were sepd on a silica gel column (1 × 45 cm) and eluted with EtOAc; 100 mg of the mixt gave 20 mg of the α-chloro ketone IV (mp 129°), which was eluted first (indicated by positive Baker's test) and 75 mg of the α-diazo ketone III (mp 69°).

Data for diazo ketone III were: ir λ_{max}^{Nujol} 2125 (diazo), 1655 cm^{-1} (C=O); nmr ($CDCl_3$) 142 (2-CH_3), 228 (4-CH_2), 155–165 (m) (5-CH_2CH_2), 312 ($COCHN_2$), 92 (CH_3, isopropylidene), 468 (C_6-H); uv λ_{max}^{EtOH} 248 mμ (ε 13,200), 277 (sh, 8600). *Anal.* ($C_{14}H_{17}N_3O_3$) C, H, N.

Data for α-chloro ketone IV were: ir: λ_{max}^{Nujol} 1740 cm^{-1}; nmr ($CDCl_3$) 142 (2-CH_3), 289 (4-CH_2), 470 (C_6-H), 92 (CH_3, isopropylidene), 158–177 (m) (5-$(CH_2)_2$), 242 (5-$COCH_2Cl$). *Anal.* ($C_{14}H_{18}NClO_3$) C, H, Cl, N.

3-Chloro-1-(α⁵-pyridoxyl)-2-propanone Hydrochloride (V).—To the crude CH_2N_2 reaction product (III and IV, 200 mg), dissolved in Et_2O (10 ml), 1 g of concd aq HCl was added within 20 min, and the mixt was stirred at room temp. After standing for 3 hr, the solvent was evapd *in vacuo*, and the oily residue was taken up in a small amt of MeOH and shaken with Darco. After filtration and evapn of the soln, a small amt of MeCN was added till turbidity developed and let crystallize. The yield was 135 mg (60%), mp 149°. The compd gave a positive Baker's test:[6] nmr (DMSO-d_6) 157 (2-CH_3) 289 (4-CH_2), 180 (5-$(CH_2)_2$), 488 (C_6-H), 273 ($COCH_2Cl$). *Anal.* ($C_{11}H_{15}Cl_2NO_3$) C, H, Cl, N.

2,2,8-Trimethyl-4*H*-3-dioxine[4,5-*c*]pyridine-5-acetyl Chloride Hydrochloride (VII).—To a stirred suspension of VI (500 mg, 2.1 mmoles) in CH_3CN (5 ml), $SOCl_2$ (600 mg, 5 mmoles) was added dropwise in *ca.* 5 min. After stirring for 15 min at room temp, the mixt was heated to 50° and was kept at this temp for 30 min. The cooled soln was filtered, and the filtrate was evapd to dryness. The residue crystd after being refluxed with dry Me_2CO. The yield was 350 mg (57%): mp 210–212° dec; ir λ_{max}^{KBr} 1805 cm^{-1} (C=O).

2,2,8-Trimethyl-4*H*-3-dioxino[4,5-*c*]pyridine-5-(3-diazo-2-propanone) (VIII).—The acid chloride VII (380 mg, 1.3 mmoles) was suspended in Et_2O (5 ml), and the suspension was added drop by drop to a stirred CH_2N_2 soln (8–10 mmoles, alcohol free) cooled to −15° with an ice-salt mixt. The soln was filtered to remove a small amt of tarry material. Tlc (EtOAc) of the filtrate showed only 1 spot. After keeping for 45 min at room temp, the reaction mixt was evapd to dryness, and the product was crystd from Et_2O–petr ether, yielding 275 mg (81%) of pale yellow crystals: mp 70°; ir λ_{max}^{KBr} 2110 cm^{-1} (N_2), 1630 cm^{-1} (C=O); nmr ($CDCl_3$) 144 (2-CH_3) 92 (CH_3, isopropylidene) 288 (4-CH_2), 208 (5-CH_2), 314 ($COCHN_2$), 474 (C_6-H). *Anal.* ($C_{13}H_{15}N_3O_3$) C, H, N.

2,2,8-Trimethyl-4*H*-3-dioxino[4,5-*c*]pyridine-5-(3-chloro-2-propanone) Hydrochloride (IX).—The diazo ketone VIII was prepd, as just described, from 380 mg (1.3 mmoles) of the acid chloride VII. The filtered ethereal soln of VIII was evapd to a small vol, and the latter was slowly added to a slight excess of ethereal HCl soln (dry), with stirring. The reaction mixt was stirred for another 15 min, and was kept at 2° overnight. Filtration and washing with a small amt of dry Me_2CO yielded 240 mg (60%) of IX, mp 205° (from Me_2CO). It gave a positive Baker's test:[6] ir λ_{max}^{KBr} 1723 cm^{-1}; nmr (DMSO-d_6) 154 (2-CH_3), 93 (CH_3, isopropylidene), 285 ($COCH_2Cl$), 250 (5-CH_2CO), 298 (4-CH_2), 493 (C_6-H). *Anal.* ($C_{13}H_{17}Cl_2NO_3$) C, H, N.

3-(Chloromethyl)-7-methyl-1,4-dihydropyrano[4,3-*c*]pyridine-3,8-diol (X) and the By-Product (XI).—Compd IX (61 mg, 0.2 mmole) was dissolved in 0.2 *N* HCl (7 ml), and the soln was stirred at room temp for 25 hr. Tlc indicated the formation of a new compd (R_f 0.42 in 80:20 $CHCl_3$–MeOH), giving a pos Gibbs test.

The solvent was evapd to dryness, and the residue was taken up in MeOH and again spotted on tlc. In addition to the previous spot, another spot (R_f 0.72) was obtained, which was also Gibbs pos.

The 2 products were separated by prep tlc. The compd with the lower R_f value (0.42) was extd from the tlc scrapings with MeOH. The MeOH soln was evapd, and the residue was treated with Me_2CO, giving 25 mg (54%) of product (X), mp 189 (from Me_2CO–MeOH). Baker's test on the compd was negative and the compd was not retarded by boric acid strip on tlc plate,[12] indicating that the 4-CH_2OH group is not free. Its ir spectrum shows no CO absorption; nmr (DMSO-d_6) 141 (7-CH_3), 466 (C_5-H), 285 (C_1-H_2), 221 (C_4-H_2), 170 (3-CH_2Cl) (doublet, J = 3 cps). *Anal.* ($C_{10}H_{12}ClNO_3$) C, H, N, Cl.

The by-product of high R_f value (0.72) was isolated from the plate, but the small amt of material obtained (15 mg) was not adequate to establish the structure unequivocally as 3-(chloromethyl)-7-methyl-1*H*-pyrano[4,3-*c*]pyridin-8-ol (XI): ir λ_{max}^{KBr} 1640 cm^{-1} (C=C); nmr (DMSO-d_6) 141 (CH_3), CH_2 groups (singlets) at 257 and 312, 1 H peaks at 367 and 462 cps.

The by-product is formed directly from compd X by treatment with 0.2 *N* HCl. Tlc of the product indicated a mixt of XI and X after 1 day at room temp. It was impossible, however, to achieve complete conversion of X to XI. Likewise a mixt of X and XI was obtd when the diazo ketone VIII was treated with 38% HCl.

3-(Chloromethyl)-7-methyl-1,4-dihydropyrano[4,3-*c*]pyridine-3,8-diol Diacetate (XII).—Compd X (35 mg, 0.15 mmole) was dissolved in a 4:1 mixt of pyridine and Ac_2O, and the resulting mixt was kept at room temp for 3 days. It was evapd *in vacuo*, treated with an $NaHCO_3$ soln, and extd with Et_2O. After drying ($MgSO_4$), the EtOAc was removed *in vacuo*, and the residual oil was dissolved in Et_2O–petroleum ether. The yield of cryst material was 25 mg (53%): mp 112–113° (from Et_2O–petr ether); ir λ_{max}^{KBr} 1740, 1760 cm^{-1} (C=O); nmr ($CDCl_3$) 494 (5-H), 142 (7-CH_3), 139 (8-OCOC**H**$_3$), 118 (3-OCOC**H**$_3$), 118 (1-H_2) (s), 254 (3-CH_2Cl) (d, J = 11 cps), 239 (d, J = 11 cps), 211 (4-H_2) (d, J = 17 cps) 181 (d, J = 17 cps). *Anal.* ($C_{14}H_{16}NClO_5$) C, H, N.

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Microsomal 3-Hydroxylation of 1,4-Benzodiazepines[1]

WOLFGANG SADÉE,[2] WILLIAM GARLAND, AND NEAL CASTAGNOLI, JR.*

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94122

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Liver microsomal oxidations of a variety of substrates are known to be mediated by a mixed function oxygenase system which utilizes molecular oxygen and requires NADPH as a reducing equivalent.[3] In the case of tertiary amines **1** it has been proposed that microsomal oxygenation leads to the formation of a carbinolamine **2**, which, because of its inherent instability, decomposes spontaneously to the observed products, the secondary amine **3** and the aldehyde **4**.[4] Evidence consistent with this pathway was recently reported by McMahon[5] who studied the incorporation of ^{18}O-enriched O_2 into benzaldehyde formed from the microsomal oxidative dealkylation of 1-benzyl-4-phenyl-4-carbethoxypiperidine. In order to minimize exchange

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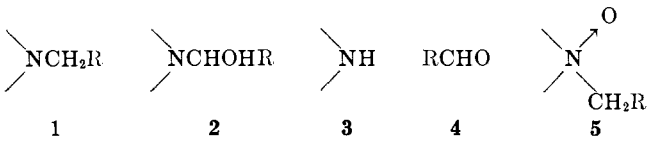
(2) NATO Postdoctoral Research Fellow, 1969–1970.

(3) A recent symposium on this subject has been published: "Microsomes and Drug Oxidations," J. R. Gillette, Ed., Academic Press, New York, N. Y., 1969.

(4) J. R. Gillette, *Advan. Pharmacol.*, **4**, 219 (1966).

(5) R. E. McMahon, H. W. Culp, and J. C. Occolowtz, *J. Amer. Chem. Soc.*, **91**, 3389 (1969).

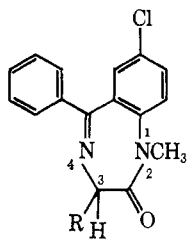
of the C=O with H_2O, aldehyde dehydrogenase was employed to convert the benzaldehyde to the nonexchangeable benzyl alcohol, analysis of which showed 25% of the theoretical incorporation of ^{18}O.



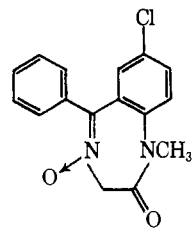
1 2 3 4 5

On the basis of these results McMahon suggested that microsomal oxidative dealkylation of tertiary amines involves direct C oxidation of **1**. An alternative proposal invokes initial attack by the oxidizing species on N to form a tertiary amine *N*-oxide **5** which subsequently is transformed to **2**.[6] Consistent with this mechanism is the known metabolic N-oxidation of a number of tertiary amines[6] and the ease with which amine *N*-oxides can be made to undergo nonenzymatic conversion to **3** and **4**.[7] Furthermore, Ziegler, *et al.*,[8] have demonstrated that a hog liver microsomal preparation will affect the demethylation of $PhN(O)Me_2$ several times more rapidly than $PhNMe_2$, suggesting an intermediary role for the *N*-oxide.

To further investigate the mechanism of microsomal oxidations of N-containing compounds, we have studied the conversion of the 1,4-benzodiazepine **6** to the 3-OH derivative **7** by a rat liver preparation.[9] In contrast to the carbinolamine **2**, the carbinolimine **7** is stable and isolable. Furthermore, since incubation of unlabeled **7** with $[^{18}O]H_2O$ (10 atom %) did not result in any detectable exchange, this system provides an opportunity to quantitate the incorporation of oxygen from ^{18}O-enriched O_2 and H_2O.



6, R = H
7, R = OH
9, R = OAc



8

The metabolite **7** was isolated by preparative tlc from incubates employing alternately $[^{18}O]H_2O$ (10 atom %) and $[^{18}O]O_2$ (90.9 atom %).[10] In order to minimize ion beam fluctuations, quantitative estimations of the ^{18}O-enrichment of **7** were obtained by high resoln peak height measurements of ions occurring at $M^+ + 2$ (*m/e* 302). At a static resoln of 42,500 (5% valley definition) the *m/e* 302 ion of unlabeled **7** displayed peaks corresponding to $^{12}C_{16}{}^{1}H_{13}{}^{14}N_2{}^{16}O_2{}^{37}Cl$, $^{12}C_{16}{}^{1}H_{13}{}^{15}N_2{}^{16}O_2{}^{35}Cl$, $^{12}C_{16}{}^{1}H_{13}{}^{18}O{}^{16}O{}^{35}Cl$, and $^{12}C_{16}{}^{13}C_2{}^{1}H_{13}{}^{14}N_2{}^{16}O_2{}^{35}Cl$, with measured abundances within 0.5% of the calcd values. Consequently, peak height measurements of the ions $^{12}C_{16}{}^{1}H_{13}{}^{18}O{}^{16}O{}^{35}Cl$ and $^{12}C_{16}{}^{1}H_3{}^{16}O_2{}^{37}Cl$ coupled with the established ratio of $^{35}Cl/^{37}Cl$ provides a means to determine accurately the ^{18}O incorporation into **7**.

Mass spectral analysis of **7** isolated from the $[^{18}O]H_2O$ incubation showed no detectable enrichment of the $^{12}C_{16}{}^{1}H_{13}{}^{14}N_2{}^{18}O{}^{16}O{}^{35}Cl$ ion, whereas analysis of **7** isolated from the $[^{18}O]O_2$ incubation showed an enrichment of this ion corresponding to an ^{18}O incorporation of 79% of theoretical. Consistent with the previously reported fragmentation pattern of **7**,[11] the ^{18}O-labeled metabolite lost the C(3) as a formyl radical to give the base peak at *m/e* 271. The ratios of the peak heights at *m/e* 271/273 for ^{18}O-labeled and unlabeled **7** were identical, establishing that the ^{18}O was incorporated exclusively at C(3).

Despite this somewhat low $[^{18}O]O_2$ incorporation value, which may have resulted from contamination of the prepared gas mixture with atmospheric O_2 or incomplete displacement of dissolved O_2 in the incubation mixture, it must be concluded that molecular O_2 and not H_2O is the principal source of the C(3)-OH function in **7**. This result confirms and extends to an imino system the observation reported by McMahon[5] that oxidative metabolism of nitrogenous bases follows a pathway requiring introduction of molecular O_2 into the substrate. If an *N*-oxide type intermediate participates in this oxidative pathway, it must undergo a rearrangement which does not involve extensive O exchange with water. Attempts to demonstrate a possible intermediary role for the nitrone **8** in the metabolic conversion of **6** to **7** have failed. Thus **8** could not be detected in the incubate of **6**. In addition, attempts to demonstrate the formation of the OH metabolite **7** in an incubation mixture of **8** have failed. However, the participation of an enzyme bound species similar to **8** in which O undergoes an intramolecular migration from N to C cannot be ruled out. In a separate study,[12] we have shown that the treatment of **8** with ^{18}O-enriched Ac_2O[13] affects an exclusively intramolecular conversion of **8** to **9**. Although the label is "scrambled" between the 2 O atoms of the AcO group of **9**, the chemical feasibility of the intramolecular N to C migration of O in this nitrone has been demonstrated. The possibility that this reaction in any way models the enzyme-mediated oxidation of **6** remains an open issue.

Experimental Section

Mass Spectroscopy.—Mass spectra were obtained on an AEI MS 902 using a direct insertion probe. The electron-ionizing voltage was 70 eV at an ionizing current of 485 mA. The source temp was 210°.

Incubation Studies.—The prepn of the 10,000*g* rat liver supernatant followed the procedures described by Schwartz and Postma.[9] The incubation mixt (30 ml, containing 1 mg of **6**) for the incorporation of ^{18}O-enriched mol O_2[10] was purged with O_2-free N_2 prior to the addn of the liver prepn (3 ml) and introduction of the ^{18}O-enriched O_2 to minimize diln with atmospheric O_2. For the ^{18}O-enriched H_2O study, the incubation medium was prepd with 10 ml of $[^{18}O]H_2O$ (BioRad Laboratories, 10 atom %) to which was added the liver prepn (1 ml) and **6** (300 μg). The

(6) For a review of the role of *N*-oxides in metabolism, see M. H. Bickel, *Pharmacol. Rev.*, **21**, 325 (1969).

(7) G. A. Russell and G. J. Mikol in "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1968, pp 185–194.

(8) D. M. Ziegler and F. H. Pettit, *Biochem. Biophys. Res. Commun.*, **15**, 188 (1964).

(9) M. A. Schwartz and E. Postma, *Biochem. Pharmacol.*, **17**, 2443 (1968).

(10) Our analysis of the ^{18}O-enriched mol O_2 obtd from Miles Lab. Inc. (92.50 atom % $[^{18}O]O_2$) showed 81.8% $^{18}O^{18}O$ + 18.2% $^{18}O^{16}O$, equivalent to 90.9% ^{18}O.

(11) W. Sadée, *J. Med. Chem.*, **13**, 475 (1970).

(12) N. Castagnoli, Jr., and W. Sadée, unpublished result.

(13) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1961 (1962).

prepn of the incubation mixt of **8** gave a final soln of 1 mg/30 ml. Each mixt was incubated for 30 min in a shaker at 37°.

Isolation Procedures.—Each incubation mixt was extd twice with Et_2O. The combined ethereal layers were washed twice with H_2O, dried (Na_2SO_4), and evapd to dryness under vacuum. The residue was dissolved in MeOH (spectrograde) and was applied to analytical precoated tlc plates (GF 254 Merck, 20 × 20 cm, 0.25 mm). Sepn of **6** (R_f 0.69) from the metabolites **7** and desmethyldiazepam (R_f 0.45) was achieved in $CHCl_3$–Me_2CO–EtOH (8:1:1). In order to resolve desmethyldiazepam from **7** the R_f 0.45 band was eluted with MeOH (spectrograde) and was subjected to a second tlc sepn using C_6H_6–EtOAc (5:1). Desmethyldiazepan (R_f 0.1) and **7** (R_f 0.2) were clearly sepd. Compd **7** was eluted with MeOH (spectrograde) in prepn for mass spectral analysis. Estimates of the yield of **7** by glpc analyses[14] indicated that about 50 μg was obtd from the $[^{18}O]H_2O$ incubation and 150 μg from the $[^{18}O]O_2$ incubation.

(14) W. Sadée and E. van der Kleijn, *J. Pharm. Sci.*, in press.

Synthesis and Pharmacology of Some N-Substituted Derivatives of 1-Amino-4,6-dimethylbenzocyclobutene

ARTHUR A. SICILIANO*[1] AND KARL A. NIEFORTH

Medicinal Chemistry Laboratories, Pharmacy Research Institute, University of Connecticut, Storrs, Connecticut 06268

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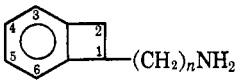
The potential medicinal applicability of benzocyclobutenes has been reported predominantly within the patent literature.[2-11] Early studies concentrated on the manipulation of 1-aminoalkylbenzocyclobutenes.



Since patents do not deal heavily in structure–activity relationships, it remained for Skorcz[2,4-6] to provide initial insight into the relative pharmacological activity of these compounds.

We describe below the synthesis and physiological action of precursors and derivatives of the heretofore unknown 1-amino-4,6-dimethylbenzocyclobutene·HCl.

Biological Evaluation.—Testing protocol consisted of suspending or dissolving all drugs in 0.5% methylcellulose soln followed by ip administration to white mice (17–20 g) at a dosage level of 100 mg/kg. Three animals were tested simultaneously with constant observation for 1 hr subsequent to injection and every 30 min thereafter for 2 hr. A final reading was taken at +24 hr.

In addition to testing the base moiety, its precursors, and derivatives, biological tests were preformed on other structurally similar compounds: 1-aminobenzocyclobutene·HCl (XII),[12] 1-indanamine·HCl (XIII),[13] benzylamine·HCl (XIV), and phenethylamine·HCl (XV).

Results are reported in Table I.

TABLE I
PHARMACOLOGIC RESULTS[a]

Compd	CNS stim	CNS depression	Biphasic act.	Other
III	0−+	−	−	
IV	−	+++	−	Transient action
V	++	−	−	Hypothalamic depression
VI	−	+++	−	Skel musc relaxant
VII	−	+	−	Skel musc relaxant
VIII	−	+	−	Skel musc relaxant
IX	−	−	++	
X	−	−	++	
XI	−	−	+	Tranquilization
XII	−	+	−	Spinal stimulant
XIII	+	−	−	Hypersensitivity
XIV	0	0	−	
XV	++	−	−	Psychotropic

[a] M. H. Malone and R. C. Robichand, *Lloydia*, **25**, 320 (1962).

The newly synthesized base compd V appears to be a moderately potent CNS stimulant differing in activity from its nonmethylated relative XII which exhibited central depression. Both side-chain fusion to the benzene ring and aromatic alkylation seem to effect the nature and strength of biological activity in this series. Acylation of V results in a nonspecific CNS depression on the order: *N*-Ac ≫ *N*-propionyl ≳ *N*-butyryl while arylation provides biphasic central action (stimulation–depression) with the latter predominating.

Experimental Section[14]

Trichloromethylmesitylene (I).—A modification of the method of Hart and Fish[15] was employed. To a stirred slurry of 670 g (5.0 moles) of anhyd $AlCl_3$ in CCl_4 (3 l.) was added over a 3-hr period 300 g (2.31 moles) of commercial mesitylene. The mixt was maintained at 40° for 4 hr and, upon cooling, poured into 4 l. of cold 5% HCl. The org layer was then washed well (H_2O), evapd *in vacuo* to 1 l., dried (Na_2SO_4), and distd to provide 414 g (69%) of product: bp 119–121° (4 mm); lit.[15] 126° (5 mm).

1,1-Dichloro-4,6-dimethylbenzocyclobutene (II).—A scale-up of a reported procedure[16] was utilized. I (50 g, 0.21 mole) was placed under N_2 in a flask fitted with a condenser and maintained at 170°. After 9 hr, 71% (of theoretical) HCl had evolved. Cooling, filtration, and recrystn (pentane) of the ppt afforded 6.5 g (67%) of white cubes: mp 50–52°; lit.[16] 55–60°.

4,6-Dimethylbenzocyclobutenone (III).—II (26.0 g, 0.13 mole) was dissolved in 200 ml of EtOH and treated with a soln of 4.88 g (0.029 mole) of $AgNO_3$ in 750 ml of EtOH (80%) while briskly stirring. The suspension was warmed (0.5 hr), filtered, and flash-evapd and the residue was extd with petr ether. The ext was dried (Na_2SO_4) and evapd in a stream of dry air giving 16.0 g (85%) of solid yellow ketone: mp 40–42°; lit.[15] 45–46°.

4,6-Dimethylbenzocyclobutenoxime (IV).—To a cooled soln of NaAc (5.6 g, 0.041 mole) and NH_2OH·HCl (4.8 g, 0.069 mole) in

(1) Present address: Gillette Toiletries Company, South Boston, Mass. 02106.

(2) J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8**, 255 (1965).

(3) Ciba, Ltd., Belgian Patent 635,901, 1964; *Chem. Abstr.*, **62**, 3987*f* (1965).

(4) J. A. Skorcz and J. E. Kaminski, *J. Med. Chem.*, **8**, 732 (1965).

(5) C. Kaiser and C. L. Zirkle, U. S. Patent 3,149,159, 1964.

(6) J. A. Skorcz, J. T. Suh, C. I. Judd, M. Finkelstein, and A. C. Conway, *J. Med. Chem.*, **9**, 656 (1966).

(7) Colgate-Palmolive Co., German Patent 1,235,903, 1967; *Chem. Abstr.*, **68**, 59371 (1968).

(8) J. E. Robertson and J. A. Skorcz, U. S. Patent 3,308,157, 1967.

(9) Ciba, Ltd., Swiss Patent 454,130, 1968.

(10) J. A. Skorcz, U. S. Patent 3,359,300, 1967; *Chem. Abstr.*, **68**, 104832 (1968).

(11) J. A. Skorcz, U. S. Patent 3,408,391, 1968.

(12) L. Horner, W. Kormše, and K. Muth, *Chem. Ber.*, **91**, 430 (1958).

(13) "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1965, p 148.

(14) Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are corrected. Spectra (ir) were recorded on a Perkin-Elmer PE-21 spectrophotometer while nmr data were obtained on a Varian A-60 instrument. Elemental analyses were performed by Baron Consulting Co., Orange, Conn., and are indicated only by symbols when within ±0.4% of theoretical values.

(15) H. Hart and R. W. Fish, *J. Amer. Chem. Soc.*, **83**, 4460 (1961).

(16) H. Hart, J. A. Hartlage, R. W. Fish, and R. F. Rafos, *J. Org. Chem.*, **31**, 2244 (1966).