by EPR spectroscopy. The EPR spectra in all cases have been found to be consistent with the respective radical anion EPR spectra reported previously.[2] The intensity of the EPR signals increases continuously with time and the amount of the radical intermediate after a specific time interval is given in Table I. Similarly, LiOBu-*t* and KOBu-*t* have also been found to generate radical anions with polynuclear hydrocarbons, but at a much slower rate compared to that of LDA.

In conclusion, the above preliminary results represent the first definitive proof that reactions of alkali metal amides and alkoxides with organic substrates such as alkyl halides and polynuclear hydrocarbons can proceed via a single electron transfer pathway, although these reactions heretofore have been generally considered to be classic S_N1 or S_N2 processes.

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Registry No. 1, 77400-57-8; lithium diisopropylamide, 4111-54-0; lithium *tert*-butoxide, 1907-33-1; potassium *tert*-butoxide, 865-47-4; trityl chloride, 76-83-5; trityl bromide, 596-43-0; trityl radical, 2216-49-1; lithium butylamide, 41487-32-5; 2,2-dimethyl-5-hexene radical, 71880-21-2; 1,3,3-dimethylcyclopentane radical, 77400-58-9; anthracene, 120-12-7; benzo[*a*]pyrene, 50-32-8; chrysene, 218-01-9; 2,3-benzanthracene, 92-24-0; phenanthrene, 85-01-8; perylene, 198-55-0; anthracene radical anion, 34509-92-7; benzo[*a*]pyrene radical anion, 34505-58-3; chrysene radical anion, 34488-57-8; 2,3-benzanthracene radical anion, 34512-30-6; phenanthrene radical anion, 34510-03-7; perylene radical anion, 34505-65-2.

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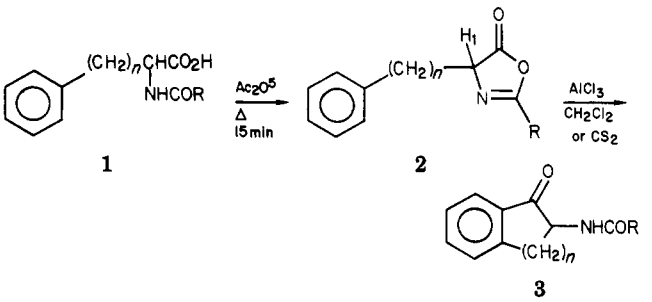
Chiral α-Amino Ketones from the Friedel–Crafts Reaction of Protected Amino Acids

Summary: The Friedel–Crafts reaction employing *N*-methoxycarbonyl-protected α-amino acids is described. This method yields chiral α-amino ketones which can be further used to prepare doubly chiral vicinal amino alcohols.

Sir: Both acyclic and cyclic vicinal amino ketones and alcohols constitute widely studied structural classes of interest as medicinal agents and as intermediates in natural product syntheses.[1,2] One of the most important features of such biologically active compounds is the chirality present at the asymmetric centers; therefore, useful chiral synthetic procedures are continually sought. In this communication, we describe the novel and preparatively useful approach to chiral α-amino ketones via a Friedel–Crafts reaction of N-protected amino acids. This retention of chirality was dependent upon the utilization of the *N*-methoxycarbonyl derivative.

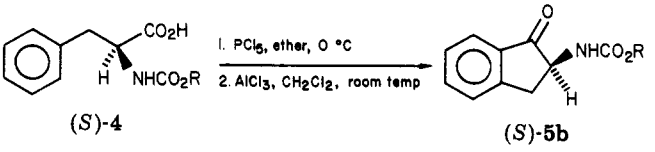
The synthesis of α-amino ketones **3** via azlactones[3,4] worked well (55–90%) for the formation of a five-, six-, or seven-membered ring. However, their known rapid racemization due to the high acidity[6] of H_1 in **2** negated their use in the formation of chiral **3**.[7]



1 2 3

a, n = 1, R = CH_3; **b**, n = 1, R = Ph; **c**, n = 2, R = CH_3; **d**, n = 2, R = Ph; **e**, n = 3, R = CH_3

Recent publications indicated that the replacement of the R substituent of **2** by an OR moiety yielded derivatives less prone to racemization.[9] In addition, these syntheses proceeded through the corresponding acid chloride, an intermediate potentially useful in a Friedel–Crafts cyclization. However, the $AlCl_3$-catalyzed reaction of the acid chloride of Cbz-protected L-phenylalanine (**4a**)[9] produced only intractable tars presumably due to the generation of benzyl carbonium ions from the Cbz substituent.



(*S*)-4 (*S*)-5b

a, R = benzyl; **b**, R = CH_3

Thus, the methoxycarbonyl derivative **4b**,[10] via its acid chloride,[11] produced **5b**[12] in 55–75% yields. The respective chiral precursors gave (*R*)- or (*S*)-**5b**[12] after an aqueous hydrochloric acid workup. Chiral shift NMR analysis[8] with $Eu(hfbc)_3$ revealed none of the opposite enantiomer, indicating a chiral purity of ≥98% for each isomer.[13]

(1) (a) Wasson, B. K.; Gibson, W. K.; Stuart, R. S.; Williams, H. W. R.; Yates, C. H. *J. Med. Chem.* **1972**, *15*, 651. (b) Howe, R.; Crowther, A. F.; Stephenson, J. S.; Rao, B. S.; Smith, L. H. *Ibid.* **1968**, *11*, 1100. (c) Morrow, D. F.; Johnson, P. C.; Tonabi, H.; Williams, D.; Wedding, D. L.; Craig, J. W.; Majewski, R. F.; Braselton, J. P.; Gallo, D. G. *Ibid.* **1973**, *16*, 736. (d) "Antihypertensive Agents"; Engelhardt, E. L., Ed.; American Chemical Society: Washington, DC, 1976. (e) Torchiana, M. L.; Porter, C. C.; Stone, C. A. *Arch. Int. Pharmacodyn.* **1968**, *114*, 118.

(2) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3088. Bowman, R. E.; Evans, D. D.; Guyett, J.; Hagy, H.; Weale, J.; Weyell, D. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 438.

(3) Carter, H. E. *Org. React.* **1946**, *3*, 198.

(4) (a) Cioranescu, E.; Buchen-Barladeanu, L. *Izv. Akad. Nauk SSSR, Otiel. Khim. Nauk* **1961**, 149; *Chem. Abstr.* **1961**, *55*, 18653. (b) Balaban, A. T.; Bally, I.; Frangopol, P. T.; Bacescu, M.; Cioranescu, E.; Buchen-Barladeanu, L. *Tetrahedron* **1963**, *19*, 169.

(5) The acetyl derivatives (R = CH_3) were generated in situ by heating the parent amino acid on a steam bath with acetic anhydride for a few minutes as indicated.

(6) Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2919.

(7) The known, partially chiral (*R*)-**2b** was cyclized to give **3b**, $[\alpha]^{25}_D$ 11.0° (*c* 0.60, dioxane). The optical rotation of (*S*)-**2b** used was $[\alpha]^{25}_D$ 19.78° (*c* 0.45, dioxane) which implies, at best, a 28% enantiomeric excess.[6] Chiral shift NMR analysis[8] indicated an enantiomeric excess for **3b**, so formed, of only 5–10%.

(8) McClure, D. E.; Arison, B. H.; Baldwin, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666.

(9) Jones, J. H.; Witty, M. J. *J. Chem. Soc., Chem. Commun.* **1977**, 281. Jones, J. H.; Witty, M. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3203.

(10) Petri, E. M.; Staverman, A. J. *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 385.

(11) Heating should be kept to a minimum during the concentration process to remove ether and $POCl_3$. Prolonged heating led to the loss of methyl chloride and formation of the *N*-carboxy anhydride derivative.[10] Routinely, solvent was removed at 25–30 °C (25 torr) and the crude acid chloride used immediately in the cyclization step.

(12) All new compounds exhibited spectral and microanalytical or high-resolution mass spectral properties completely consistent with the assigned structures.

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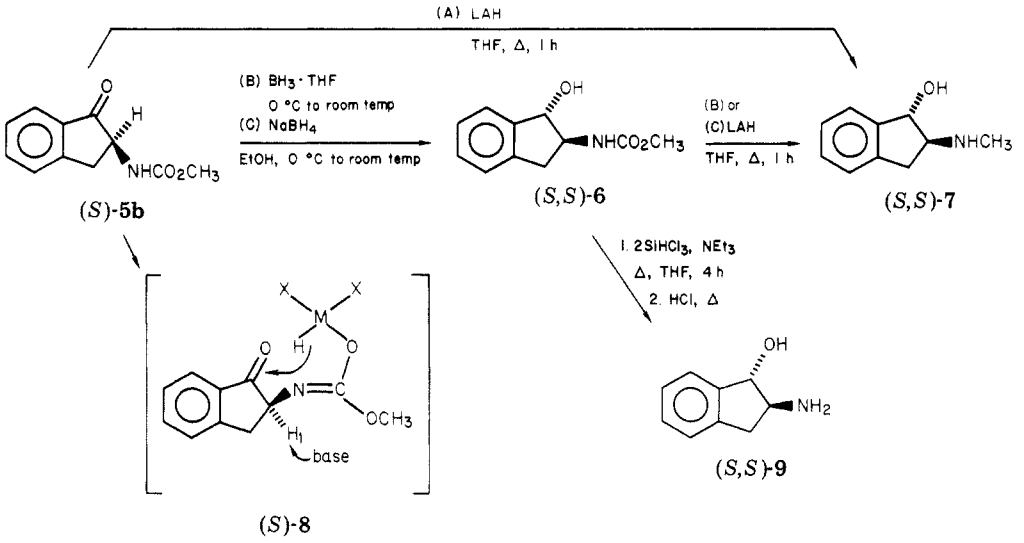
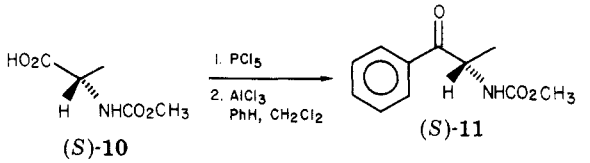
Scheme I



The reduction of **5b** was next examined to determine if chirality could be induced at the prochiral center. The three procedures described below resulted predominantly[14] in the formation of *trans*-**7**[12] in 80–90% yields.[16] A mixture of enantiomers of **7** in a ratio of 88/12 based on rotations and of 86/14 based on chiral shift NMR analysis was formed via route C (Scheme I). Examination of (*S,S*)-**6** derived from routes B or C corroborated these chiral ratios for intermediate **6**. These results suggested that the partial racemization occurred prior to the initial reduction perhaps through an intermediate **8** or its equivalent, a structure potentially sensitive to trace amount of extraneous bases[17] based on analogy with azlactones.[2] Such an intermediate was apparently involved since the reactions exhibited a high preference for the formation of the trans product. Chirally pure (*R,R*)-**7**[12,16] was obtained from (*R*)-**5b** via LAH (A) reduction.

The parent amino alcohol [(*S,S*)-**9**] was also prepared from (*S,S*)-**6** via reaction with trichlorosilane/triethylamine followed by acidic hydrolysis. Since this reaction has been shown to proceed with extremely high chiral retention in other cases,[20] it is highly probable that (*S,S*)-**9** obtained in this manner was enantiomerically pure.[21] In fact, comparison of the optical rotations of (*S,S*)-**9**·HCl and (*R,R*)-**9**·HCl previously obtained via resolution[21] indicated that our material exhibited a higher chiral purity.

In a preliminary investigation of the corresponding intermolecular Friedel–Crafts reaction, the retention of chirality was found to be quite high. The reaction of the acid chloride from *N*-(methoxycarbonyl)alanine [**10** or (*S*)-**10**] and benzene under $AlCl_3$ catalysis provided the acyclic N-protected α-amino ketone [**11** or (*S*)-**11**][12,22] as an oil in 50–60% yield after chromatography. Chiral shift NMR analysis[8] of (*S*)-**11** revealed the presence of 3–4% of the corresponding *R* isomer. The retention of chirality, even under our unoptimized conditions, is therefore synthetically useful in both the intra- and intermolecular modes.



This approach to the synthesis of chiral vicinal amino ketones and alcohols which depends on high enantiomeric retention in the Friedel–Crafts reaction should constitute an extremely valuable addition to the synthetic repertoire in organic and medicinal chemistry. To further explore this methodology, we are presently investigating the generality of the described processes and application to various chiral targets including α-methylnorepinephrine and related species.[1e]

(13) The compounds **5b** had the following properties. Racemic **5b**, mp 141–143 °C. (*S*)-**5b**: mp 164–166 °C; $[\alpha]^{25}_D$ 133.70° (*c* 0.54, $CHCl_3$). (*R*)-**5b**: mp 162–163 °C; $[\alpha]^{25}_D$ −132.05° (*c* 0.44, $CHCl_3$). The methyl signal of the methoxycarbonyl moiety was particularly useful for chiral shift NMR analysis. Occasionally, chiral **5b** was found to be contaminated with trace amounts of the opposite enantiomer (2–3%).

(14) Comparison with the authentic cis isomer[15] related to racemic **7** showed it to be different. The examination of NMR spectra, melting points, and the TLC characteristics of both isomers confirmed the identity of the major product as *trans*-**7** and of the minor product from the LAH reduction as the cis isomer.

(15) (a) Huebner, C. F.; Conoghue, E. M.; Novak, C. J.; Dorfman, L.; Wenkert, E. *J. Org. Chem.* **1970**, *35*, 1149. (b) Huebner, C. F.; Strachan, P. L.; Cahoon, N.; Dorfman, L.; Margerison, R.; Wenkert, E. *Ibid.* **1967**, *32*, 1126.

(16) The products derived from procedures A and/or B had the following characteristics. Racemic **7**, mp 112–114 °C. (*S,S*)-**7**: mp 139–141 °C; $[\alpha]^{25}_D$ 38.9° (*c* 0.47, CH_3OH). (*R,R*)-**7**: mp 139–141 °C; $[\alpha]^{25}_D$ −38.9° (*c* 0.506, CH_3OH). Racemic **6**, mp 178–180 °C. (*S,S*)-**6**: mp 177–179 °C; $[\alpha]^{25}_D$ 23.85° (*c* 0.52, CH_3OH). Chiral shift NMR analysis showed no contamination of the chiral species by the opposite enantiomer (chiral purity ≥98%).

(17) Attempts to eliminate this problem by a change in solvent or counterion for the BH_4^- reduction were unsuccessful. Thus, the reaction of (*S*)-**5b** with $NaBH_4$ in wet THF or in KH_2PO_4-buffered EtOH, with recrystallized $NaBH_4$[18] in EtOH or in dry diglyme, or with $Zn(BH_4)_2$[19] in ether/THF exhibited varying degrees of racemization for intermediate product **6** (25–80% ee).

(18) Brown, H. C.; Mead, E. J.; Rao, B. C. S. *J. Am. Chem. Soc.* **1955**, *77*, 6209.

(19) The presumably less basic $Zn(BH_4)_2$ was generated in situ from commercial $NaBH_4$. (a) Fieser, M.; Fieser, L. F. "Reagents for Organic Synthesis"; Wiley-Interscience: New York, 1972; Vol. 3. (b) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

(20) (a) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781. (b) Pirkle, W. H.; Hockstra, M. S. *Ibid.* **1974**, *39*, 3904.

(21) The absolute configurations of chiral *cis*- and *trans*-**9** have been established: (a) Dornhege, E. *Justus Liebigs Ann. Chem.* **1971**, *743*, 42. (b) The properties of (*S,S*)-**9**·HCl from recrystallized (*S,S*)-**9** were as follows: mp 207–209 °C; $[\alpha]^{25}_D$ 15.1° (*c* 0.58, H_2O) [lit.[21a] for (*R,R*)-**9**·HCl mp 206–209 °C; $[\alpha]^{25}_D$ −13.4° (*c* 0.75, H_2O)].

(22) After flash chromatography, an optical rotation of $[\alpha]^{25}_D$ −10.4° (*c* 0.69, $CHCl_3$) was exhibited by (*S*)-**11**. An additional thick-layer plate chromatography gave (*S*)-**11** with $[\alpha]^{25}_D$ −9.4° (*c* 0.954, $CHCl_3$). Chiral shift NMR analyses showed that both samples were 95–97% (*S*)-**11** [3–5% *R* isomer present].

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Acknowledgment. We thank Ms. Ruth Nutt and Drs. Roger Freidinger and J. R. Huff for helpful discussions during the course of this work.

Registry No. (±)-**4b**, 77357-58-5; (*R*)-**4b**, 67401-65-4; (*S*)-**4b**, 41844-91-1; (±)-**5b**, 77357-59-6; (*R*)-**5b**, 77447-92-8; (*S*)-**5b**, 77447-93-9; (±)-**6**, 77357-60-9; (*S,S*)-**6**, 77447-94-0; (±)-**7**, 77357-61-0; (*R,R*)-**7**, 77447-95-1; (*S,S*)-**7**, 77447-96-2; (*S,S*)-**9**, 32151-02-3; (±)-**10**, 1670-98-0; (*S*)-**10**, 59190-99-7; (±)-**11**, 77357-62-1; (*S*)-**11**, 77447-97-3.

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Biomimetic Approach to *Elaeocarpus* Alkaloids. A Synthesis of (±)-Elaeocarpidine

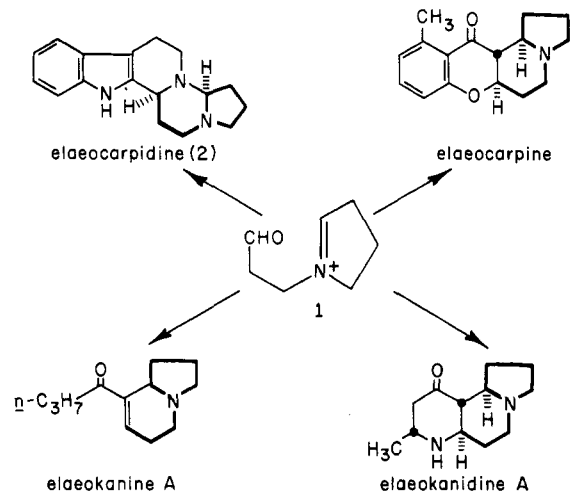
Summary: A short, convergent synthesis of (±)-elaeocarpidine (**2**) is described wherein the final step features a regioselective condensation between tryptamine (**3**) and amine bisacetal **5**. The latter unit is readily assembled from acrolein and cyanide in six steps.

Sir: The *Elaeocarpus* alkaloids comprise a relatively new class of about 20 biogenetically interesting plant products that contain the indolizidine or pyrrolizidine ring system.[1] All of these alkaloids conceivably can arise from a common biosynthetic intermediate, 3-(1-Δ^1-pyrrolinium)propionaldehyde (**1**), which may be derived from ornithine and a three-carbon bioreagent. The incorporation of **1** in several *Elaeocarpus* alkaloids is shown in Scheme I.

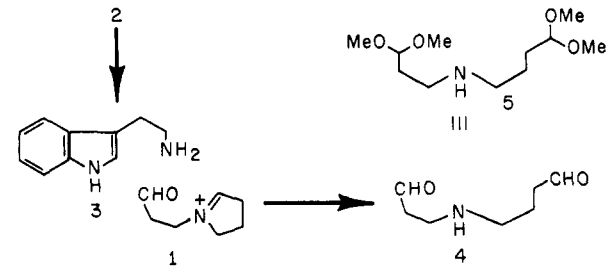
Although several synthesis of selected *Elaeocarpus* alkaloids have been reported,[1-3] none addresses this general biogenesis postulated[4] for these alkaloids. We delineate herein a synthesis of (±)-elaeocarpidine (**2**) involving the in situ generation of **1** and its subsequent condensation with tryptamine (**3**), as shown retrosynthetically in Scheme II.

We anticipated that amine dialdehyde **4**, obtained by hydrolyzing amine bisacetal **5**,[5] would clearly prefer cyclizing to **1** (5-exo-trig[6]) than to the alternative four-membered-ring immonium ion (4-exo-trig) or to reacting intermolecularly with tryptamine (**3**). Furthermore, immonium aldehyde **1**, once formed, is predestined to react with tryptamine (**3**) in the desired regioselective fashion to give elaeocarpidine (**2**).

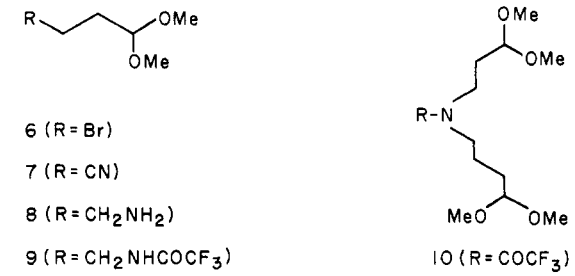
Scheme I



Scheme II



The starting amine bisacetal **5** was synthesized as follows. 3-Bromo-1,1-dimethoxypropane (**6**) was prepared from acrolein (HBr, MeOH, 0 °C; MeOH, 25 °C; 70%)[7] and then converted to 3-cyano-1,1-dimethoxypropane (**7**)[8] (aqueous NaCN, cat. *n*-Bu_3N, reflux, 2 h; 86%).[9] Reduction of **7** to 4-amino-1,1-dimethoxypropane (**8**) was accomplished with $LiAlH_4$ (Et_2O, reflux; 62%)[10] or better with sodium (EtOH, reflux; 77%).[11] Trifluoroacetylation proceeded smoothly to give **9** (TFAA, Et_2O, Et_3N, 0 °C; 25 °C, 2 h; 94%) as an oil [bp 85 °C (0.65 torr)].[12,13]



(1) For a review, see: Johns, S. R.; Lamberton, J. A. *Alkaloids (NY)* **1973**, *14*, 325.

(2) For previous syntheses of **2**, see: (a) Harley-Mason, J.; Taylor, C. G. *J. Chem. Soc., Chem. Commun.* **1969**, 281; (b) Gribble, G. W. *J. Org. Chem.* **1970**, *35*, 1944.

(3) (a) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1972**, *25*, 817. (b) Onaka, T. *Tetrahedron Lett.* **1971**, 4395. (c) Tanaka, T.; Ijima, I. *Tetrahedron* **1973**, *29*, 1285. (d) Howard, A. S.; Meerholz, C. A.; Michael, J. P. *Tetrahedron Lett.* **1979**, 1339. (e) Tufariello, J.; Ali, S. A. *Ibid.* **1979**, 4445. (f) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372. (g) Watanabe, T.; Nakashita, Y.; Katayama, S.; Yamauchi, M. *Heterocycles* **1980**, *14*, 1433. (h) Howard, A. S.; Gerrano, G. C.; Meerholz, C. A. *Tetrahedron Lett.* **1980**, 1373. (i) Watanabe, T.; Nakashita, Y.; Katayama, S.; Yamauchi, M. *Heterocycles* **1981**, *16*, 39.

(4) Onaka, T. *Tetrahedron Lett.* **1971**, 4395.

(5) The acid hydrolysis (pH 5.83) of 4-aminobutyraldehyde diethyl acetal proceeds without nitrogen assistance: Anderson, E.; Capon, B. *J. Chem. Soc., Perkin Trans. 2* **1972**, 515.

(6) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(7) We used a modification of the procedure reported by: Ayer, W. A.; Dawe, R.; Eisner, R.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 473.

(8) This material can also be purchased from ROC/RIC Corporation, Belleville, NJ.

(9) Procedure of: Reeves, W. P.; White, M. R. *Synth. Commun.* **1976**, *6*, 193.

(10) Lukes, R.; Trojanek, J. *Chem. Listy* **1952**, *46*, 383; *Chem. Abstr.* **1953**, *47*, 4282.

(11) Manske, R. H. F. *Can. J. Res.* **1931**, *5*, 598.

(12) Satisfactory analytical data (combustion or high-resolution mass spectrum) were obtained for this new compound.

0022-3263/81/1946-2433$01.25/0