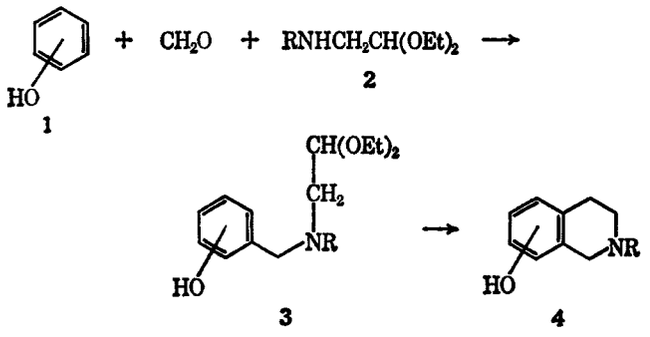
acid-catalyzed cleavage, ring closure, and reduction of benzyl amino acetals formed by reductive alkylation of aminoacetaldehyde acetal with suitable aromatic aldehydes. We have now been able to prepare the benzyl amino acetals by a simple Mannich reaction on suitable phenols.[4] The method has been especially useful for preparation of 6,7,8-trioxygenated isoquinolines.

The appropriate phenols (**1**) were allowed to react with formaldehyde and suitably substituted amino acetals (**2**, R = H or CH_3) to yield the benzyl amino



acetals (**3**) which were converted into isoquinolines (**4**) by acid treatment followed by hydrogenation over palladium on carbon.[3] The Mannich bases were not isolated. The results are given in Table I. Two products (**5** and **6**) were obtained when the reaction was carried out with guaiacol, but they were easily separable by crystallization and the combined yield was nearly quantitative. The Mannich condensations with methyl amino acetal were carried out at room temperature,[5] but those with amino acetal required reflux temperature in ethanol.

Two of the compounds, **7** and **10**, are known alkaloids, anhalidine and anhalamine, respectively.[6] Methylation of **10** with diazomethane led to the alkaloid, anhalinine (6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline). All three alkaloids were synthesized by a more laborious method by Späth and his coworkers.[7,8] Anhalamine and anhalidine have been prepared more recently by Brossi and his coworkers.[9] Compound **11** was prepared from vanillin. The 5-methyl group was formed by reduction of the aldehyde group during the hydrogenation step. The nmr spectra of all of the compounds, known and unknown, were measured and are in agreement with the assigned structures.

Experimental Section[10]

Reaction of Guaiacol to Yield 5 and 6.—A mixture of guaiacol (2.48 g, 0.02 mol), 3.00 g of 40% aqueous formaldehyde (0.04 mol), and 3.60 g of methylaminoacetaldehyde dimethyl acetal (0.03 mol) in 25 ml of ethanol was stirred at room temperature for 24 hr. The solvent was removed on a rotary evaporator and the resulting thick oil was dissolved in 50 ml of cold 6 *N* HCl and washed with ether. The acidic solution was stirred at room temperature for 15 hr. The last traces of ether were removed on a rotary evaporator and the solution was hydrogenated over 4 g of 5% palladium on carbon at room temperature and atmospheric pressure until no more hydrogen was absorbed (about 0.02 mol). The catalyst was removed by filtration and the solution was concentrated on a rotary evaporator to a yellow syrup. The syrup was treated with 50 ml of hot ethanol and cooled. Crystals formed and were collected to yield 1.20 g of the crude hydrochloride of **6**, (26%) mp 281–284°. The compound was recrystallized from methanol.

The mother liquor after the removal of **6** was concentrated and cooled to yield the crystalline crude hydrochloride of **5** (3.12 g, 68%), mp 208–212°. The analytical sample, mp 212–214°, was crystallized from absolute ethanol.

Preparation of Mannich Bases (3). General Procedure.[5]—The tertiary bases (**3**, R = CH_3) were prepared by stirring a mixture of the phenol (0.02 mol), formaldehyde (0.04 mol of 40% aqueous), and methylaminoacetaldehyde dimethyl acetal[11] (0.03 mol) in 25 ml of ethanol for 24 hr at room temperature. The secondary amines (**3**, R = H) were prepared by stirring similar mixtures (with aminoacetaldehyde dimethyl acetal[11]) at reflux temperature for 6–8 hr. In each case, the solvent was removed on a rotary evaporator and the crude Mannich bases were not purified.

1,2,3,4-Tetrahydroisoquinolines (4).—The crude Mannich bases were dissolved in 50 ml of cold 6 *N* HCl, washed three times with ether, and stirred at room temperature for 15 (leading to **9**) or 36 hr (leading to **7**, **8**, **10**, and **11**). The last traces of ether were removed, and the acid solutions were hydrogenated as described above. The catalyst was removed by filtration, and the solutions were evaporated on a rotary evaporator to yield slightly colored syrups. The syrups were treated with hot absolute ethanol (50 ml) and evaporated again. In some cases, this procedure was repeated twice more. The products crystallized during the evaporation or upon alcohol addition. They were collected by filtration and washed with cold absolute ethanol. Analytical samples were prepared by recrystallization from ethanol.

6,7,8-Trimethoxy-1,2,3,4-tetrahydroisoquinoline (Anhalinine).—Compound **10** (0.3 g) was treated with the diazomethane from 5 g of nitrosomethylurea. The mixture was allowed to stand in a refrigerator for 5 days and was evaporated to a syrup. The sryup was taken up in ether again, washed with 5% aqueous NaOH, dried over Na_2SO_4, and saturated with gaseous HCl. The crude hydrochloride (0.18 g) precipitated and was collected and recrystallized from absolute ethanol to yield anhalinine hydrochloride, mp 248–250° (lit.[7] mp 248–250°).

Registry No.—**5**, 19462-72-7; **8**, 19462-73-8; **11**, 19462-74-9.

(4) This research was suggested during a lecture given at Connecticut by Professor J. H. Burckhalter of the University of Michigan.

(5) E. L. Eliel, *J. Amer. Chem. Soc.*, **73**, 43 (1951).

(6) See L. Reti in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. IV, Academic Press, New York, N. Y., 1954, p 7.

(7) E. Späth and I. Roder, *Monatsh.*, **42**, 97 (1921); **43**, 93 (1922); *Chem. Abstr.*, **16**, 100, 3303 (1922).

(8) See footnote *d*, Table I.

(9) A. Brossi, F. Schenker, and W. Leimgruber, *Helv. Chim. Acta*, **47**, 2089 (1964).

(10) Melting points were measured on a Thomas–Hoover apparatus and are uncorrected. Microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich and the Baron Consulting Co. of Orange, Conn.

(11) Sometimes the diethyl acetal was used with similar results.

The Formation of Tetramethylpyrazine and 2-Isopropyl-4,5-dimethyl-3-oxazoline in the Strecker Degradation of DL-Valine with 2,3-Butanedione

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The Strecker degradation is a well-documented reaction in which an α-amino acid is simultaneously decarboxylated and deaminated to yield a structurally related aldehyde containing one less carbon atom.[1] The reaction is usually observed when α-amino acids are heated in the presence of 1,2-di- or 1,2,3-tricarbonyl

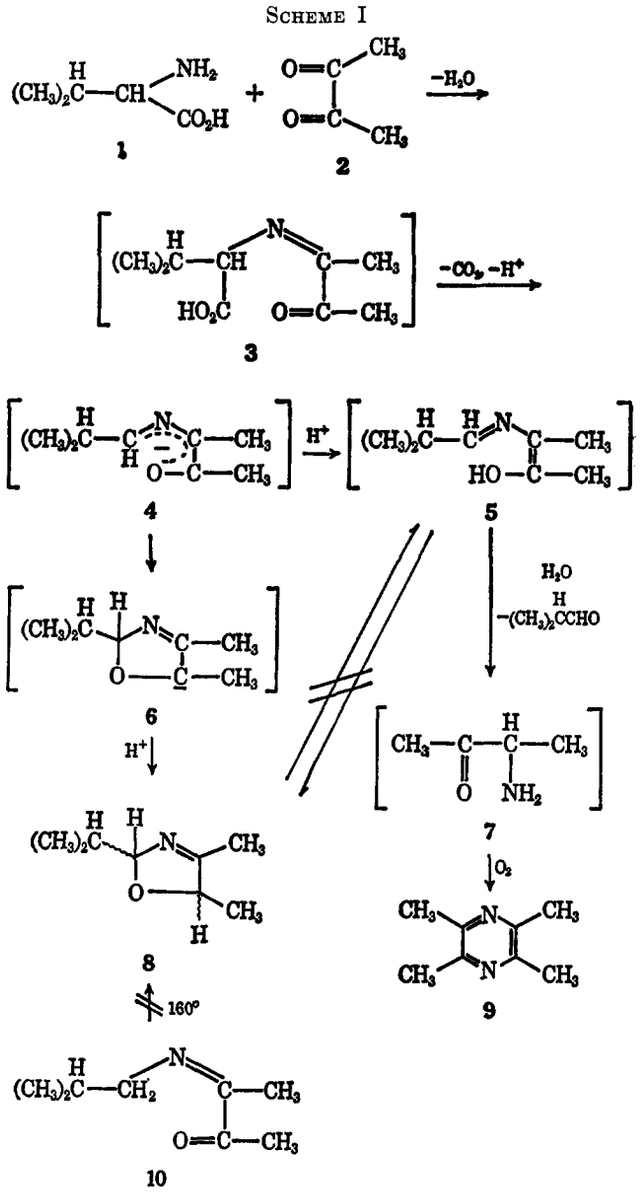
(1) A. Schönberg and R. Moubacher, *Chem. Rev.*, **50**, 261 (1952).

compounds. Historically the Strecker degradation has been studied as an "aldehyde-forming" process, and the fate of the amino acid nitrogen has not received much attention. A general reaction mechanism proposed by Schönberg, *et al.*,[2] suggested that reductive amination of the di- or polycarbonyl moiety takes place. An example of the evidence cited for this type of reductive amination is the formation of Ruhemann's purple in the α-amino acid–ninhydrin reaction.[3] In this Note we wish to present additional data to substantiate and elaborate Schönberg's reductive amination mechanism.

When equimolar amounts of DL-valine (**1**) and 2,3-butanedione (**2**) were refluxed in diglyme (*ca.* 160°), carbon dioxide was rapidly evolved and the diketone was completely consumed after 45 min as evidenced by the disappearance of its characteristic yellow color. The reaction mixture was steam distilled to separate volatile reaction products. Besides diglyme, the distillate contained isobutyraldehyde, tetramethylpyrazine (**9**, 9%),[4] and a mixture of *cis*- and *trans*-2-isopropyl-4,5-dimethyl-3-oxazoline (**8**, 4%). Compound **8** apparently represents the first example of a simple 3-oxazoline to be reported in the literature.[5,5a] The oxazoline structure was established by ir and nmr spectroscopy and from the fact that dehydrogenation of **8** with chloranil produced 2-isopropyl-4,5-dimethyloxazole in high yield. The nmr spectrum of **8** served to distinguish the 3-oxazoline from the otherwise possible 2-oxazoline isomer. A doublet centered at δ 1.29 ppm (J = 6 Hz) was attributed to the 5-methyl group. The hydrogen atom at C-5 gave a broad quartet centered at δ 4.48 ppm (J = 6 Hz). The methyl substituent at C-4 appeared as two sharp singlets at δ 1.92 and 1.94 ppm which together integrated for three protons.

A plausible explanation for the formation of the novel Strecker degradation products is shown in Scheme I. Initially **1** and **2** react with elimination of water to form a thermally unstable Schiff base **3**.[2] Decarboxylation of **3** probably leads to the mesomeric species **4**,[6] which, after protonation and hydrolysis, is transformed into isobutyraldehyde and 3-amino-2-butanone (**7**). The reductive amination product **7** was not observed, but, as expected,[7] underwent self-condensation and oxidation with molecular oxygen to yield **9**. The formation of **8** is still not clearly understood. Compound **8** could have been formed by ring–chain tautomerism involving **5**. This seemed unlikely, however, since no **9** formed when **8** was heated at 160° in aqueous diglyme. If **8** and **5** existed in equilibrium at 160°, part of the **5** present would likely have undergone hydrolysis to yield **7** and thence **9**. The fact that no **9** was formed suggested that

SCHEME I



equilibration of **5** and **8** did not occur under our reaction conditions. Ketimine **10** which could have been formed by decarboxylation of **3** was also shown not to be a precursor of **8**. A sample of **10** prepared by an alternate route gave no **8** upon heating for 1 hr at 160° in a sealed tube. In addition, **8** and **9** were not formed when an equimolar mixture of isobutylamine and **2** were subjected to the original Strecker degradation conditions. A more likely mechanism for the formation of **8** could involve cyclization of **4** followed by protonation of the resulting 3-oxazolinide ion **6**.

Experimental Section[8]

Reaction of DL-Valine (1) and 2,3-Butanedione (2).—A mixture containing 17.55 g of reagent grade **1** (0.150 mol), 12.00 ml

(2) A. Schönberg, R. Moubacher, and A. Mostafa, *J. Chem. Soc.*, 176 (1948).

(3) M. Friedman and C. W. Sigel, *Biochemistry*, **5**, 478 (1966).

(4) Under similar conditions benzil and alanine produced tetraphenylpyrazine; *cf.* C. D. Hurd and C. M. Buess, *J. Amer. Chem. Soc.*, **78**, 5667 (1956).

(5) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed, Interscience Publishers, New York, N. Y., 1967, p 316.

(5a) NOTE ADDED IN PROOF.—2,4,5-Trimethyl-3-oxazoline was recently reported to be a flavor constituent in boiled beef; *cf.* S. S. Chang, *et al.*, *Chem. Ind.* (London), 1639 (1968).

(6) F. G. Baddar, *J. Chem. Soc.*, S163 (1949). It is also possible that **5** may have been formed directly from **3** *via* a concerted process involving a cyclic transition state.

(7) Compound **7** was expected to yield **9** by analogy with 2-amino-1-phenyl-3-butanone which undergoes spontaneous conversion into 2,5-dibenzyl-3,6-dimethylpyrazine in high yield; *cf.* P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **79**, 95 (1928).

(8) Infrared spectra were obtained with a Perkin-Elmer Model 137 Infracord spectrophotometer. Samples were examined as liquid films unless otherwise noted. Ir absorption maxima data were rounded off to the nearest 0.05 μ. Nmr spectra were obtained using Varian HA-100 and A-60 instruments. Samples were run as 5–10% solutions in the solvents indicated and the data are recorded as follows: chemical shift in δ units downfield from tetramethylsilane (multiplicity, integrated number of protons, coupling constant, structural assignment). Multiplicity is indicated by letters: s = singlet, d = doublet, t = triplet, q = quartet, and m = complex multiplet. The mass spectrum of compound **8** was taken on an Atlas Model CH-4 spectrometer. Melting points were observed in open capillaries and are uncorrected. Microanalyses were performed by Mr. T. Atanovich and associates of these laboratories.

of redistilled **2** (0.137 mol) and 50 ml of freshly redistilled diglyme was stirred and refluxed for 45 min under N_2. The cooled reaction mixture was steam distilled and the 300 ml of pale yellow distillate obtained was saturated with NaCl and extracted three times with ether. The ether solution was dried ($MgSO_4$), concentrated and distilled to yield 7.56 g of oil, bp 52–70° (19 mm). Glpc analysis on a 5 ft × 0.25 in. column packed with 30/60 mesh Chromosorb W containing 15% Carbowax 20M indicated three compounds: isobutyraldehyde,[9] 0.3%, retention time (R_T) at 107°, 1.0 min; diglyme, 88%, R_T 15.2 min; and **8**, 11%, R_T 10.4 min. Samples of each substance were condensed from the glpc effluent (He) at Dry Ice temperature for characterization. Isobutyraldehyde and diglyme were identified by R_T and by their ir spectra. Compound **8** was a colorless, mobile liquid with a peculiar vegetablelike odor: ir 3.40, 3.50, 6.0 (C=N), 6.85, 7.00, 7.25, 7.30, 7.85, 8.15, 9.10, 9.30, 10.00 and 10.50 μ; 100 MHz nmr (CCl_4) δ 0.94 [d, 6, J = 6 Hz, $(CH_3)_2CH$], 1.29 (d, 3, J = 6 Hz, $CHCH_3$), 1.78 (broad m, 1, J = 6 Hz, >CH–), 1.92 and 1.94[10] (s, 3, CH_3C=), 4.48 (broad q, 1, J = 6 Hz, >CHCH$_3$) and 5.08 ppm [m, 1, –(O)CHN=]; mass spectrum (70 eV) m/e 141 (molecular ion) 139, 124, 98 (base peak), 97, 82, 71, 55, 56, 43, 42, 41, 39.

Anal. Calcd for $C_8H_{15}NO$: N, 9.92. Found: N, 9.9.

Treatment of the original distillation residue with excess picric acid in ethanol at 25° gave 3.62 g (9%) of **9** dipicrate, mp 185–190°. Recrystallization from ethanol gave yellow needles, mp 196.5–198° (lit.[11] mp 198.5–199.5°).

Anal. Calcd for $C_{20}H_{18}N_8O_{14}$: C, 40.41; H, 3.05; N, 18.84. Found: C, 39.9; H, 3.0; N, 18.7.

Decomposition of the picrate with aqueous NH_3 gave pure **9** whose ir spectrum (CS_2) was identical with that of an authentic specimen.

Chloranil Dehydrogenation of 8.—A solution of **8** (0.380 g, 0.00270 mol) in 4 ml of diglyme was treated with 0.749 g (0.00304 mol) of freshly recrystallized chloranil. The mixture was stirred and heated to 100° for 1 hr. On cooling, 0.688 g of solid (presumably tetrachlorohydroquinone) was filtered off and the filtrate was distilled. A single product was formed which codistilled with diglyme, bp 60.5–64.5° (14 mm). The compound was separated by preparative glpc using the column described above and was shown to be 2-isopropyl-4,5-dimethyloxazole by comparing ir and R_T data with those of the authentic substance. The oxazole was formed in 80% yield.

2-Isopropyl-4,5-dimethyloxazole was prepared by the method of Theilig[12] from isobutyramide and 3-bromo-2-butanone (Eastman Organic Chemicals, Rochester, N.Y.). The compound was a colorless liquid: bp 76–77° (20 mm); yield 70%; ir (CH_2Cl_2) 3.45, 6.05, 6.40, 7.25, 8.35, 8.85, 9.15, 9.40, 10.15 and 10.50 μ; 100 MHz nmr ($CDCl_3$) δ 1.28 [d, 6, J = 7 Hz, $(CH_3)_2CH$], 2.00 (s, 3, ring CH_3), 2.14 (s, 3, ring CH_3) and 2.94 ppm [m, 1, J = 7 Hz, $(CH_3)_2CH$].

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.6; H, 9.2; N, 9.5.

N-(1-Methyl-2-oxopropylidene)isobutylamine (10).—A solution containing 4.00 ml (0.0457 mol) of **2** in 100 ml of benezene was treated with 4.55 ml (0.0457 mol) of isobutylamine and refluxed under a Dean-Stark water separator for 1 hr (0.92 ml of water separated). The benezene solution was concentrated and the residue was distilled giving 3.13 g (49%) of **10**: bp 65–67° (16 mm); ir 3.40, 5.85 (C=O), 6.10 (C=N), 6.80, 7.40, 7.75, 9.00 and 10.20 μ; 60 MHz nmr ($CDCl_3$) δ 0.95 [d, 6, J = 6 Hz, $(CH_3)_2CH$], 1.80 and 1.82 [s, 4, (includes isopropyl methine H), CH_3C=N], 1.93 (m, J = 6 Hz, >CHCH$_2$), 2.22 (s, 3, CH_3C(=O)–), 3.10 and 3.12[13] (d, 2, J = 7 Hz, =NCH$_2$).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.4; H, 10.6; N, 10.3.

(9) No attempt was made to recover the bulk of the isobutyraldehyde which was presumably lost during distillation.

(10) Two nearly superimposed sharp singlets were observed, apparently due to a difference in chemical shifts of the 4-methyl group hydrogens in *cis* and *trans* **8**. The isomers of **8** were partially resolved on a 10 ft × 0.125 in. glpc column packed with 60/80 mesh Chromosorb W (HMDS treated) containing 15% SF-96.

(11) T. Ishiguro, E. Kitamura, and M. Matsumura, *Yakugaku Zasshi*, **78**, 150 (1959); *Chem. Abstr.*, **53**, 13163 (1959).

(12) G. Theilig, *Chem. Ber.*, **86**, 96 (1953).

(13) Two singlets and two doublets believed due to *syn* and *anti* forms of the imine; *cf.* G. J. Karabatsos and S. S. Lande, *Tetrahedron*, **24**, 3907 (1968).

Registry No.—**1**, 516-06-3; **2**, 431-03-8; **8** (*cis*), 19519-42-7; **8** (*trans*), 19519-43-8; **9**, 1124-11-4; **10**, 19519-44-9; 2-isopropyl-4,5-dimethyloxazole, 19519-45-0.

Addition of Thiobenzophenone to Benzenediazonium-2-carboxylate[1]

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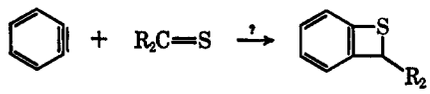
One possible way to prepare benzothietes[2] is by a 1,2 cycloaddition of a thiocarbonyl group to benzyne(1,2-dehydrobenzene). Examples are known of the cycloaddition of a thiocarbonyl group to double bonds,[3] but



the only reported interaction with a benzyne occurs with formation of a benzothiazole.[4] A number of 1,2 cycloadditions of benzyne with other types of compounds are known.[5]

To check the feasibility of adding thiocarbonyl groups to benzyne, thiobenzophenone and propylene oxide were added to a solution of the hydrochloride of benzenediazonium-2-carboxylate in 1,2-dichloroethane[6] and the solution was refluxed. Gas and heat were evolved and a white solid was obtained (44.5% yield, purified) which was identified as 2,2-diphenyl-3,1-benzoxathian-4-one (**1**), the δ-lactone of *o*-[(α-hydroxybenzhydryl)thio]benzoic acid, which has not been prepared before although a number of 3,1-benzoxathian-4-ones have been synthesized by other methods.[7] The identification was accomplished by determination of the compound's molecular weight, its empirical formula by analysis for elements, its mass spectrum, infrared

(1) This work was aided by Grant GP 5513 of the National Science Foundation and by Grant CA 08250 of the National Cancer Institute, National Institutes of Health.

(2) These compounds are interesting because of the possibility that their anions might show relative stabilization (they are formally 10-π-electron systems). The intervention of an anion in the reduction of a naphthothiete sulfone has been considered: D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964). Several substituted benzothiete derivatives not suited for the preparation of thiete anions have been prepared by the reduction of sulfones: L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965).

(3) H. Staudinger, *Helv. Chim. Acta*, **3**, 862 (1920); E. T. Kaiser and T. F. Wulfers, *J. Amer. Chem. Soc.*, **86**, 1897 (1964); W. J. Middleton, *J. Org. Chem.*, **30**, 1395 (1965); G. Tsuchihashi, M. Yamauchi, and M. Fukuyama, *Tetrahedron Lett.*, 1971 (1967); P. Rioult and J. Vialle, *Bull. Soc. Chim. Fr.*, 2883 (1967); K. Yamada, M. Yoshioka and N. Sugiyama, *J. Org. Chem.*, **33**, 1240 (1968).

(4) B. F. Hrutford and J. F. Bunnett, *J. Amer. Chem. Soc.*, **80**, 2021 (1958).

(5) (a) Reviewed by R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967; (b) L. L. Muller and J. Hamer, "1,2-Cycloaddition Reactions," Interscience Publishers, New York, N. Y., 1967.

(6) For this method of preparation of benzyne, see L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963).

(7) (a) D. T. Mowry, W. H. Yanko and E. L. Ringwald, *ibid.*, **69**, 2358 (1947); (b) A. Senning and S.-O. Lawesson, *Acta Chem. Scand.*, **14**, 2230 (1960); *Arkiv Kemi*, **17**, 261, 387, 489 (1961), and **18**, 95 (1961); (c) W. G. Bentrude and J. C. Martin, *J. Amer. Chem. Soc.*, **84**, 1564 (1962). See also references cited in these publications.