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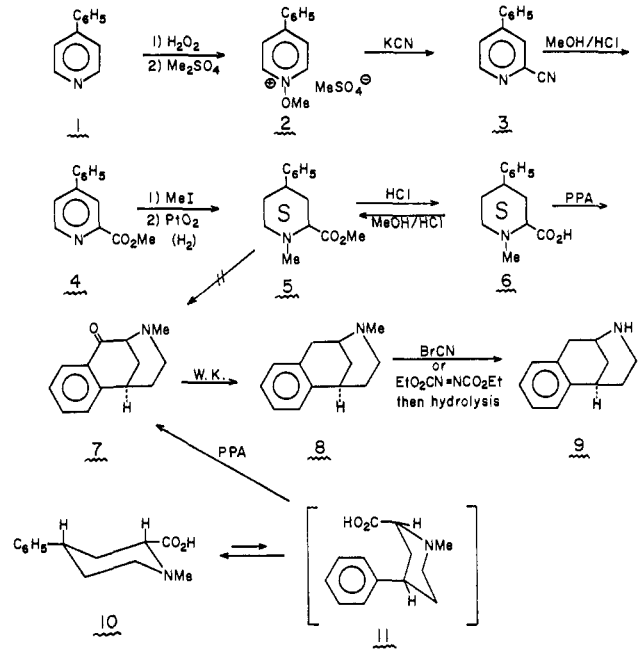
Synthesis of 6,7-Benzomorphan from 4-Phenylpyridine

Sir:

We wish to report the synthesis of 6,7-benzomorphan (**9**),[1] the parent structure of a series of potent analgesics[2] of which two (phenazocine[3] and pentazocine[4]) are in medical use.[5] With this parent structure available other congeners may now be prepared, and the importance and role of the quaternary carbon in morphinelike structures (morphine, codeine, the morphinans) can be better assessed.

The conventional methods hitherto used for benzomorphan and morphinan syntheses[2,6] were refractory for **9**.[7] At length, a scheme based on 2-cyano-4-phenylpyridine (**3**),[8] prepared from 4-phenylpyridine (**1**) by a modification of the published method,[8] was used. Thus, **1** was converted to its N-oxide by the procedure of Ochiai[9] which, with dimethyl sulfate, gave the 1-methoxy methosulfate **2**. Treatment of **2** with aqueous potassium cyanide[10] produced **3**, mp 99°, λ_{max}^{KBr} 4.44 μ (CN), methanolyzed to **4**, bp 170–175° (3 mm), $\delta_{TMS}^{CDCl_3}$ 4.01 ppm (3 H, singlet, CO_2CH_3), λ_{max}^{neat} 5.78, 5.86 μ (CO_2Me); methiodide mp 141–142°. This methiodide was hydrogenated (PtO_2, methanol, normal temperature and pressure, 10–15 hr) to 2-carbomethoxy-1-methyl-4-phenylpiperidine (**5**), bp 145–150° (2.5 mm), $\delta_{TMS}^{CDCl_3}$ 2.33 (3 H, singlet, NCH_3), 3.78 (3 H, singlet, CO_2CH_3), and 7.30 (5 H, singlet, C_6H_5) ppm, λ_{max}^{neat} 5.8 and 5.85 (sh) μ (CO_2Me). Compound **5** and refluxing 12 *M* hydrochloric acid gave the hydrochloride of **6**, mp 228–229°, λ_{max}^{Nujol} 5.8 μ (CO_2H), which was cyclized to 2-methyl-8-oxo-6,7-benzomorphan (**7**) [picrate mp 194°; free base, oil, λ_{max}^{neat} 5.95 μ (C=O), $\delta_{TMS}^{CDCl_3}$ 2.41 (3 H, singlet, NCH_3), 7.33 (3 H, complex multiplet, aromatic H), and 8.00 (1 H, complex multiplet, 4′-H deshielded by the C=O) ppm] with polyphosphoric acid (PPA) (oil bath temperature, 145–155°, 15 hr).



At 80° only traces of **7** were obtained. At 120° the yield was 5%; at 150–180°, 25% plus tars. Wolff–Kishner reduction of **7** yielded, after short-path distillation at 160–180° (0.3 mm), 2-methyl-6,7-benzomorphan (**8**), pale yellow oil; hydrochloride mp 225–225.5° dec, *m/e* 187, $\delta_{TMS}^{D_2O}$ 2.95 (3 H, singlet, NCH_3) and 7.30 (4 H, singlet, C_6H_4) ppm. Treatment of **8** (base) with either cyanogen bromide[11] or diethyl azodicarboxylate[12] followed by hydrolysis with 6% hydrochloric acid or pyridine hydrochloride, respectively, gave **9**; hydrochloride mp 261–262°, *m/e* 173; picrate mp 171–173°.

Yields in this sequence of reactions were 85–95% except in the cyclization (35%) and N-demethylation (20% with cyanogen bromide, 40% with diethyl azodicarboxylate) reactions. Methyl ester **5** could not be converted to **7** with PPA probably because the geometry of the most stable conformation (the 2,4-diequatorial isomer) would defy cyclization.[13] Furthermore, the fact that the corresponding acid, **6**, gave an ester with methanolic hydrogen chloride identical with **5** indicates that its stereochemistry is comparable to that of **5**.[14] Presumably, inversion of **10** to the 2,4-diaxial compound **11**, a very favorable conformer for cyclization, takes place to some extent in the presence of hot (150°) PPA. At temperatures higher than the optimal 150°, the formation of decomposition products is apparently in competition with the inversion–cyclization process (**10** → **11** → **7**).

All compounds reported gave correct percentages in elemental analysis.[15] Mass spectral and nmr data for **8** and **9** amply confirmed their structures. Com-

(1) *Chemical Abstracts* name: 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine.

(2) E. L. May and L. J. Sargent, in "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter IV; N. B. Eddy and E. L. May, "Synthetic Analgesics," Part IIB, Pergamon Press Ltd., Oxford, 1966, p 115 ff.

(3) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294, 1386 (1959); J. G. Murphy, J. H. Ager, and E. L. May, *ibid.*, **25**, 1386 (1960); trade names: Prinadol, Narphen.

(4) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, 7, 123 (1964); trade name: Talwin.

(5) A marked separation of analgesic efficacy and dependence liability has been demonstrated for the benzomorphan class, generally,[2,3] especially with *levo* isomers: E. L. May and N. B. Eddy, *ibid.*, **9**, 851 (1966), and unpublished results.

(6) R. Grewe, *Angew. Chem.*, **59**, 194 (1947); J. Hellerbach, O. Schnider, H. Besendorf, and B. Pellmont, "Synthetic Analgesics," Part IIA, Pergamon Press Ltd., Oxford, 1966, pp 1–115.

(7) Other failures included a sequence based on the isomorphinan synthesis [see M. Gates and W. G. Webb, *J. Am. Chem Soc.*, **80**, 1186 (1958), for a leading reference] and two from other naphthalene derivatives; details will be presented later.

(8) F. H. Case and T. J. Kasper, *J. Am. Chem. Soc.*, **78**, 5842 (1956).

(9) E. Ochiai, *J. Org. Chem.*, **18**, 549 (1953).

(10) W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959).

(11) In the von Braun method, the intermediate N-cyano compound could be hydrolyzed only with difficulty. After prolonged treatment with boiling 6% hydrochloric acid, a mixture of the N-cyano and N-carbamido compounds and desired **9** resulted.

(12) A. Pohland and H. R. Sullivan, U. S. Patent 3,342,824 (Sept 19, 1967).

(13) See N. Sugimoto and S. Ohshiro, *Tetrahedron*, 8, 296 (1960).

(14) It is possible, of course, that the chair form of the 2,4-diequatorial ester is in equilibrium with the boat form at higher temperatures. Molecular models indicate, however, that only the chair diaxial form is in favorable conformation for cyclization. Evidently, there is not sufficient energy available to overcome the steric interaction of the bulky phenyl and ester groups in the chair 2,4-diaxial form.

(15) By P. Parisius, A. Wong, and B. Baer of this laboratory.

pound **8** is comparable in analgesic activity to the corresponding 5-methyl homolog.[2,16]

Acknowledgment. We are indebted to Mrs. Ann Wright and to Dr. Henry Fales, both of the National Institutes of Health, for the nmr and mass spectral data, respectively.

(16) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).
(17) Visiting Associate from Nagoya University, Japan.

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Ring Inversion in 1-Methylenecyclohexane

Sir:

The study of the conformations of six-membered rings of sp^3-hydridized atoms has been an active area of research in the past few years.[1] Of the many physical and chemical techniques that can be applied to these conformational problems, nuclear magnetic resonance spectroscopy is especially useful in that nmr spectra can often be made to yield the rates of conformational interconversions. It is therefore possible to deduce the energetics of these processes and thereby gain additional information about the nonbonded interactions rampant in the molecule. A number of experiments with deuterated and fluorinated cyclohexanes have shown that the rate of chair–chair interconversion in this molecule is 7.1×10^{-2} sec^{-1} at $-105°$.[1f] The activation parameters $\Delta F^{\pm}$, $\Delta H^{\pm}$, and $\Delta S^{\pm}$ are about 10.2 kcal/mole, 10.8 kcal/mole, and 3 eu, respectively, for this motion.[1d,f,2]

A report has also described an nmr study of the conformational properties of cyclohexene, a carbocycle with four tetrahedral and two trigonal (sp^2) carbon atoms.[3] The free-energy barrier to ring inversion of cyclohexene is about 5 kcal/mole, much less than the barrier in cyclohexane.

There has been considerable interest in the conformational behavior of cyclohexyl systems with a single trigonal carbon atom. This system would correspond to the ring skeleton of cyclohexanone[4,5] as well as to the basic geometry expected of the cyclohexyl carbonium ion.[6,7] The chair form of this ring is presumably the most stable and one would anticipate a chair–chair interconversion in this system analogous to that found in cyclohexane.[8] The rates of interconversion of six-membered rings with one trigonal carbon have not, to our knowledge, been determined, and we report here preliminary proton magnetic resonance experiments with 1-methylenecyclohexane which permit an estimate of this rate.

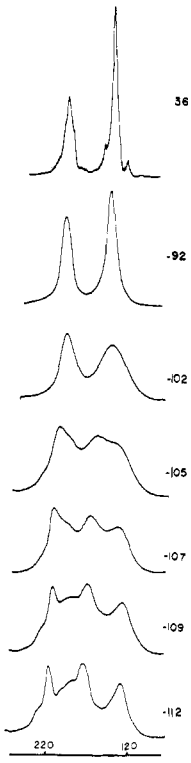
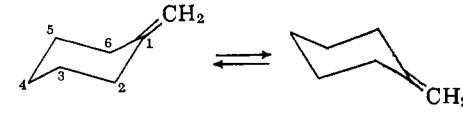


Figure 1. The alkyl portion of the pmr spectrum of methylenecyclohexane at 100 MHz. The peak positions, in hertz, are relative to internal TMS.

The pmr spectrum of methylenecyclohexane at ambient temperature consists of three signals: (a) a barely resolved triplet of lines (apparent J = 0.9 Hz, relative area 2) centered at 4.49 ppm, (b) a broad triplet (apparent J = 4.7 Hz, relative area 4) centered at 2.06 ppm, and (c) an ill-defined multiplet (relative area 6) centered at 1.52 ppm downfield from internal tetramethylsilane. These signals can comfortably be assigned to the vinyl protons, the 2- and 6-methylene



groups, and the 3-, 4-, and 5-methylene groups, respectively. As the temperature of the sample is progressively lowered, the methylene portion of the spectrum broadens and finally, at temperatures below $-100°$ evolves into at least four broad signals centered at 2.16, 1.96, 1.74, and 1.29 ppm (Figure 1). Experiments at both 60 and 100 MHz confirm that the separations between these four envelopes correspond to chemical shifts.[9] The width of the peaks must be due to extensive spin–spin coupling since both the vinyl and the reference signals remain sharp at all temperatures.

(1) For reviews see (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y. 1965; (b) H. Feltkamp and N. C. Franklin, *Angew. Chem. Intern. Ed. Engl.*, **4**, 774 (1965); (c) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965. Some more recent work includes (d) S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nararajan, and J. D. Roberts, *J. Am. Chem. Soc.*, **89**, 88 (1967); (e) J. B. Lambert and R. G. Keske, *ibid.*, **88**, 620 (1966); (f) F. A. L. Anet and A. J. R. Bourn, *ibid.*, **89**, 760 (1967).
(2) F. A. Bovey, F. P. Hood, E. W. Anderson, and R. L. Kornegay, *J. Chem. Phys.*, **41**, 2041 (1964).
(3) F. A. L. Anet and M. A. Haq, *J. Am. Chem. Soc.*, **87**, 3147 (1965).
(4) Reference 1a, p 112.
(5) B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962).
(6) S. Winstein and N. J. Holness, *ibid*, **77**, 5562 (1955).
(7) H. Kwart and T. Takeshita, *ibid.*, **86**, 1161 (1964).
(8) W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1961).

(9) Spectra were recorded with Varian Associates HA-100 and JEOL C-60H spectrometers using a 10% sample of methylenecyclohexane (Aldrich) in Freon-11. Temperatures were determined with a Digitec Model 560 digital thermometer and are believed to be accurate to a least 1°.