evidence of reaction. After the mixture had cooled to room temperature, ethanol (50 ml) and water (50 ml) were added, and the mixture was boiled gently. It was then cooled and extracted with ether (three 75-ml portions). The ether extracts were concentrated to about 75 ml and vacuum distilled. The distillate (51.2 g, 81% crude), which was collected at 60–110° (1 mm), came over mostly light yellow and finally light red. Fractional distillation gave four fractions (all boiling points are at 1 mm): (1) 6.10 g, bp 60–64°, $n^{21.8}$D 1.5838 (which did not yield a crystalline picrate); (2) 6.19 g, bp 64–90°, $n^{21.5}$D 1.5942; (3) 13.70 g, 22%, bp 91–96°, $n^{20.8}$D 1.6012; and (4) 17.69 g, 28%, bp 96–101°, $n^{20.4}$D 1.6002. Fractions 3 and 4, which gave picrates as brick red needles, mp 158–161° dec uncor and 162–163° dec uncor, respectively, were combined and redistilled (at 1 mm), giving four more fractions: (5) 0.68 g, 1%, bp 80–90°, $n^{23.5}$D 1.5963; (6) 2.55 g, 4%, bp 90–94°, $n^{23.5}$D 1.5998; (7) 0.94 g, 1%, bp 94–96°, $n^{23.5}$D 1.6019; (8) 20.09 g, 32%, bp 97–100°, $n^{23.5}$D 1.6023; total of fractions 6–8 was 5.58 g, 37%; lit. 36%,[72] bp 94–96° (1 mm),[72] 180° (20 mm),[73] 275° (atm).[74] Fraction 8 gave a picrate as brick red needles: mp 164–165° dec; lit. mp 155–156° dec,[75] 158–159°,[71,76] and 164.5°.[72] Fraction 7 was analyzed: $\lambda_{max}^{95\%\ EtOH}$ 223 mμ (log ε 4.56), 273 (3.97), 278 infl (3.95), and 289 infl (3.76); ν_{NH} 3330 s cm^{-1} neat. Elemental analyses have not previously been reported.

Anal. Calcd for $C_{10}H_{11}N$ (145.20): C, 82.72; H, 7.64; N, 9.65. Found: C, 82.39; H, 7.63; N, 10.27.

2,4-Dimethylindole-3-carboxaldehyde (with R. J. Sperley, 1962).—The procedure is that of James and Snyder[49] for formylation of indole to indole-3-carboxaldehyde. Phosphorus oxychloride (49.1 g, 0.320 mole) was added dropwise with vigorous stirring over a period of 35 min to N,N-dimethylformamide (32.4 g, 0.438 mole) cooled to 0° in an ice–salt bath. After about one-half the phosphorus oxychloride had been added, the solution began to turn faintly pink. After the addition was complete, a solution of 2,4-dimethylindole (46.0 g, 0.317 mole) in N,N-dimethylformamide (32.4 g, 0.438 mole) was added dropwise with stirring over a period of 65 min while the reaction temperature was kept below 5°. After about one-fourth of the solution had been added, the reaction solution turned a milky pink. After the addition was complete, the ice–salt bath was removed and the reaction was kept at 35–38° in a water bath for 1 hr, during which the solution turned light yellow. The reaction solution was then recooled in the ice–salt bath for 10 min, and then snow (110 g) was added, causing the resulting mixture to turn light tan and thicken to a slurry. The mixture was then washed with water (50 ml) onto ice (64 g), giving a red-brown solution. A solution of sodium hydroxide (128 g, 3.20 moles) in water (341 ml) was then added dropwise with stirring until about one-half the alkaline solution had been added and the mixture had changed from red-brown to yellow, after which the remaining half was added rapidly. The mixture was then heated rapidly to boiling, but a tan precipitate remained undissolved. The mixture was then cooled to room temperature and kept in a refrigerator overnight. Addition of water and filtration removed the precipitate as a tan powder (48.8 g, 89%), mp 175–181°. Recrystallization from methanol–water, with charcoal, gave a whitish powder: mp 191–192°; $\lambda_{max}^{95\%\ EtOH}$ 216 mμ (log ε 4.52), 248 (4.29), 268 (4.02), and 313 (4.07); ν_{NH}^{Nujol} broad absorption around the Nujol peak and $\nu_{C=O}^{Nujol}$ 1621 s cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO$ (173.21): C, 76.27; H, 6.40; N, 8.08. Found: C, 76.09; H, 6.37; N, 8.33.

2,3,4-Trimethylindole (with R. J. Sperley, 1962).—The procedure is a modification of that of Leete and Marion[49] for reduction of indole-3-carboxaldehyde to skatole. A solution of lithium aluminum hydride (10.0 g, 0.264 mole) in anhydrous ether (100 ml) was added slowly to a solution of 2,4-dimethylindole-3-carboxaldehyde (25.0 g, 0.144 mole) in anhydrous ether (400 ml) under dry nitrogen. A vigorous reaction took place at first, followed by gentle bubbling. The solution was refluxed for 3 hr under nitrogen, and then moist ether (200 ml) was added to decompose unreacted hydride. The resulting yellow solution was filtered and the ether was distilled off. The residual yellow oil solidified upon cooling, to a mass of yellowish white plates (21.4 g, 93%), mp 57–62°. Recrystallization from methanol–water yielded white plates, mp 63–64.5°, which turned yellow quickly when dried in air, but seemed to keep better when dried in a vacuum desiccator over phosphorus pentoxide: $\lambda_{max}^{95\%\ EtOH}$ 230 mμ (log ε 4.51), 278 infl (3.84), 284 (3.86), and 292 infl (3.77). The infrared spectrum in Nujol was identical with that of the sublimed sample described below.

Anal. Calcd for $C_{11}H_{13}N$ (159.22): C, 82.97; H, 8.23; N, 8.80. Found: C, 82.03; H, 8.18; N, 8.51.

Sublimation of the crude sample in the absence of light at 65° (0.05 mm) for 48 hr gave a light pink solid, mp 56–58°, ν_{NH}^{Nujol} 3380 s cm^{-1}. The compound is very sensitive to air oxidation.

Anal. Found: C, 83.17; H, 7.61; N, 8.62.

(73) G. Plancher and R. Ciusa, *Atti Accad. Naz. Lincei Rend. Classe Sci. Fis. Mat. Nat.*, [5] **15**, 447 (1906); *Chem. Zentr.*, II, 1847 (1906); *J. Chem. Soc.*, **92**, 80 (1907).

(74) M. Dennstedt, *Chem. Ber.*, **24**, 2559 (1891).

(75) M. Dennstedt, *ibid.*, **21**, 3429 (1888).

(76) H. Booth, A. W. Johnson, and F. Johnson, *J. Chem. Soc.*, 98 (1962).

Pyridylmethylnaphthalene and Pyridylmethylindan Derivatives

DON M. LYNCH AND WAYNE COLE

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

Received May 25, 1966

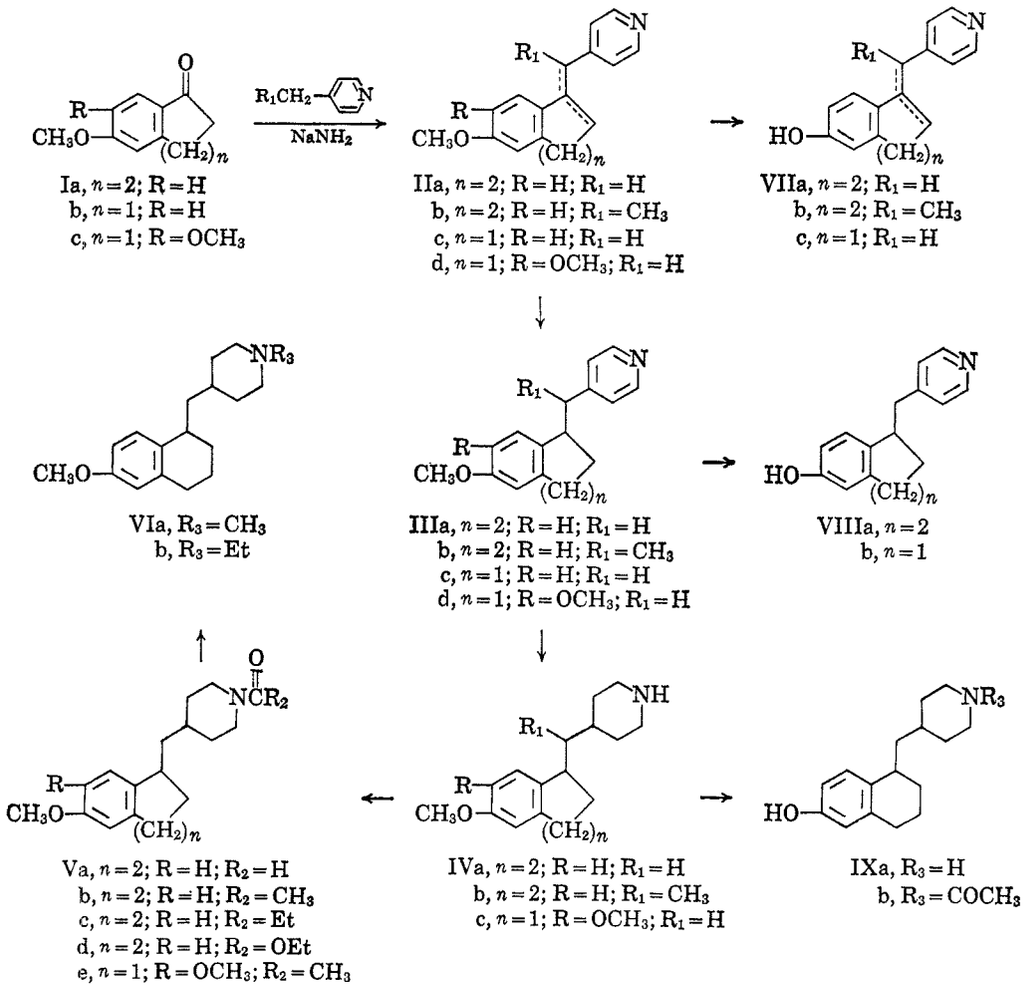
Several pyridylmethylnaphthalene and piperidylmethylnaphthalene derivatives, and the corresponding indan analogs, were made for evaluation as endocrine agents. These ring systems were obtained by condensing the sodium salt of an alkylpyridine with a 1-tetralone or 1-indanone, followed by elimination and hydrogenation steps as required. Restricted rotation about the C–N amide bond of the N-acylpiperidyl compounds is evidenced by long-range shielding effects shown by nmr.

A series of pyridine and piperidine derivatives having the tricyclic ring system shown by II was made. These compounds were among those desired for biological evaluation as possible endocrine agents because their molecules offered semirigid structures in which two polar groups may assume a spacing of about 11 A, as occurs in the natural estrogens. The synthesis of a number of these structures was achieved by condensing the sodium salt of γ-picoline or 4-ethylpyridine with a substituted 1-tetralone Ia or 1-indanone Ib,c. The intermediate tertiary alcohols were not isolated but readily dehydrated to the unsaturated compounds. Although the condensation of α-picoline with 1-indanone is known to give a tertiary alcohol,[1] it appears that the presence of a methoxy substituent *para* to the carbinol function, as is present in the systems under study, facilitates the dehydration of 5-methoxy-1-indanol.[2]

The condensation of γ-picoline with 6-methoxy-1-tetralone (Ia) gave isolable material containing roughly a 50:50 mixture of the endocyclic and exocyclic double-bond isomers IIa. Integration of the vinyl hydrogen triplet at 347 cps in the nmr spectrum of the endocyclic

(1) J. Sam, J. N. Plampin, and D. W. Alwani, *J. Org. Chem.*, **27**, 4543 (1962).

(2) D. G. Lindsay, B. J. McGreevy, and C. B. Reese, *Chem. Commun.*, **16**, 379 (1965).



isomer, and comparison with the integration of the 513-cps absorption due to the hydrogens *ortho* to the nitrogen atom, permitted an approximation of the composition of this mixture. The two isomers could not be separated by fractional crystallization; however, thin layer chromatography indicated slightly different R_f values for the isomers.

In contrast with the above case, the condensation of γ-picoline with 5-methoxy-1-indanone (Ib) or 5,6-dimethoxy-1-indanone (Ic) gave products (IIc and IId, respectively) containing the exocyclic double-bond isomers exclusively. The reaction of 4-ethylpyridine with 6-methoxy-1-tetralone gave a single isomer IIb in which the double bond is endocyclic.

The unsaturation in the five-membered ring system compared with that in the six-membered ring system, except for the case of IIb, appears to be in agreement with Brown's generalization[3] regarding the formation of *exo* and *endo* double bonds in five- and six-membered ring compounds.[4,5]

Factors such as conjugation between the two aromatic rings and steric hindrance play an important role in determining the relative stability of the isomeric unsaturated systems under study. Thus an exocyclic double-bond isomer IIb would, because of the planar requirement of the ethylenic group, contain large steric interaction between the 8-hydrogen atom of the naphthalene ring and the methyl group (or with the pyridine ring, in the geometric isomer). The endocyclic isomer IIb, actually isolated, does not have these planar structure and strain requirements.

Demethylation of these condensation products with pyridine hydrochloride provided the indanol VIIc and the naphthols VIIa and VIIb having unsaturation corresponding to that of their methyl ethers. Hydrogenation of the methyl ethers with a palladium catalyst afforded the corresponding dihydro derivatives III. The indanol VIIIb and the naphthol VIIIa were obtained by demethylation of the corresponding methyl ethers.

Hydrogenation of the dihydro derivatives with a rhodium catalyst led to the 4-piperidyl derivatives IV. Demethylation of the hydrochloride of IVa with pyridine hydrochloride provided the phenolic amine IXa, which upon acetylation and work-up with base gave the phenolic amide IXb.

The N-acyl derivatives (V) were obtained by treating IVa, IVb, and IVc with formic acid–acetic anhydride, acetyl chloride, propionyl chloride, or ethyl chloroformate. The tertiary amines VIa and VIb were formed on reduction of the corresponding amides Va and Vb with diborane.

The nmr spectra of the N-acyl compounds V and IXb are worthy of comment. In 1-acetylpiperidine the

(3) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(4) For a criticism of Brown's generalization, see R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **80**, 1424 (1958).

(5) For two studies regarding the relative stability of endocyclic and exocyclic olefins, see E. Gil-Av and J. Shabtai, *Chem. Ind.* (London), 1630 (1959); A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, and Z. Jacura, *J. Am. Chem. Soc.*, **81**, 3153 (1959).

hydrogens α to the nitrogen atom give a broad signal at about 210 cps (half-width 7 cps). In this molecule the shielding of axial and equatorial protons α to nitrogen is averaged to a single value because of rapid ring inversions of the two chair conformations. In piperidines such as V, which have a substituent in the 4 position, one conformation predominates and separate signals for axial and equatorial protons are observed. The axial protons usually absorb at higher fields.[6] A methyl substituent in the piperidines is sufficient for this effect to be observed.[7]

Compound Vb gives a broad, low-field equatorial proton doublet at 275 cps ($J_{gem} \cong 13$ cps) and a doublet at 225 cps (also an equatorial proton) that is partially hidden by the aromatic methoxy signal. The axial protons α to the nitrogen atom are hidden in the benzylic hydrogen region around 140–200 cps. This magnetic nonequivalence of the equatorial protons must result from restricted rotation about the C–N amide bond which possesses partial double-bond character.[8] That is, there is a rotational energy barrier existing between two equally preferred conformations (Figure 1),

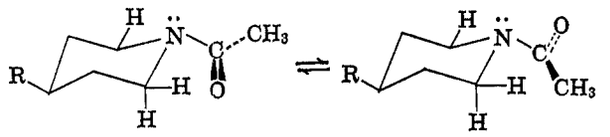


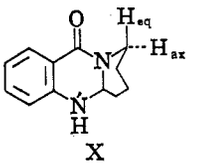
Figure 1.

which provide for maximum overlap of the nitrogen lone pair with the π orbital of the carbonyl group. In each of these preferred conformations one equatorial hydrogen is on the same side as the carbonyl group (*cis*) and the other equatorial hydrogen is *trans* to the carbonyl group. Thus, the deshielding effects due to the anisotropy of the amide group are unequal and give rise to the two absorptions observed. The *cis* equatorial hydrogen is in the plane of the carbonyl group,[9] and probably gives rise to the low-field absorption at 275 cps, while the *trans* equatorial hydrogen being away from the carbonyl group absorbs at higher field.

That the signal at 225 cps is due to an equatorial proton rather than an axial one is substantiated by the nmr spectrum of IXb in which the interfering methoxy group has been removed. This spectrum reveals a broad one-proton doublet at 225 cps ($J_{gem} \cong 13$ cps) with an intensity distortion similar to that of the 275-cps absorption, being characteristic of an equatorial proton coupled to an axial proton at higher field. A similar pattern has been observed for the equatorial protons β to the nitrogen atom in 4-t-butylcyclohexanone oxime.[10]

The nmr spectra of compounds Va, Vc, and Ve are similar to those described above. The nmr spectrum of the urethan Vd, however, does not show this pattern. Both equatorial protons appear at 240–245 cps but are masked by the methylene quartet. This finding suggests a smaller energy barrier to rotation about the C–N bond of the urethan, and is consistent with the decreased C–N double-bond character which may be predicted for urethans from resonance considerations.

A sample of 1-acetyl-4-methylpiperidine was prepared in order to provide a model with no benzylic hydrogens. The nmr absorptions of the hydrogens α to nitrogen in this compound are as follows: an equatorial proton doublet at 274 cps ($J_{gem} \cong 13$ cps), an equatorial proton doublet at 230 cps ($J_{gem} \cong 13$ cps), and two overlapping axial proton triplets centered at 182 and 154 cps ($J_{gem} \cong J_{aa} \cong 13$ cps). Assignment of the 182- and 154-cps signals can be made if one assumes that the rotational barrier about the C–N amide bond is of the same order of magnitude for 1-acetyl-4-methylpiperidine and 1-acetylpiperidine, and that the broad 210-cps absorption of 1-acetylpiperidine is a time-averaged signal resulting from rapid ring inversion and slow interconversion of the two favored rotational conformers. The broad signal may be considered to result from overlapping of the signals of the *cis*- and *trans*-methylene protons. Each of these methylene absorptions is expected to be a time-averaged signal midway between the absorptions of the axial and equatorial protons of a similar system in which ring inversion is restricted.[11] Thus in 1-acetyl-4-methylpiperidine the axial proton giving a signal at 154 cps is geminal to the equatorial proton absorbing at 274 cps (time average 214 cps), while the axial proton absorbing at 182 cps is geminal to the equatorial proton absorbing at 230 cps (time average 206 cps). The overlapping of these two time-averaged signals is actually observed as the broad, unresolved 210-cps absorption. These geminal proton assignments as well as the *cis–trans* assignments are consistent with the reported absorptions of the *cis* equatorial (~270 cps) and axial (~156 cps) hydrogens in the lactam X.[12]



X

The temperature dependence of this spectrum is shown in Figure 2. The averaging of the axial protons as well as the equatorial protons at high temperatures results from an increase in the rate of rotation about the C–N amide bond.

Experimental Section

Melting points are corrected; boiling points are uncorrected. Infrared spectra were recorded by Mr. William H. Washburn and associates on a Perkin-Elmer Model 421 spectrophotometer using chloroform solutions. Nmr spectra were recorded by Mrs. R. S. Stanaszek and Dr. R. W. Mattoon on a Varian A-60 instrument. Values are in cps downfield from tetramethylsilane, using deuteriochloroform solutions. Catalytic reductions were performed by Mr. M. Freifelder and Mr. D. Dunnigan. Thin layer chromatography and gas–liquid partition chromatography were carried out by Mrs. Evelyn Baker and associates. Ultraviolet spectra were recorded by Messrs. J. Sutherland and D.

(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 116.

(7) "NMR Spectra Catalog," Varian Associaties, Inc., Vol. II, Palo Alto, Calif., 1963, Spectrum 479.

(8) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 65.

(9) R. H. Bible, Jr., ref 8, p 18.

(10) W. F. Trager and A. C. Huitric, *Tetrahedron Letters*, 825 (1966).

(11) A similar situation exists in the case of cyclohexanone oxime except that the time-averaged absorptions of the *cis*- and *trans*-methylene groups do not overlap. See ref 10.

(12) J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, and A. H. Redcliffe, *Australian J. Chem.*, **19**, 151 (1966).

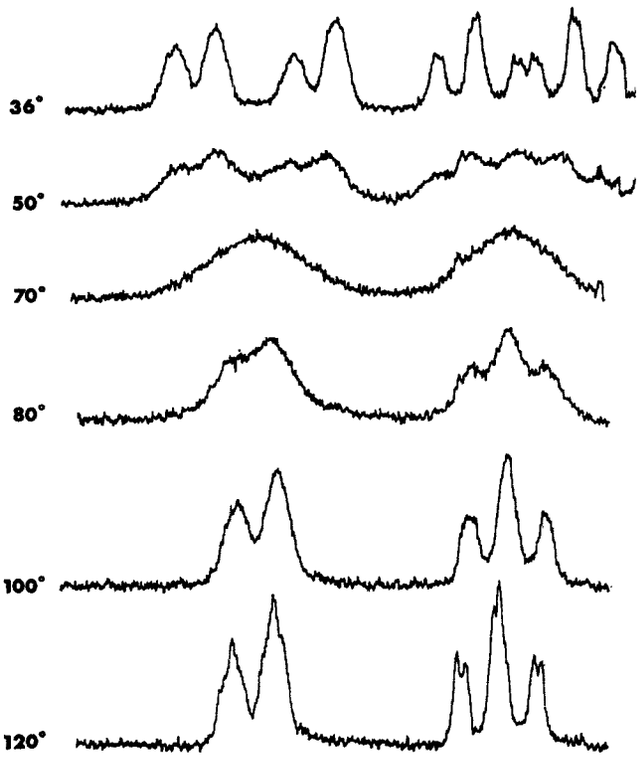


Figure 2.—Nmr spectrum for CH_2 hydrogens α to the nitrogen atom in 1-acetyl-4-methylpiperidine as a function of temperature at 60 Mc, pure liquid.

Williamson. Microanalyses were by Mr. O. Kolsto and his staff.

6-Methoxy-1-(4-pyridylmethylene)-1,2,3,4-tetrahydronaphthalene and 3,4-Dihydro-6-methoxy-1-(4-pyridylmethyl)naphthalene (IIa).—To 250 ml of liquid ammonia containing a crystal of ferric nitrate hydrate in a three-neck flask fitted with a dropping funnel, Dry Ice condenser, and mechanical stirrer was added, portionwise with stirring, 10 g of sodium. The flask was cooled in a Dry Ice–acetone bath and 43 ml of γ-picoline was added dropwise with stirring over a 10-min period. The cooling bath was removed, and after 15 min the Dry Ice condenser was replaced by an air condenser. Dry ether (100 ml) was added dropwise while the ammonia evaporated. The flask was warmed in a hot water bath to drive off the last of the ammonia. Alternatively commercial sodiumamide may be added to γ-picoline cooled in an ice bath. The residual dark oil was cooled in an ice bath and 25 g of 6-methoxy-1-tetralone in 85 ml of γ-picoline was added very rapidly. This mixture was stirred overnight at room temperature and then poured onto ice.

The dark oil so obtained was extracted with ether (some chloroform was added to keep a white solid in solution). Removal of solvent from the washed and dried ether solution left 38 g of an amber oil. The last traces of γ-picoline were removed by distillation at low pressure. The residue was taken up in 10% hydrochloric acid, and the unreacted tetralone was separated by suction filtration.

The filtrate was made alkaline with 20% sodium hydroxide solution and extracted with ether. The ether extract was washed, dried, and evaporated to leave 25.7 g of a yellow-brown oil. This oil was dissolved in absolute ethanol and treated with ethereal HCl. A crude yellow solid was obtained. This solid is a mixture of the hydrochlorides of IIa. An analytical sample (from ethanol–ether) melted at 172–184°.

Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.95; H, 6.30; N, 4.87. Found: C, 70.85; H, 6.07; N, 4.99.

The crude hydrochlorides were dissolved in water and this solution was made alkaline with 10% aqueous sodium hydroxide. Work-up *via* ether extraction yielded 21.2 g of an amber oil. Crystallization of this oil from ether–hexane afforded 16.3 g (42%; when commercial sodiumamide was used the yield was 29%) of IIa as nearly white crystals, mp 61–75°. Thin layer chromatography on silica gel revealed two poorly resolved spots on development with 90:10 acetone–ether and detection with ammonium molybdate. The infrared spectrum shows no CO or OH absorption. The nmr spectrum indicates about a 50:50 mixture of the double-bond isomers. Fractional crystallization failed to separate the two isomers.

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.78; H, 6.98; N, 5.53.

3,4-Dihydro-6-methoxy-1-[1-(4-pyridyl)ethyl]naphthalene (IIb).—This compound was prepared from 4-ethylpyridine and 6-methoxy-1-tetralone in the manner described in the previous example. After removal of the last traces of 4-ethylpyridine and treatment with 10% hydrochloric acid, it was necessary to extract the acidic filtrate with ether in order to remove all of the unreacted tetralone. The nmr spectrum suggested that the crude product was contaminated with *dl* and *meso*-2,3-bis(4-pyridyl)-butane. The desired product was eluted from a column of silica gel with ether while the contaminant was not. Using commercial sodiumamide an 18% yield of IIb was obtained as white crystals from benzene–hexane: mp 73–75°, λ_{max}^{EtOH} 265 mμ (ϵ 12,450). The nmr spectrum showed signals at 88.5 cps (doublet, J = 7 cps, 3 H), 242.5 cps (quartet, J = 7 cps, 1 H), 356 cps (triplet, J = 4 cps, one vinyl H).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.46; H, 7.01; N, 5.18.

A hydrochloride was obtained as white crystals from ethanol–ether: mp 150–153°.

Anal. Calcd for $C_{18}H_{20}ClNO$: C, 70.19; H, 5.89; N, 5.12. Found: C, 70.33; H, 5.85; N, 5.00.

5-Methoxy-1-(4-pyridylmethylene)indan (IIc).—This compound was obtained from γ-picoline and 5-methoxyl-1-indanone in the manner described for the preparation of IIa. A 47% yield of IIc was obtained as dark yellow crystals from benzene–hexane: mp 141.5–144.5°; λ_{max}^{EtOH} 340 mμ (ϵ 34,370), 307 (17,350), 296 (13,180 shoulder), 238 (10,380). The nmr spectrum included signals at 400 (singlet, one vinyl H) and 182 cps (4 H single peak).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.97; H, 6.30; N, 5.91.

The hydrochloride of IIc crystallized from water as orange needles, mp 235–240° dec.

Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.19; H, 5.89; N, 5.12. Found: C, 69.94; H, 5.71; N, 5.15.

5,6-Dimethoxy-1-(4-pyridylmethylene)indan (IId).—The reaction of γ-picoline with 5,6-dimethoxy-1-indanone in the manner described above gave a 36% yield of IId as light yellow crystals (from benzene): mp 147.5–149.5°; λ_{max}^{EtOH} 350 mμ (ϵ 30,600), 305 (12,500), 295 (10,700), 241 (11,500). The nmr spectrum showed signals at 397 (singlet, one vinyl H) and 183 cps (single peak, 4 H).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.62; H, 6.42; N, 5.07.

The hydrochloride separated from water as yellow-orange crystals, mp 224–226°.

Anal. Calcd for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.09; H, 6.22; N, 4.84.

6-Methoxy-1-(4-pyridylmethyl)-1,2,3,4-tetrahydronaphthalene (IIIa).—A 6-g sample of IIa was hydrogenated at 50–60° under 30–40 psi in methanol solution with a palladium-on-carbon catalyst. An 84% yield of IIIa was obtained as a colorless oil, bp 199.5–200.5° (3 mm).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.52; H, 7.57; N, 5.51.

The hydrochloride separated from ethanol–ether as white crystals, mp 216–218°.

Anal. Calcd for $C_{17}H_{20}ClNO$: C, 70.44; H, 6.96; N, 4.83. Found: C, 70.58; H, 6.91; N, 4.90.

6-Methoxy-1-[1-(4-pyridyl)ethyl]-1,2,3,4-tetrahydronaphthalene (IIIb).—Hydrogenation of IIb in ethanol with a palladium catalyst afforded a 92% yield of IIIb as a colorless oil, bp 185–188.5 (1.8 mm). Although the C-methyl region of the nmr spectrum of this material indicates the presence of diastereoisomers, resolution by both thin layer and gas–liquid partition chromatography was unsuccessful.

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.96; H, 7.70; N, 5.20.

A white hydrochloride, mp 145–152°, was obtained from ethanol–ether.

Anal. Calcd for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30; N, 4.61. Found: C, 71.41; H, 7.54; N, 4.79.

5-Methoxy-1-(4-pyridylmethyl)indan (IIIc).—Hydrogenation of IIc with a palladium catalyst in ethanol provided a 92%

yield of IIIc as white crystals, mp 68–71°, from benzene–hexane.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.38; H, 7.22; N, 5.79.

The hydrochloride separated from ethanol–ether as a white powder, mp 195–197°.

Anal. Calcd for $C_{16}H_{18}ClNO$: C, 69.68; H, 6.58; N, 5.08. Found: C, 69.81; H, 6.52; N, 5.22.

5,6-Dimethoxy-1-(4-pyridylmethyl)indan (IIId).—Hydrogenation of IId in ethanol gave IIId in 92% yield as white crystals: mp 80–82.5°, from benzene–hexane; λ_{max}^{EtOH} 290 mμ (shoulder, ε 5370), 288 (5460), 264 (2760), 257 (3070), 230 (shoulder, 7980).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.44; H, 7.11; N, 5.20. Found: C, 74.69; H, 6.95; N, 5.52.

The hydrochloride separated from ethanol as white crystals, mp 190–193°.

Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.78; H, 6.51; N, 4.37.

6-Methoxy-1-(4-piperidylmethyl)-1,2,3,4-tetrahydronaphthalene (IVa).—A 3.32-g sample of IIIa in 100 ml of ethanol was hydrogenated under 40 psi at 60° in the presence of 1 g of a 5% rhodium on alumina catalyst. Hydrogen uptake was complete at about 4 hr. The product was separated in 90% yield as a colorless oil (IVa): bp 185–187° (2 mm); λ_{max}^{EtOH} 287 mμ (ε 1820), 280 (1950), 220 (7740).

Anal. Calcd for $C_{17}H_{25}NO$: C, 78.71; H, 9.72; N, 5.40. Found: C, 78.71; H, 9.62; N, 5.59.

The hydrochloride crystallized from ethanol–ether as a white powder, mp 265–267.

Anal. Calcd for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.85; N, 4.73. Found: C, 68.86; H, 8.84; N, 4.64.

6-Methoxy-1-[1-(4-piperidyl)ethyl]-1,2,3,4-tetrahydronaphthalene (IVb).—Hydrogenation of 4.12 g of IIIb in 100 ml of ethanol containing 1.5 ml of concentrated hydrochloric acid at 50–60° and 30 psi in the presence of 1.25 g of a 5% rhodium-on-carbon catalyst provided a nearly quantitative yield of IVb. The colorless oil distilled at about 170° (0.5 mm).

Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.96; N, 5.12. Found: C, 78.92; H, 9.78; N, 5.12.

A hydrochloride was obtained from ethanol–ether as white crystals, mp 237–244°.

Anal. Calcd for $C_{18}H_{28}ClNO$: C, 69.77; H, 9.11; N, 4.52. Found: C, 69.60; H, 8.82; N, 4.43.

5,6-Dimethoxy-1-(4-piperidylmethyl)indan (IVc).—This compound was prepared from IIId in the manner described for the preparation of IVb but using ethanol–water as a solvent. A 77% yield of IVc was obtained as white crystals: mp 79.5–81.5°, from benzene–hexane; λ_{max}^{EtOH} 291 mμ (shoulder, ε 4870), 287 (5060), 228 (shoulder, 7040), 220 (7270).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.16; H, 9.23; N, 5.32.

The hydrochloride was obtained from ethanol as white crystals, mp 250–253° dec.

Anal. Calcd for $C_{17}H_{26}ClNO_2$: C, 65.47; H, 8.41; N, 4.49. Found: C, 65.17; H, 8.50; N, 4.44.

4-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylmethyl)-1-piperidinecarboxaldehyde (Va).—To 5.65 g of IVa dissolved in 32 ml of 98% formic acid cooled in an ice bath was added 17.5 ml of acetic anhydride over a 15-min period. This solution was stirred for 30 min at 15° and for 2 hr at room temperature. Ice–water was added and stirring was continued for 45 min. Work-up with ether, including washing with bicarbonate solution, provided 3.07 g (49%) of Va as a colorless oil: bp 235–242° (~3 mm), ν_{max} 1665 cm^{-1}. The nmr spectrum showed a formyl proton singlet at 482 cps.

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.38; H, 8.88; N, 5.08.

1-Acetyl-4-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylmethyl)-piperidine (Vb).—To 2.8 g of IVa dissolved in 95 ml of dry ether was added 1.5 ml of triethylamine followed by 0.76 ml of acetyl chloride in 95 ml of dry ether. This mixture was stirred for 45 min at room temperature. The addition of ice–water and work-up *via* ether extraction provided 2.8 g (86%) of Vb as a colorless oil: bp 200–205° (0.2 mm), ν_{max} 1616 cm^{-1}.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.55; H, 9.19; N, 4.84.

4-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylmethyl)-1-propionylpiperidine (Vc).—This propionamide was prepared from IVa in the same manner as Vb substituting propionyl chloride for acetyl chloride. A 59% yield of Vc was obtained in the form of white crystals from benzene–hexane: mp 74–77°, ν_{max} 1623 cm^{-1}.

Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.10; H, 9.22; N, 4.31.

4-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylmethyl)-1-carboethoxypiperidine (Vd).—This urethan was prepared from IVa in the same manner as Vb employing ethyl chloroformate in place of acetyl chloride. An 80% yield of Vd was obtained as a colorless oil with a boiling point of about 227° (2.3 mm), ν_{max} 1673 cm^{-1}.

Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.16; H, 9.07; N, 4.35.

1-Acetyl-4-(5,6-dimethoxy-1-indanylmethyl)piperidine (Ve).—The same procedure described for Vb starting with IVc gave an 81% yield of Ve as white crystals from benzene–hexane: mp 90–92.5°, ν_{max} 1623 cm^{-1}.

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.81; H, 8.58; N, 4.41. Found: C, 71.86; H, 8.39; N, 4.25.

4-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylmethyl)-1-methylpiperidine Hydrochloride (VIa).—To 9 ml of an ice-cooled commercial[13] solution of approximately 1 *M* borane in tetrahydrofuran was added, in a nitrogen atmosphere dropwise with stirring, 1.39 g of Va in 20 ml of anhydrous tetrahydrofuran over a 5-min period. The colorless solution was heated under reflux for 1 hr and cooled to room temperature. Water (25 ml) followed by 2 ml of 6 *N* hydrochloric acid was added, and the tetrahydrofuran was removed by distillation at atmospheric pressure. The residue was made alkaline with 50% aqueous sodium hydroxide and worked up *via* ether extraction to yield 1.31 g of crude material.

Methanolic HCl was added, and the mixture was warmed on a steam bath until solution was complete. This precaution decomposes any borine coordination compound formed during the reaction. Removal of the solvent at reduced pressure, treatment with sodium hydroxide solution, and work-up with ether provided 1.1 g of an oil. This oil was dissolved in absolute ethanol and ethereal HCl was added giving 923 mg (62%) of the hydrochloride of VIa as white crystals, mp 211–213°.

Anal. Calcd for $C_{18}H_{28}ClNO$: C, 69.77; H, 9.11; N, 4.52. Found: C, 69.80; H, 9.19; N, 4.52.

1-Ethyl-4-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylmethyl)-piperidine Hydrochloride (VIb).—This compound was prepared in 57% yield from Vb in the manner described for the preparation of VIa. The white hydrochloride had mp 236–238°.

Anal. Calcd for $C_{19}H_{30}ClNO$: C, 70.45; H, 9.34; N, 4.33. Found: C, 70.70; H, 9.29; N, 4.30.

5-(4-Pyridylmethylene)-5,6,7,8-tetrahydro-2-naphthol and 7,8-Dihydro-5-(4-pyridylmethyl)-2-naphthol (VIIa).—A mixture of 2 g of IIa and 6.5 g of pyridine hydrochloride was heated at 205–210° with stirring under nitrogen for 40 min, cooled in an ice bath, and diluted with water. This mixture was made alkaline with 5% aqueous sodium hydroxide and extracted with ether. The aqueous layer was acidified with Dry Ice and worked up *via* ether extraction to yield 263 mg (15%) of VIIa as a cream-colored solid from ethanol–benzene–hexane, mp 191–195°. The nmr spectrum indicates the presence of about 40% of the endocyclic double-bond isomer.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.09; H, 6.24; N, 6.02.

7,8-Dihydro-5-[1-(4-pyridyl)ethyl]-2-naphthol (VIIb).—In the same manner as described for the preparation of VIIa, a 56% yield of VIIb was obtained by demethylation of IIb. The cream-colored solid melted at 185–188°. The nmr spectrum showed signals at 88 (doublet, J = 7 cps, 3 H), 238 (multiplet, 1 H), and 353 cps (vinyl H).

1-(4-Pyridylmethylene)-5-indanol (VIIc).—Demethylation of IIc in the manner described for the preparation of VIIa gave an insoluble, dark red solid that resisted purification. The solid in methanol–ether was treated with aqueous sodium hydrosulfite and worked up *via* chloroform extraction to give a yellow solid. Crystallization of this material from methanol–hexane afforded a low yield of yellow crystals melting with decomposition at about 205°. The nmr spectrum in dimethyl sulfoxide (vinyl hydrogen singlet, 401 cps, four-proton singlet, 182 cps) is consistent with the structure VIIc.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.95; H, 6.16; N, 6.11.

5-(4-Pyridylmethyl)-5,6,7,8-tetrahydro-2-naphthol (VIIIa).—This compound was prepared in 56% yield from IIIa in the

(13) Metal Hydrides Inc., Beverly, Mass.

manner described for the preparation of VIIa. White crystals separated from ethanol, mp 187–189°.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 79.64; H, 7.05; N, 5.87.

Although the carbon value is low, the nmr spectrum is consistent with the expected structure.

1-(4-Pyridylmethyl)-5-indanol (VIIIb).—Demethylation of IIIc in the manner described above provided a 58% yield of VIIIb as fine, white crystals from benzene–ethanol, mp 223–226°.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.68; H, 6.77; N, 6.26.

5-(4-Piperidylmethyl)-5,6,7,8-tetrahydro-2-naphthol (IXa).—Demethylation of IVa in the manner described above provided a 24% yield of IXa as fine, white crystals from ethanol–hexane, mp 184–186°.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.07; H, 9.51; N, 5.80.

5-(1-Acetyl-4-piperidylmethyl)-5,6,7,8-tetrahydro-2-naphthol (IXb).—To a 1.5-g sample of IXa suspended in 50 ml of dry ether was added 1.7 ml of triethylamine followed by 0.87 ml of acetyl chloride in 10 ml of dry ether. This mixture was stirred for 50 min at room temperature, treated with ice–water, and extracted with chloroform. The chloroform layer was extracted with Claisen's alkali, and the basic extract was acidified with 6 *N* hydrochloric acid. Crystallization of the solid so obtained from ethanol gave 1.12 g (64%) of IXb as white crystals: mp 173–176°; ν_{max} 3598, 3250 (broad), and 1615 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.03; H, 8.76; N, 4.93.

1-Acetyl-4-methylpiperidine.—This amide was prepared by acetylating 4-methylpiperidine according to the procedure described for the preparation of Vb. The colorless oil had bp 91.5–93.0° (5.9 mm), ν_{max} 1623 cm^{-1}.

Anal. Calcd for $C_8H_{15}NO$: C, 68.06; H, 10.71; N, 9.92. Found: C, 67.84; H, 10.91; N, 10.04.

Acknowledgment.—The authors are grateful to Drs. Jack Tadanier and Milton Levenberg for helpful discussions and suggestions.

Preparation and Geometric Isomerism of Dipiperonylidenesuccinic Acid and Anhydride

D. P. CHAKRABORTY, THOMAS SLEIGH, ROBERT STEVENSON,

Department of Chemistry, Brandeis University, Waltham, Massachusetts

GERTRUDE A. SWOBODA, AND BORIS WEINSTEIN

Department of Chemistry, Stanford University, Stanford, California

Received May 12, 1966

Yellow *trans,trans*-α,α′-dipiperonylidenesuccinic anhydride was transformed by light into reddish orange *cis,trans*-α,α′-dipiperonylidenesuccinic anhydride. The configurational assignments are supported by spectral data and several chemical transformations.

The "fulgenic acids" are a large group of colored, crystalline arylmethylenesuccinic acids generally prepared by a Stobbe condensation of an aromatic aldehyde or ketone with a monoalkylidenesuccinate ester or diethyl succinate.[1–5] They are convertible into more deeply colored anhydrides, called "fulgides,"[6] which exhibit a structural change, sometimes reversible, by the action of iodine, heat, or light, and generally in acetone or benzene solution.[7–10] An interpretation of this last phenomenon is complicated by the ready oxidative cyclization of the fulgides under related conditions to afford naphthalene derivatives.[11–13]

It is probable that previous workers on the fulgide isomerization puzzle considered the color changes to be a consequence of double-bond isomerization; however, no definite configurational assignments appear to have been made for any particular set of fulgenic acid to fulgide interconversions, although discrete free-radical intermediates[14] and mesomeric forms[15] have been offered as suggestions to explain the behavior of these compounds. In connection with two recent studies,[16,17] there simultaneously arose the opportunity of solving one phase of this problem, and our joint results are reported at this time.

Piperonal reacted with diethyl succinate in ether using either sodium methoxide[18–22] at −10° or potassium *t*-butoxide in *t*-butyl alcohol[12] at reflux as the catalyst to give *trans,trans*-α,α′-dipiperonylidenesuccinic acid (Ia).[23] The addition of diazomethane to the diacid Ia afforded the corresponding dimethyl ester (Ib),[22,24,25] which was desired for further comparison work. Treatment of the diacid Ia with either acetyl chloride or acetic anhydride produced yellow *trans,trans*-dipiperonylidenesuccinic anhydride (Ic).[18,21,25] The *trans,trans* configurations for Ia and Ic are strongly supported by their symmetrical nmr spectra, particularly in the case of the anhydride. The simple vinyl and aromatic patterns as well as the single methylenedioxy peak seen for these two compounds imply that

(1) Many of these substances are described in an extensive work by Stobbe, *et al.*, *Ann.*, **380**, 1 (1911).
(2) H. Stobbe, G. Ljungren, and J. Freyberg, *Ber.*, **59**, 265 (1926).
(3) F. G. Baddar, L. S. El-Assal, and M. Gindy, *J. Chem. Soc.*, 1270 (1948).
(4) L. Hänel, *Naturwissenschaften*, **37**, 91 (1950).
(5) R. Cluzel and P. Cordier, *Compt. Rend.*, **235**, 622 (1952).
(6) H. Stobbe and P. Naoúm, *Ber.*, **37**, 2240 (1904).
(7) H. Stobbe, *ibid.*, **37**, 2465 (1904).
(8) H. Stobbe, *ibid.*, **37**, 2656 (1904).
(9) H. Stobbe and K. Leuner, *ibid.*, **38**, 3897 (1905).
(10) H. Stobbe, *Z. Elektrochem.*, **14**, 473 (1908).
(11) H. Stobbe, *Ber.*, **40**, 3372 (1907).
(12) L. S. El-Assal and A. H. Shehab, *J. Chem. Soc.*, 2983 (1963).
(13) D. C. Ayres, B. G. Carpenter, and R. C. Denney, *ibid.*, 3578 (1965).
(14) A. Schonberg, *Trans. Faraday Soc.*, **32**, 514 (1936).
(15) C. V. Gheorghiu, *Bull. Ecole Polytech. Jassey*, **2**, 141 (1947); *Chem. Abstr.*, **42**, 1514c (1948).
(16) D. Brown and R. Stevenson, *J. Org. Chem.*, **30**, 1759 (1965).
(17) G. A. Swoboda, K.-T. Wang, and B. Weinstein, *J. Chem. Soc.*, in press.
(18) H. Stobbe, W. Viewig, R. Eckert, and G. Reddelien, *Ann.*, **380**, 78 (1911).
(19) R. Dietzel and J. Naton, *Ber.*, **58**, 1314 (1925).
(20) S. Keimatsu, T. Ishiguro, and Y. Nakamura, *J. Pharm. Soc. Japan*, **55**, 775 (1935).
(21) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 1985 (1938).
(22) K. Freudenberg and T. Kempermann, *Ann.*, **602**, 184 (1957).
(23) For the purpose of definition, the stereochemistry as shown in the first set of drawings is called *trans,trans*, in the sense that the phenyl substituents are located *trans* to the central carbon–carbon bridge of the butadiene system. The second set of drawings is utilized for the *cis,trans* series.
(24) B. H. Alexander and W. F. Barthel, *J. Org. Chem.*, **23**, 381 (1958).
(25) L. S. El-Assal and S. A. M. El-Wahhab, *J. Chem. Soc.*, 849 (1960).