

NMR Spectroscopy in Distinguishing Between 3-Piperidyl- and 2-Pyrrolidylmethyl Alcohols, Amines, Esters, and Amides (1)

Joseph G. Cannon* and Larry D. Milne

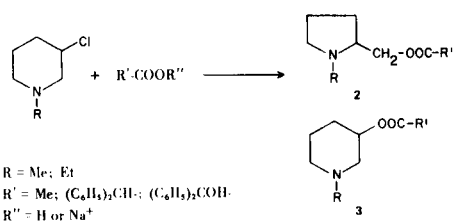
Division of Medicinal Chemistry and Natural Products, College of Pharmacy,
The University of Iowa, Iowa City, Iowa 52242

Received March 1, 1976

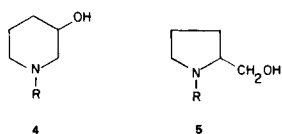
Nmr analysis was found to be superior to an older ir technique for assigning structures in a study involving ring contraction-expansion of 3-hydroxypiperidine \rightleftharpoons 2-hydroxymethylpyrrolidine systems and their ester derivatives. Nmr was not useful in studies of 3-aminopiperidines and 2-aminomethylpyrrolidines, but it could be applied to certain of their *N*-acyl derivatives. The nmr method was used to determine that esterification reactions of 1-methyl-3-(*p*-toluenesulfonyl)-piperidine and the sodium or potassium salts of some highly substituted carboxylic acids gave the ring-contracted pyrrolidine esters. In contrast, 1-methyl-3-aminopiperidine formed an amide with benzoic acid in which the piperidine ring remained unchanged. Aminolysis of methyl benzilate with 1-methyl-3-aminopiperidine resulted in a novel decarbonylation of the ester and isolation of benzophenone and 1-methyl-3-formylamidopiperidine.

J. Heterocyclic Chem., 13, 685 (1976).

In the course of a study of hallucinatory agents, various esters of 1-methyl-3-hydroxypiperidine were required. In 1961, Biel, *et al.*, (2) and Brain and co-workers (3) described contraction of the ring in the course of esterification reactions on 1-alkyl-3-chloropiperidines (1), to form mixtures containing 2-pyrrolidylmethyl esters (2) in addition to the expected ester 3.

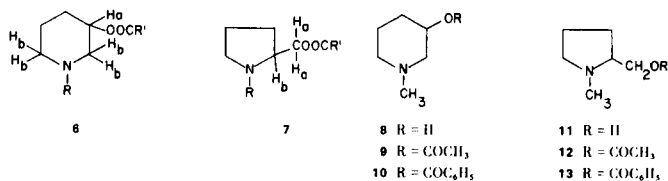


Brain (3) described conditions under which 2-chloromethylpyrrolidine systems expanded to a 3-chloropiperidine system. Biel (2) had established the identity of the ester products 2 and 3 by an acid hydrolysis of the ester, isolation of the free amino alcohol mixture, 4 and 5, and an empirical interpretation of the ir spectra of the two isomeric systems, separate and in mixture.



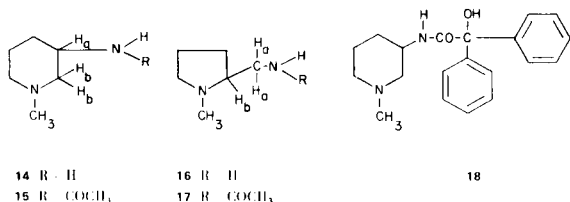
The Biel hydrolysis-isolation procedure is lengthy, and it seems uncertain whether the composition of the freed amino alcohols reflects the chemical nature of the esters themselves. The procedure does not allow for distillation of the aminoalcohols, since this has been shown, in some instances, to lead to ring expansion of pyrrolidylmethyl systems to 3-piperidinol systems. Therefore, the ir spectra must be obtained on crude amino alcohols, and since there were reported to be only subtle differences between the ir spectra of 4 and 5, it would seem that the impurities could distort or obscure these differences, leading to misinterpretations.

Nmr spectroscopy seemed a less ambiguous method for determination of ring size of the aminoalcohol portion of esters 2 and 3. A 1-alkyl-3-piperidyl ester (6) would be expected to exhibit a multiplet for H_a; the H_b protons (adjacent to the ring nitrogen) would be expected to appear upfield from the H_a signal, without overlap of the signals.



In contrast, a pyrrolidylmethyl ester **7** should exhibit a doublet for the H_a protons. Accordingly, compounds **8-13** were selected for study. Brain, *et al.*, (3), prepared **11** in 31% yield by treatment of 1-methyl-3-chloropiperidine with aqueous base. In the present study, use of 1-methyl-3-(*p*-toluenesulfonyl)piperidine instead of the chloro compound resulted in a 91% yield of **11**. Brain (3) had reported that esterification of **8** and **11** with acetyl or benzoyl chlorides in boiling benzene produced no changes in ring size, and this procedure was employed for the esters in the present study. Compound **12** could not be isolated in a pure state, but it always seemed (on the basis of its spectra) to be contaminated with varying amounts of unesterified aminoalcohol. The nmr study was conducted using this impure material. Nmr data for **8-13** are listed in Table I. In the pyrrolidylmethyl esters **12** and **13**, the H_a signals appeared as a distinct doublet. It appeared that nmr is useful in establishing ring size in heterocyclic alcohols and esters.

Further to evaluate the utility of nmr in establishing ring size, the amines and amides **14-17** were studied.



The aminopiperidine **14** showed a multiplet (2H) at δ 2.60 and a multiplet (1H) at 2.85, while the aminomethylpyrrolidine **16** showed a doublet (2H) at 2.75 and a multiplet (1H) at 3.00. This proximity of positions of the H_a signals is not unexpected, in that the protons in **14** and **16** are equivalent in their proximity to an amino nitrogen. However, the amides **15** and **17** reflect the

changes in environments of H_a relative to H_b . Compound **15** showed a multiplet (4H) at δ 2.45 and a multiplet (1H) at 4.15, while **17** showed a multiplet (2H) at 3.05 and a multiplet (1H) at 3.55. Formation of an amide of the primary amino group thus changed the effect of that nitrogen on the chemical shift of the neighboring protons; this was demonstrated by the pronounced downfield shift (1.3 ppm) of H_a in **15**. In **17**, H_b is still adjacent to an amino nitrogen, but it is β - to the amide nitrogen, and therefore it is more highly shielded than is H_a of **15** and it is less affected by the acylation of the primary amine. Therefore H_b of **17** appears farther upfield. Conversion of the free amines to their acetamides made possible nmr interpretations which could not be accomplished on the free amines.

1-Methyl-3-aminopiperidine was treated with benzoic acid in refluxing benzene. The nmr spectrum of the resulting amide **18** showed a multiplet at δ 4.15 (1H) and a multiplet at 2.40 (2H), and on these bases, it is concluded that, as would be anticipated from the proposed mechanism (3,4) for the pyrrolidine-piperidine interconversion, no ring contraction reaction(s) occurred, and the amide product contains a piperidine ring system.

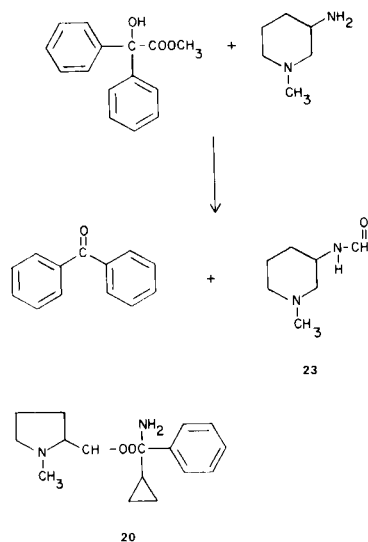
In another experiment, preparation of **18** was attempted by aminolysis of methyl benzilate with 1-methyl-3-aminopiperidine in dioxane. An oil was isolated whose ir spectrum showed an amide carbonyl band at 1675 cm^{-1} , but no absorption in the aromatic region. The nmr spectrum of this material showed a signal at δ 8.15 (1H) which is in the region in which the C-proton of formamides appears (5). A signal at δ 6.55 (1H) which disappeared on deuterium oxide exchange and an ir band at 2710 cm^{-1} (C-H stretch of aldehyde or formamide) led to the conclusion that this oil was 1-methyl-3-formamidopiperidine. This was verified by unequivocal synthesis from 1-methyl-3-aminopiperidine and formic acid. When the aminolysis of methyl benzilate was carried out in highly purified dioxane,

Table I

Nmr Spectral Data for Piperidine and Pyrrolidine Alcohols and Esters

Compound No.	R	Ring System	H_a	H_b
8	H	piperidine	δ 3.75 (m, 1H)	δ 2.50 (m, 4H)
9	Ac	piperidine	4.90 (m, 1H)	2.50 (m, 4H)
10	COC ₆ H ₅	piperidine	5.10 (m, 1H)	2.85 (m, 4H)
11	H	pyrrolidine	3.55 (m, 2H)	3.10 (m, 1H)
12	Ac	pyrrolidine	4.10 (d, 2H)	----
13	COC ₆ H ₅	pyrrolidine	4.35 (d, 2H)	3.15 (m, 1H)

in ethylene glycol, or in hexane, the same formamide derivative was isolated. Reinvestigation of the original aminolysis mixture revealed the presence of benzophenone, which was identified by preparation of its 2,4-dinitrophenylhydrazone. The overall reaction can be shown as follows:



The literature did not reveal close precedent for this decarboxylation of an ester of benzilic acid and formation of a formamide.

When the sodium salt of cyclopropylphenylglycine was permitted to react with 1-methyl-3-(*p*-toluenesulfonyl)piperidine, the resulting ester was shown by nmr analysis to be the ring-contracted pyrrolidylmethyl product **20**. Biel, *et al.*, (2), had reported that high vacuum distillation of a 2-pyrrolidylmethyl benzilate induced complete ring expansion to the 3-piperidyl benzilate as the sole product of the distillation. In the present work, the nmr spectrum of the distillate of **20** was identical to that of the undistilled material. Potassium 2,2'-pyridylate was permitted to react with 1-methyl-3-(*p*-toluenesulfonyl)piperidine and the resulting ester was purified by distillation to give a product whose nmr spectrum showed a doublet at δ 4.45 (2H), indicating that the ester product was the ring-contracted one. Apparently, the thermally induced ring expansion is not as general nor as facile as was originally proposed by the Biel group. However, critical factors in the ring expansion-contraction remain to be defined.

EXPERIMENTAL

All melting points are corrected and were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus. Analyses were by Hufmann Microanalytical Laboratories, Wheatridge, Colorado and Galbraith Laboratories, Knoxville, Tennessee. Ir

spectra were recorded on Beckman IR-5A, Beckman IR-10, or Perkin-Elmer 137B infrared spectrometers. Nmr spectra were recorded on Varian Associates T-60 and A-60 instruments.

1-Methyl-3-(*p*-toluenesulfonyl)piperidine Hydrochloride (**21**).

This was prepared by the method of Freiter, *et al.*, (6), m.p. 148-150°. [lit. (6) m.p. 146-148°]; nmr (deuteriochloroform): δ 1.95 (m, 4H), 2.55 (s, 3H), 3.05 (s, 3H), 3.55 (m, 4H), 5.05 (m, 1H), 7.80 (m, 4H).

1-Methyl-3-(*p*-toluenesulfonyl)piperidine (**22**).

This was prepared by treating a solution of 1 part of **21** in 10 parts of water with excess sodium bicarbonate, and immediately extracting with ether. The ether was removed under reduced pressure and the resulting tan oil was used immediately; nmr (carbon tetrachloride): δ 1.65 (m, 4H), 2.12 (s, 3H), 2.40 (m, 7H), 4.35 (m, 1H), 7.45 (m, 4H). A picrate salt was recrystallized from ethanol, m.p. 159-160°.

Anal. Calcd. for $C_{19}H_{22}N_4O_{10}S$: C, 45.78; H, 4.42; N, 11.24. Found: C, 45.72; H, 4.75; N, 11.09.

1-Methyl-2-hydroxymethylpyrrolidine (**11**).

Compound **21** (3.05 g., 0.01 mole) was stirred in 100 ml. of 5% sodium hydroxide solution at room temperature for 12 hours. Initially, the solution separated into two layers, but upon continued stirring, it became homogeneous. The solution was extracted repeatedly with chloroform, the combined extracts were dried (sodium sulfate), and the volatiles were removed under reduced pressure to yield 1.05 g. (91%) of a clear oil, b.p. 56-57° (5 mm.) [lit. (3) b.p. 67-69° (12 mm.)]; nmr (deuteriochloroform): δ 1.85 (m, 4H), 2.35 (s on m, 5H), 3.10 (s on m, 2H), 3.55 (m, 2H); deuterium oxide exchange: s at δ 3.10 disappeared. A methiodide salt was recrystallized from anhydrous ethanol, m.p. 288-290°, [lit. (3) m.p. 293-294°].

1-Methyl-3-aminopiperidine (**14**).

This was prepared by the method of Tomita (7), b.p. 78-79° (44 mm.) [lit. (7) b.p. 81-83° (48 mm.)]; nmr (deuteriochloroform): δ 1.10 (m, 2H), 1.45 (s, 2H), 1.75 (m, 4H), 2.10 (s, 3H), 2.60 (m, 2H), 2.85 (m, 1H).

Reaction of Methyl Benzilate with 1-Methyl-3-aminopiperidine (**14**).

Methyl benzilate (1.0 g., 0.004 mole) and 0.7 g. (0.006 mole) of **14** were refluxed in 200 ml. of 1,4-dioxane for 24 hours, then the solvent was removed under reduced pressure. The residue was taken up in 10% hydrochloric acid and the resulting solution was extracted with chloroform. The aqueous solution was reserved for further study. The pooled chloroform extracts were dried (sodium sulfate) and the solvent was removed to yield an oil which was treated with 2,4-dinitrophenylhydrazine test solution. After standing at room temperature for 12 hours, the reaction mixture deposited a yellow solid which was collected on a filter and recrystallized from ethanol, m.p. 237-239° [lit. (8) m.p. of benzophenone 2,4-dinitrophenylhydrazone, 239°]. The ir spectra (chloroform) of this product and of an authentic sample of benzophenone 2,4-dinitrophenylhydrazone were identical.

The reserved aqueous solution was cooled in an ice bath and was carefully basified with 10% sodium hydroxide solution, and the resulting mixture was extracted repeatedly with chloroform. The pooled extracts were dried (sodium sulfate) and the chloroform was removed under reduced pressure to yield 0.35 g. (62%) of a light tan oil, b.p. 89-90° (0.5 mm.). The ir (chloroform) and nmr (deuteriochloroform) spectra of this oil were identical

to those of an authentic sample of 1-methyl-3-formamidopiperidine **23**.

1-Methyl-3-formamidopiperidine (**23**).

Compound **14** (1.15 g., 0.01 mole) and 3.3 g. (0.06 mole) of 88% formic acid were refluxed in 125 ml. of benzene in a Dean-Stark apparatus. After 3 days, an additional 3.3 g. portion of 88% formic acid was added and refluxing was continued for 2 days. The benzene solution was extracted repeatedly with 5% hydrochloric acid, and the combined extracts were cooled in an ice bath and were treated with excess solid sodium bicarbonate. The resulting solution was extracted with chloroform, the pooled extracts were dried (sodium sulfate), and the chloroform was removed under reduced pressure to yield a light tan oil, b.p. 90-91° (0.5 mm.), yield, 0.95 g. (67%); nmr (deuteriochloroform): δ 1.65 (m, 4H), 2.25 (s, 3H), 2.35 (m, 4H), 4.15 (m, 1H), 6.55 (m, 1H), 8.15 (s, 1H); deuterium oxide exchange: m at δ 6.55 disappeared.

Anal. Calcd. for $C_7H_{14}N_2O$: C, 59.16; H, 9.86; N, 19.72. Found: C, 59.20; H, 9.98; N, 19.91.

1-Methyl-3-acetamidopiperidine (**15**).

The hydriodide salt of this compound was prepared by the method of Tomita (7), m.p. 184-185° [lit. (7) m.p. 182-184°]. The free base was liberated by treatment with excess sodium bicarbonate and extraction with chloroform. Removal of the solvent left a light yellow solid, m.p. 75-77°; nmr (deuteriochloroform): δ 1.65 (m, 4H), 2.00 (s, 3H), 2.28 (s, 3H), 2.45 (m, 4H), 4.15 (m, 1H), 6.35 (m, 1H); deuterium oxide exchange: m at δ 6.35 disappeared.

1-Methyl-2-aminomethylpyrrolidine (**24**).

A mixture of 3.05 g. (0.01 mole) of freshly prepared **22** and a large excess of liquid ammonia was permitted to stand at room temperature in a bomb for 24 hours. The excess ammonia was allowed to evaporate; the residue was taken up in 20% potassium hydroxide solution, and this solution was extracted with ether in a continuous extractor for 36 hours. The ether was removed under reduced pressure, to leave a clear oil, b.p. 77-78° (45 mm.), 153-154° (750 mm.), yield, 0.9 g. (79%); nmr (deuteriochloroform): δ 1.29 (s, 2H), 1.75 (m, 2H), 2.15 (m, 4H), 2.30 (s, 3H), 2.75 (d, 2H), 3.00 (m, 1H); deuterium oxide exchange: δ 1.29 signal disappeared, lit. (9) b.p. 152-153° (760 mm.).

1-Methyl-2-acetamidomethylpyrrolidine (**17**).

Compound **24** (0.8 g., 0.007 mole) and 0.7 g. (0.009 mole) of acetyl chloride were refluxed in 20 ml. of anhydrous benzene for 1 hour. The benzene was removed under reduced pressure, the residual oil was dissolved in 50 ml. of water, excess sodium bicarbonate was added, and the resulting solution was extracted several times with chloroform. The combined extracts were dried (sodium sulfate) and the chloroform was removed under reduced pressure to yield 0.6 g. (55%) of a light yellow oil, b.p. 114° (0.2 mm.); ir (chloroform): 1660 cm^{-1} (amide C=O); nmr (deuteriochloroform): δ 1.70 (m, 4H), 2.00 (s, 3H), 2.30 (s on m, 5H), 3.05 (m, 2H), 3.54 (m, 1H), 6.15 (m, 1H); deuterium oxide exchange: the δ 6.15 signal disappeared.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.54; H, 10.26; N, 17.95. Found: C, 61.27; H, 10.36; N, 18.16.

1-Methyl-3-benzoylamidopiperidine (**18**).

A solution of 0.6 g. (0.005 mole) of **14** and 3.0 g. (0.015 mole) of benzoic acid in 100 ml. of anhydrous benzene was refluxed in a Dean-Stark apparatus for 3 days, then an additional 2.0 g. (0.01

mole) of benzoic acid was added and the reaction mixture was refluxed for 4 days more. The benzene was removed under reduced pressure to leave a yellow mass which was treated with 100 ml. of 5% sodium hydroxide solution. This mixture was extracted repeatedly with chloroform and the combined extracts were dried (sodium sulfate). The chloroform was removed under reduced pressure to leave a thick oil which solidified on standing and was recrystallized from ethanol-ether to yield 0.90 g. (56%) of crystals, m.p. 151-153°; ir (chloroform): 3400 cm^{-1} (OH), 1655 (amide C=O); nmr (deuteriochloroform): δ 1.55 (m, 4H), 1.70 (s, 3H), 2.20 (m, 2H), 2.40 (m, 2H), 4.15 (m, 1H), 6.60 (m, 1H), 7.25 (m, 10H), 7.95 (m, 1H); deuterium oxide exchange: signals at δ 6.60 and 7.95 disappeared.

The hydrochloride salt was prepared by dissolving the amide in ethanol, adding excess 5% hydrochloric acid, and removing the volatiles under reduced pressure. The crude salt was recrystallized from ethanol-ethyl acetate, m.p. 274-276°.

Anal. Calcd. for $C_{20}H_{25}ClN_2O_2$: C, 66.57; H, 6.94; N, 7.77. Found: C, 66.72; H, 7.12; N, 7.82.

Sodium Cyclopropylphenyl- α -aminoacetate (**25**).

Cyclopropylphenyl- α -aminoacetic acid (5.0 g., 0.026 mole, Aldrich Chemical Co.) was vigorously stirred with 75 ml. of methanol while 1.5 g. (0.028 mole) of solid sodium methoxide was added in small portions. The methanol was removed from the resulting solution under reduced pressure, leaving a white solid which was recrystallized from ethanol-ether to yield 3.95 g. (74%) of product, m.p. 233-234°.

Anal. Calcd. for $C_{11}H_{12}NNaO_2$: C, 61.97; H, 5.63; N, 6.57. Found: C, 56.13; H, 5.57; N, 10.20.

Potassium 2,2'-Pyridilate (**26**).

To a hot solution of 18 g. (0.32 mole) of potassium hydroxide in 130 ml. of 1-butanol was slowly added 12.1 g. (0.10 mole) of 2,2'-pyridil (Aldrich Chemical Co.). The resulting mixture was refluxed for 0.25 hour. The mixture was cooled to room temperature and the dark yellow solid which separated was collected on a filter, washed with 2-butanol and with cold anhydrous ether, and recrystallized from anhydrous ethanol to yield 18.96 g. (78%) of crystals, m.p. 332-334°; ir (Nujol): 3300 cm^{-1} (OH), 1610 (C=O).

Anal. Calcd. for $C_{12}H_9KN_2O_3$: C, 53.73; H, 3.36; K, 14.55; N, 10.45. Found: C, 44.30; H, 2.98; K, 26.22; N, 8.29.

1-Methyl-2-pyrrolidylmethyl 2,2'-Pyridilate (**27**).

To a solution of freshly prepared **22** (from 3.05 g., 0.01 mole of the hydrochloride salt) in anhydrous acetone was added 5.4 g. (0.02 mole) of **26**. The resulting mixture was stirred under anhydrous conditions for 48 hours; it was then filtered and the acetone was removed from the filtrate under reduced pressure. Anhydrous ether was added to the dark brown gummy residue, and this mixture was allowed to stand for 6 hours. The ether was decanted and retained, and this washing procedure was repeated 4 times. The combined ether washes were dried (sodium sulfate) and the ether was removed under reduced pressure to leave a viscous oil which was distilled, b.p. 121-122° (0.5 mm.) to afford 0.65 g. (20%) of product; ir (chloroform): 3390 cm^{-1} (OH), 1730 (C=O), 1180 (C-O-C); nmr (deuteriochloroform): δ 1.91 (m, 4H), 2.36 (m, 2H), 2.50 (s, 3H), 2.92 (m, 1H), 4.45 (d, 2H), 6.75 (s, 1H), 7.80 (m, 8H).

Anal. Calcd. for $C_{18}H_{21}N_3O_3$: C, 66.06; H, 6.42; N, 12.84. Found: C, 66.26; H, 7.06; N, 12.51.

1-Methyl-2-pyrrolidylmethyl Cyclopropylphenyl- α -aminoacetate (20).

This was prepared by the method described for **27**, using the same molar amounts. A waxy semi-solid was obtained from the combined ether washes, which was purified by a dry column chromatographic technique (10) using neutral alumina and eluting with chloroform, yield, 0.65 g. (22%), b.p. 192-193° (0.3 mm.), m.p. 41-43°; ir (chloroform): 3400 cm^{-1} and 3340 (NH_2), 1725 ($\text{C}=\text{O}$), 1230 ($\text{C}-\text{O}-\text{C}$); nmr (deuteriochloroform): δ 0.50 (m, 4H), 1.25 (m, 4H), 1.65 (m, 2H), 2.30 (m, 5H), 2.50 (m, 1H), 4.15 (d, 2H), 7.40 (m, 5H); deuterium oxide exchange: m at δ 2.30 integrates for 3 H.

Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: C, 70.83; H, 8.34; N, 9.72. Found: C, 71.07; H, 8.53; N, 9.42.

Acknowledgment.

This investigation was supported in part by Grant MH-07775, National Institute of Mental Health.

REFERENCES AND NOTES

- (1) Abstracted from a thesis submitted by L. D. M. in partial fulfillment for the requirements for the Ph.D. degree, University of Iowa, 1970.
- (2) J. H. Biel, L. G. Abood, W. K. Hoya, H. A. Leiser, P. A. Nuhfer, and E. F. Kluchesky, *J. Org. Chem.*, **26**, 4096 (1961).
- (3) E. G. Brain, F. P. Doyle, and M. D. Mehta, *J. Chem. Soc.*, 633 (1961).
- (4) C. F. Hammer and S. R. Heller, *Chem. Commun.*, 919 (1966).
- (5) F. A. Bovey, "NMR Tables for Organic Compounds," Vol. I, Interscience Publishers, New York, N. Y., 1964, pp. 21,25.
- (6) E. R. Freiter, J. G. Cannon, L. D. Milne, and L. G. Abood, *J. Med. Chem.*, **11**, 1041 (1968).
- (7) K. Tomita, *J. Pharm. Soc. Jap.*, **71**, 220 (1951).
- (8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th Ed., John Wiley & Sons, Inc., New York, N. Y., 1964, p. 364.
- (9) J. H. Biel, W. K. Hoya, and H. A. Leiser, *J. Am. Chem. Soc.*, **81**, 2527 (1959).
- (10) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).