120 g. (34%) of product, m.p. 46.5-48° (lit. (10) m.p. 47°).

Thiaindan-6-one Oxime (IVa).

The procedure described by Buzas and Teste (11) was followed. From 0.28 g. (0.002 mole) of thiaindan-6-one (2) there was obtained product which, after recrystallization from cyclohexane, weighed 0.21 g. (75%); m.p. 128.5-130°; ν max (KBr), 1660 cm^{-1}.

2-Chloro-5-methylthiaindan-6-one Oxime (IVc).

A mixture of 1.86 g. (0.01 mole) of 2-chloro-5-methylthiaindan-6-one (2), 1.25 g. (0.018 mole) of hydroxylamine hydrochloride, and 1.0 g. (0.007 mole) of crystalline sodium acetate in 15 ml. of 33% methanol was heated under reflux for 4 hours. The reaction mixture was cooled and the precipitated solid removed by filtration, washed with water, dried and recrystallized twice from methanol-water to give 0.9 g. (45%) of product. The material was recrystallized from cyclohexane; m.p. 133-135°; ν max (KBr), 1654 cm^{-1}.

Anal. Calcd. for C_8H_8ClNOS: C, 47.64; H, 4.00; Cl, 17.58; N, 6.95; S, 15.90. Found: C, 47.81; H, 4.01; Cl, 17.84; N, 6.87; S, 15.83.

5-Chloro-2-propionylthiophene Oxime (XVI).

The procedure described for the preparation of IVc was followed using 3.0 g. (0.017 mole) of 5-chloro-2-propionylthiophene, 2.5 g. (0.036 mole) of hydroxylamine hydrochloride and 2.0 g. (0.014 mole) of crystalline sodium acetate. The product, after repeated recrystallization from cyclohexane, weighed 0.5 g. (19%) and melted at 143-144°.

Anal. Calcd. for C_7H_8ClNOS: C, 44.32; H, 4.25; Cl, 18.69; N, 7.38; S, 16.90. Found: C, 44.29; H, 4.41; Cl, 18.74; N, 7.28; S, 16.73.

5-Methylthiaindan-6-one Oxime Benzenesulfonate (IVd).

The procedure described by Fabrichnyi and associates (4) for the rearrangement of thiophenocycloalkanone oximes was followed. To a solution of 10 g. (0.06 mole) of 5-methylthiaindan-6-one oxime (2) (IVb) in 100 ml. of dry pyridine was added a solution of 10 g. (0.06 mole) of benzenesulfonyl chloride in 20 ml. of pyridine. The resulting solution was shaken for 10 minutes and then allowed to stand overnight. The solution was cooled in an ice bath, and 200 ml. of 4*N* hydrochloric acid was added with vigorous stirring. The oil which separated was extracted three times with 150-ml. portions of ether. The ethereal solution was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residual solid was recrystallized from ethanol to give 9.7 g. (97%) of white crystals, m.p. 60-63°. The infrared spectrum in carbon tetrachloride showed a C=N stretching absorption at 1640 cm^{-1}, and two sulfonic ester absorptions at 1385 and 1200 cm^{-1}, respectively. Hydroxyl absorption above 3000 cm^{-1} was absent.

Anal. Calcd. for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found: C, 54.77; H, 4.28; N, 4.76.

5-Methylthiaindan-4-one Oxime Benzenesulfonate (Ib).

The procedure for the preparation of IVd was followed using 10 g. (0.06 mole) of 5-methylthiaindan-4-one oxime (2) (Ia). The product (9.6 g., 96%) after recrystallization from ethanol melted at 86-87°. The infrared spectrum in carbon tetrachloride showed a C=N stretching absorption at 1640 cm^{-1}, and two sulfonic ester absorptions at 1385 and 1200 cm^{-1}, respectively.

Anal. Calcd. for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found: C, 54.92; H, 4.21; N, 4.56.

TABLE I

Ultraviolet Absorption Maxima (and Log Extinction Coefficients)

Compound No.	λ max (HCl), mμ		log ε max	λ max (NaOH), mμ	log ε max
III	211		4.42	220	3.98
	246		4.04	246	4.09
VIa	240		3.67	241	3.70
	270		3.77	269	3.72
VIb	234		3.87	234	3.88
	241		3.90	242	3.90
	270		4.04	268	4.08
VIc	(255)		3.66	(255)	3.67
	279		3.82	277	3.80
IX (a)	233		3.86	228	3.40
				265	3.26
2-thiophenecarboxylic acid	250	248 (b)	3.95	246	3.91
	270	270 (b)	3.87	260	3.82
5-chloro-2-thiophenecarboxylic acid	250	256 (b)	3.89	252	3.89
	282	280 (b)	4.08	283	4.08
3-thiophenecarboxylic acid		241 (b)			

(a) Ultraviolet spectrum of hydrolysis product of IX. (b) Values reported by Y. Sugimoto, S. Nishimura, and E. Imoto, *Bull. Univ. Osaka Prefect., Ser. A*, 8, (1), 71 (1959); *Chem. Abstr.*, 55, 12030a (1961).

N-Ethyl-5-chloro-2-thiophenecarboxamide (XVII). Method A.

A suspension of 0.4 g. (0.002 mole) of 5-chloro-2-propionylthiophene oxime (XVI) in 15 g. of commercial polyphosphoric acid (PPA) was heated with manual stirring in an oil bath. At a temperature of 125°, the temperature rose sharply to 130-135°. The mixture was maintained at 130-135° for 15 minutes and thereafter allowed to stand at room temperature overnight. The viscous mixture was poured, with stirring, into 80 g. of crushed ice and then extracted four times with 25-ml. portions of chloroform. The combined chloroform extracts were washed with water and dried over anhydrous sodium sulfate. The chloroform was distilled and the residual solid recrystallized successively from methanol-water and cyclohexane to give 0.2 g. (50%) of product, m.p. 121-122°; ν max (KBr), 1615, 1550 cm^{-1}; n.m.r. ($CDCl_3$ + Me_2SO) 2.2 (1H, broad), 2.83 (2H, AB), 6.6 (2H, quartet split into doublet), 8.81 (3H, triplet).

Anal. Calcd. for C_7H_8ClNOS: C, 44.32; H, 4.25; Cl, 18.69; N, 7.38; S, 16.90. Found: C, 44.48; H, 4.39; Cl, 18.70; N, 7.26; S, 16.76.

Method B.

The method employed was essentially the same as that of Craig and Willis (12). To a suspension of 0.56 g. (0.003 mole) of 5-chloro-2-propionylthiophene oxime (XVI) in 8 ml. of dry ether cooled in ice, was added 0.9 g. of phosphorus pentachloride. The reaction mixture was allowed to stand at room temperature for 30 minutes. One milliliter of water was added dropwise to the reaction mixture at such a rate that the internal temperature remained below 20°. A dilute solution of sodium hydroxide was added with ample cooling until *p*H of 5-6 was obtained. The ether phase was separated and the aqueous phase further extracted with 25-ml. portions of ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of ether gave a solid which was recrystallized successively from benzene-petroleum ether (b.p. 30-60°), cyclohexane and ethanol-water. There was obtained 0.11 g. (20%) of off-white crystals, m.p. 121-122°. A mixture melting point with the sample obtained by Method A showed no depression. The infrared spectra were identical.

4,5-Dihydrothieno[2,3-*c*]pyrid-7(6*H*)-one (Va).

Method A described for the preparation of *N*-ethyl-5-chloro-2-thiophenecarboxamide (XVII) was followed. From 0.1 g. (0.65 mmole) of thiaindan-6-one oxime (IVa) and 5 g. of PPA, there was obtained 0.1 g. of product. Vacuum sublimation (0.3 mm.) followed by recrystallization of the sublimate from benzene-petroleum ether (b.p. 30-60°) gave 20 mg. (20%) of colorless needles, m.p. 123.5-125°; ν max (KBr), 1621-1661 cm^{-1}. This broad band was characteristic of all the dihydrothienopyridones studied.

Anal. Calcd. for C_7H_7NOS: C, 54.87; H, 4.61; N, 9.14; S, 20.92. Found: C, 55.15; H, 4.49; N, 9.06; S, 20.77.

4,5-Dihydro-5-methylthieno[2,3-*c*]pyrid-7(6*H*)-one (Vb). Method A.

Method A for the preparation of *N*-ethyl-5-chloro-2-thiophenecarboxamide (XVII) was followed. From 1.85 g. (0.011 mole) of 5-methylthiaindan-6-one oxime (2) (IVb) there was obtained 0.86 g. (47%) of product which was purified by sublimation under reduced pressure (0.3 mm.) and recrystallization of the sublimate from cyclohexane; m.p. 108-109°; ν max (KBr), 1641-1665 cm^{-1}.

Anal. Calcd. for C_8H_9NOS: C, 57.48; H, 5.39. Found: C, 57.50; H, 5.58.

Method B.

A solution of 27.9 g. (0.09 mole) of 5-methylthiaindan-6-one oxime benzenesulfonate (IVd), 100 g. of anhydrous potassium acetate, 750 ml. of water, and 300 ml. of ethanol was heated on a steam bath for 24 hours. The ethanol was distilled *in vacuo* and the remaining hot aqueous solution was treated with charcoal, filtered, and cooled. The aqueous solution was extracted three times with 150-ml. portions of ether. The ethereal solution, after being washed twice with 300-ml. portions of 10% sodium bicarbonate solution, was distilled to give 3.0 g. of product, b.p. 190°/2 mm., m.p. 107-109°. The infrared spectrum was identical with that obtained in Method A.

3-(2-Hydroxypropyl)-2-thiophenecarboxylic Acid δ-Lactone (VIIa).

The aqueous acid solution after chloroform extraction in the prepa-

ration of Vb (Method A) was allowed to remain at room temperature for one week and then extracted with three 50-ml. portions of ether. The extract was washed with water and dried over anhydrous magnesium sulfate. There was recovered 0.77 g. of solid which on vacuum sublimation (0.3 mm.) gave 0.74 g. (40% from IVb) of crystalline material, m.p. 80-85°. Recrystallization from cyclohexane gave colorless needles m.p. 91-93°; ν max (KBr), 1700 cm^{-1}; n.m.r. ($CDCl_3$) 2.35 (1H, doublet), 3.0 (1H, doublet), 4.9-5.5 (1H, quartet split into 16 peaks), 6.7-7.5 (2H, two doublets each split into a doublet), 8.49 (3H, doublet).

Anal. Calcd. for $C_8H_8O_2S$: C, 57.13; H, 4.8; S, 19.06. Found: C, 57.54; H, 4.58; S, 18.64.

4,5-Dihydro-2-chloro-5-methylthieno[2,3-*c*]pyrid-7(6*H*)-one (Vc).

Method A for the preparation of *N*-ethyl-5-chloro-2-thiophenecarboxamide (XVII) was followed. From 5.0 g. (0.025 mole) of 2-chloro-5-methylthiaindan-6-one oxime (IVc) there was obtained 3.0 g. (60%) of product from which was obtained by sublimation under reduced pressure (0.25 mm.), 2.6 g. (52%) of crystalline material. Recrystallization from cyclohexane gave colorless needles, m.p. 141-143°; ν max (KBr), 1659-1674 cm^{-1}; n.m.r. ($CDCl_3$) 3.2 (1H, broad), 3.25 (1H, singlet), 5.8-6.4 (1H, sextet), 7.2-7.5 (2H, triplet), 8.66 (3H, doublet).

The same material was obtained by the PPA rearrangement of the crude oxime recovered from the recrystallization solvent of the oxime.

Anal. Calcd. for C_8H_8ClNOS: C, 47.64; H, 4.00; Cl, 17.58; N, 6.95; S, 15.90. Found: C, 47.80; H, 4.10; Cl, 17.56; N, 6.23; S, 15.85.

5-Chloro-3-(2-hydroxypropyl)-2-thiophene Carboxylic Acid δ-Lactone (VIIb).

The aqueous acid solution after chloroform extraction in the preparation of Vc was allowed to remain at room temperature for 4 days. The mixture was extracted with three 50 ml. portions of ether and the extract washed with water and dried over anhydrous magnesium sulfate. Evaporation of ether gave 1.6 g. of solid. Vacuum sublimation (0.3 mm.) gave 1.54 g. (30%) of crystalline material melting at 102°. Recrystallization from cyclohexane gave colorless needles, m.p. 102-103°; ν max (KBr), 1700 cm^{-1}; n.m.r. ($CDCl_3$) 3.19 (1H, singlet), 5.2 (1H, quintet split into doublets), 7.2 (2H, triplet), 8.49 3H, doublet).

Anal. Calcd. for $C_8H_7ClO_2S$: C, 47.5; H, 3.49; Cl, 17.53; S, 15.85. Found: C, 47.25; H, 3.48; Cl, 17.44; S, 16.01.

6,7-Dihydro-6-methylthieno[3,2-*c*]pyrid-4(5*H*)-one (II).

The procedure described above was followed. From 2.0 g. (0.012 mole) of 5-methylthiaindan-4-one oxime (2) (Ia) there was obtained 1.2 g. (60%) of product which was purified by sublimation under reduced pressure (0.3 mm.). The sublimate was recrystallized from cyclohexane; m.p. 122.5-124.5°; ν max (KBr), 1667-1674 cm^{-1}; n.m.r. ($CDCl_3$) 2.75 (2H, AB), 3.3 (1H, broad), 5.7-6.3 (1H, complex pattern), 6.9-7.2 (2H, triplet), 8.63 (3H, doublet).

The same product was obtained by the PPA rearrangement of the crude viscous material recovered from the recrystallization solvent of the oxime.

Anal. Calcd. for C_8H_9NOS: C, 57.48; H, 5.39; S, 19.18. Found: C, 57.70; H, 5.52; S, 19.09.

4,6,7,8-Tetrahydro-5*H*-thieno[3,2-*b*]azepin-5-one (IX).

The procedure described above was followed. From 1.55 g. (0.009 mole) of 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one oxime (4) (VIII) there was obtained 0.35 g. (63%) of product. The latter was dissolved in a minimum amount of benzene, passed through a column of alumina and thereafter eluted with petroleum ether (b.p. 30-60°) and cyclohexane. The fraction eluted by cyclohexane was recrystallized from cyclohexane; m.p. 132-133° (lit. (4) m.p. 135°); ν max (KBr), 1650 cm^{-1}.

Hydrolysis of the Lactams.

Two to four milligrams of the lactam was treated with 1 ml. of 6 *N* hydrochloric acid and heated under reflux for 1 hour. The clear solution was diluted with water to 25 ml. Two milliliters of this solution, diluted to 25 ml., provided an acid solution for ultraviolet studies. Another 2 ml. sample was treated with 2.5 ml. of 0.25 *N* aqueous sodium hydroxide and diluted with water to 25 ml. to provide an alkaline solution for ultraviolet studies. The ultraviolet spectra of the two solutions were recorded and are indicated by λ max (HCl), and λ max (NaOH), respectively (Table I).

REFERENCES

(1a) The authors are grateful to Bristol Laboratories for financial support of the project. (b) Presented before the Medicinal Section, American Chemical Society meeting, Detroit, Michigan, April, 1965.

(2) J. Sam and A. C. Thompson, *J. Pharm. Sci.*, **52**, 898 (1963).

(3) J. Sam and A. C. Thompson, *ibid.*, **53**, 535 (1964).

(4) B. P. Fabrichnyi, I. F. Shalavina, and Ya. L. Gol'dfarb, *Zh. Obshch. Khim.*, 31, 1244 (1961); *Chem. Abstr.*, 55, 23488b (1961).

(5) L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

(6) A. P. Terent'ev and A. N. Makarova, *Vestn. Moskov. Univ.*, No. 4, 101 (1947); *Chem. Abstr.*, 42, 1590g (1948).

(7) J. Cymerman Craig and A. R. Naik, *J. Am. Chem. Soc.*, 84, 3410 (1962).

(8) All melting points are corrected. Infrared spectra were determined in pressed disks of potassium bromide on a Perkin-Elmer Model 137 Infracord spectrophotometer. The ultraviolet spectra were obtained using a Perkin-Elmer Model 202 Ultraviolet-Visible recording spectrophotometer. The authors are grateful to Mr. David F. Whitehead and Mr. Albert L. Vulcano of Bristol Laboratories, Syracuse, N. Y. for the n.m.r. spectra and the interpretation of the data.

(9) H. D. Hartough, "Thiophene and its Derivatives," Interscience, New York, N. Y., 1952, p. 104.

(10) N. P. Buu-Hoi and Nguyen-Hoan, *Rec. Trav. Chim.*, 68, 441 (1949).

(11) A. Buzas and J. Teste, *Bull. Soc. Chim. France*, 359 (1960).

(12) J. Cymerman Craig and D. Willis, *J. Chem. Soc.*, 1071 (1955).

Received August 23, 1966 University, Mississippi 38677