The n.m.r. spectrum of this material (15%, CCl_4) showed two fairly well-resolved quartets ($J \sim 3$ c.p.s.), as expected for the equatorial protons at C-1 and C-2; these absorptions were centered at 4.29 and 5.33 p.p.m. (tetramethylsilane = 0).

trans-4-*t*-**Butylcyclohexene Oxide.**—The chloro ester 1, 3.4 g. (0.01 mole), was dissolved in 50 ml. of refluxing methanol. To this solution was added 4 g. of potassium carbonate dissolved in approximately 5 ml. of water. The mixture was refluxed with occasional swirling for 1 hr., after which the contents were taken up in water and extracted twice with pentane. The pentane was dried with potassium carbonate and evaporated; the residue was flash distilled to give 1.4 g. of *trans*-4-*t*-butylcyclohexene oxide (91%). The infrared spectrum was essentially identical with that of the mixed *cis* and *trans* epoxides, and showed no carbonyl absorption. Vapor phase chromatography (DEGS) indicated a purity of >99%.

trans-**2-Chloro**-*cis*-**4**-*t*-**Butylcyclohexyl** *p*-**Nitrobenzoate.**—The second crops from the three initial recrystallizations of isomer 1 were combined and recrystallized four times from methanol to give 44 g. of material, m.p. 71–72°. This was found to be a mixture of about 80% 2 and 20% 1 by examination of the epoxides obtained on base-catalyzed hydrolysis. Repeated recrystallization from methanol failed to change this ratio appreciably, indicating the probable formation of a mixed compound. Recrystallization from aqueous acetic acid gave poor yields of material with a wide melting point range; 1.5 g. of product, m.p. 60–81°, was obtained after numerous recrystallizations and found to be about 95% 2, 5% 1 by hydrolysis to epoxide. The melting point range is indicative of a eutectic containing a high per cent of 2. Because of the poor yields, additional efforts along these lines were abandoned, and this slightly impure material was used for analysis.

Anal. Found: C, 60.2; H, 6.5.

The n.m.r. spectrum of 2 was very similar to that of 1, two quartets centered at 4.40 and 5.22 p.p.m., indicating again equatorial protons attached to the carbon atoms bearing polar substituents.

Configuration of the Epoxides.—The *trans* epoxide was identified by lithium aluminum hydride reduction, which gives as the major product *trans*-3-*t*-butylcyclohexanol, as expected by diaxial opening of the epoxide. In analogous manner, the *cis* epoxide gave mainly *cis*-4-*t*-butylcyclohexanol. A more extensive discussion of this reaction is reserved for a later communication.

Acknowledgment.—The authors are indebted to the American Chemical Society Petroleum Research Fund for support of this work.

Identification and Separation of the Isomeric 2-Methylpyrazine Mono-N-oxides[1]

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Oxidation of 2-methylpyrazine with an equivalent of hydrogen peroxide in acetic acid was reported by Koelsch and Gumprecht[2a] to lead to two isomeric mono-N-oxides, the 1-oxide (I) and the 4-oxide (II). The 1-oxide was identified[3] by rearrangement with acetic anhydride[4] to yield, after saponification, pyrazinemethanol. The sample thought to have been the 4-oxide, under the same conditions, gave a compound (m.p. 68–69°) assumed to be 5-methyl-2(1H)-pyrazinone.[2b]

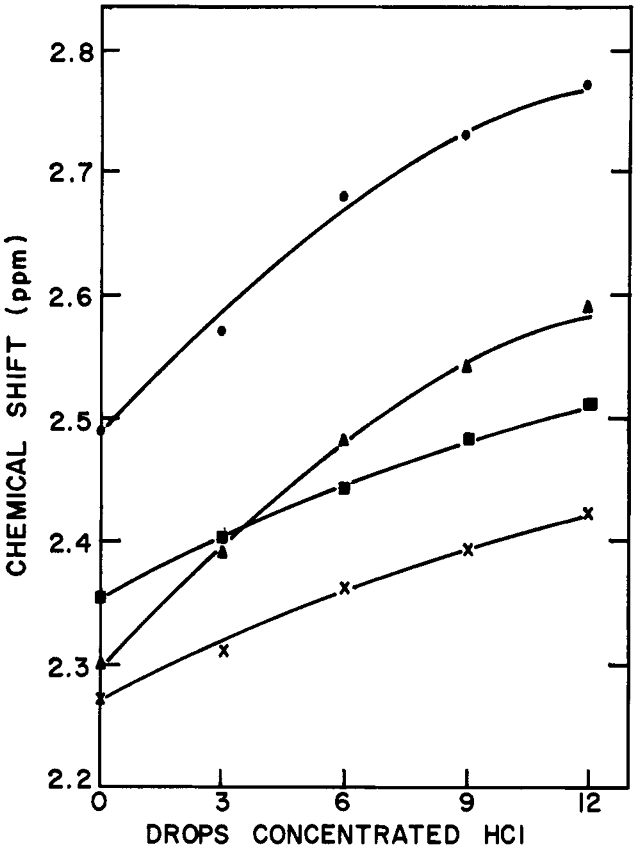
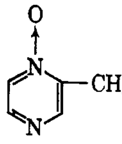


Fig. 1.—Effect of protonation on the chemical shifts for the methyl group in the n.m.r. spectra of pure 2-methylpyrazine 4-oxide (●), 2-methylpyrazine 1-oxide (■), and a eutectic mixture of the 1- and 4-oxides (×, ▲).



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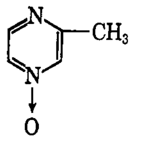

II

Klein and Berkowitz[5a] have questioned the existence of 2-methylpyrazine 1-oxide in concluding that the two samples that they obtained from the mono-N-oxidation were actually polymorphs of the 4-oxide melting at 45 and 80–82°.[5b] Their chemical evidence for polymorphism was the preparation of the same *picrate* from the two samples, and conversion of both in the low yields to 3-chloro-2-methylpyrazine.[6] The exist-

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(1) Presented in part at the 4th Omnibus Conference on Experimental Aspects of NMR Spectroscopy, Pittsburgh, Pa., March 2, 1963.

(2) (a) C. F. Koelsch and W. H. Gumprecht, *J. Org. Chem.*, **23**, 1603 (1958). (b) At the time, the authors were unaware of the melting point of 126–128° reported for this pyrazinone by G. Karmas and P. E. Spoerri [*J. Am. Chem Soc.*, **74**, 1580 (1952)].

(3) See also M. Asai, *J. Pharm. Soc. Japan*, **79**, 1273 (1959); *Chem. Abstr.*, **54**, 4607*i* (1960).

(4) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

(5) (a) B. Klein and J. Berkowitz, *ibid.*, **81**, 5160 (1959). (b) Selective N-oxidation at one of the two heteronitrogens in 2-methylpyrazine would be surprising, especially since the formation under the same conditions of both possible mono-N-oxides of 2,6-dimethylpyrazine is reported in this reference. The described separation of the polymorphs by distillation also must be considered unusual since molecular interaction in the vapor phase would not be expected to have a significant influence on orientation in the crystal lattice.

(6) If it is recalled that their higher melting sample melted 10° lower than that reported by Koelsch and Gumprecht, then it would seem likely that their 2-methylpyrazine 1-oxide was contaminated, probably with the 4-oxide.

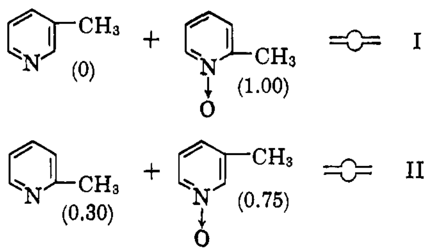

Fig. 2.—Chemical shifts in parentheses of the methyl groups in the n.m.r. spectra of 2- and 3-picolines and their N-oxides (in p.p.m. relative to 3-picoline), and relation of these structures to the 2-methylpyrazine mono-N-oxides.

ence of higher and lower melting forms of isoquinoline N-oxide was cited as precedent.[7]

We now present physico-chemical data for the formation of both 2-methylpyrazine 1- and 4-oxides under mono-N-oxidation conditions. Examination of the n.m.r. spectra of aqueous solutions of samples of these materials, separated in this work by careful fractional crystallization and melting at 90–91° and 44–45°, has shown that the higher melting material contains a single type of methyl group, whereas the lower melting substance contains two types of methyl groups (y-intercepts of the three lower curves in Fig. 1). The presence of two methyl group types in the 44–45° sample indicates that it is a eutectic mixture. The composition of the mixture, based on the areas under the methyl group peaks, was 53% of the component with the larger chemical shift and 47% of the other, which essentially agrees with the values of 52 and 47% determined by vapor phase chromatography.

The displacement of the chemical shifts of the methyl groups from each other in the n.m.r. spectrum of the eutectic is only 0.03 p.p.m. Because this difference is very small, it is not possible to relate positively either of the components in the mixture to the pure isomer by comparison of spectra. The minuteness of this difference was predicted by measurement of the positions of the methyl groups in the spectra of 2- and 3-picolines and their N-oxides, followed by summation and comparison of the proper values for relating these structures to the equivalent 2-methylpyrazine N-oxides (Fig. 2). A difference of 0.05 p.p.m. is predicted from these measurements and calculations.

The fact that protonation occurs at the unoxidized nitrogen in mono-N-oxides of pyrazine derivatives[2a,8] was used to resolve more completely the chemical shifts of the methyl groups in the n.m.r. spectrum of the eutectic, and thereby permit relation of one of the components to the pure isomer (Fig. 1). The relation indicates that the component in lower concentration (see above) is identical with the pure isomer melting at 90–91°. The position of protonation also was used to identify the isomers. It is well known[9] that electronic changes occurring in an aromatic system have a more pronounced effect on the chemical shifts of substituents the nearer these groups are to the site of the change. On this basis, the isomer melting at 90–91°, being less affected by protonation than the major component of the eutectic (Fig. 1), is 2-methylpyrazine 1-oxide.[10] This conclusion is in agreement with earlier findings[2a,3] and was further verified by n.m.r. identification of a new sample of pyrazinemethanol prepared from this isomer.

The remaining task was to obtain a pure sample of 2-methylpyrazine 4-oxide for comparison in protonation behavior with the major constituent of the eutectic. The closeness of the melting point (64–67°) of the sample of this component obtained from the vapor phase chromatograph (see Experimental) to that reported by Koelsch and Gumprecht for 5-methyl-2(1H)-pyrazinone and by Asai[3] for the 4-oxide indicated that these materials might be identical. This possibility had been suggested by Asai and Klein[5a] to explain the inconsistent properties of Koelsch and Gumprecht's "pyrazinone." The expected inertness[11] of the 4-oxide to acetic anhydride was used to separate it from the 1-oxide in the eutectic, a process which Koelsch and Gumprecht undoubtedly effected in the preparation of their "pyrazinone." The sample of 2-methylpyrazine 4-oxide, m.p. 69–70°, thus obtained parallels the behavior of the second component of the eutectic on protonation (Fig. 1).

Experimental[12]

Preparation and Fractional Crystallization of 2-Methylpyrazine Mono-N-oxides.—The procedure of Koelsch and Gumprecht[2a] was used to oxidize 386 g. (4.10 moles) of 2-methylpyrazine with 4.00 moles of hydrogen peroxide (as a 30% aqueous solution) in 4700 ml. of acetic acid. The mono-N-oxides were separated from a small amount of 2-methylpyrazine 1,4-dioxide by vacuum distillation, giving 406 g. (90%) of the mixture. The "diamond" procedure[13] of fractional crystallization was performed on five 20-g. portions of this mixture using anhydrous ether as solvent. It was found that treatment of the mother liquors with Darco activated carbon just prior to crystallization of the more soluble fraction increased the ease of crystallization and purity of this fraction. There were obtained from the fractionation 58 g. (29%) of a less soluble fraction, m.p. 90–91°, and 80 g. (40%) of a more soluble fraction, m.p. 44–45°.

Vapor phase chromatography of the two fractions using a tetramethylene adipate column at 170–200° revealed that the higher melting fraction had a purity of 99% in one component, whereas the lower melting fraction contained two components. These two components were trapped from the exit of the column. The more volatile component, present as 47% of the mixture, melted at 90–91°. The less volatile component, forming 52% of the mixture, melted at 64–67°.

N.m.r. Studies.—The n.m.r. spectra of redistilled 2- and 3-picolines and their N-oxides were measured in tetrachloroethylene solution using the Varian Model V-4311 n.m.r. spectrometer. The results of these measurements are shown in Fig. 2.

The Varian A-60 n.m.r. spectrometer was used in the study of the chemical shifts associated with the methyl groups of the isomeric 2-methylpyrazine mono-N-oxides in aqueous solution. The use of field-frequency control in the A-60 greatly facilitated the measurements. It might be thought that the use of a water-soluble internal reference with the conventional spectrometer might be adequate. However, this assumption overlooks the probability of shifts of the reference peak owing to changing pH. Furthermore, unless the time-consuming technique of extrapolation to infinite dilution is used, it is difficult to assess the dif-

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[7] M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956). This reference, in fact, describes isoquinoline N-oxide of different degrees of hydration and, therefore, of different melting points.

[8] J. K. Landquist, *J. Chem. Soc.*, 1885 (1956).

[9] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 258–266.

[10] In the original identification of the isomeric 2-methylpyrazine mono-N-oxides a confusion of samples occurred, leading to an interchange of the melting points reported in ref. 2a.

[11] B. Klein, J. Berkowitz, and N. E. Hetman, *J. Org. Chem.*, **26**, 126 (1961).

[12] Melting points are corrected.

[13] A. Weissberger, "Physical Methods of Organic Chemistry," Vol. III, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 491.

ferent effects of the two structures on the chemical shift of the reference material. The results of the study are shown graphically in Fig. 1; no importance should be placed upon the absolute chemical shifts, since no attempt was made to set the instrument at zero.

Verification of the Compound Melting at 90–91° as 2-Methylpyrazine 1-Oxide (I).—In order to remove the confusion of this material with 2-methylpyrazine 4-oxide,[10] a 22.0 g. (0.20 mole) sample was treated with 58 ml. of acetic anhydride[4] in the manner described by Koelsch and Gumprecht.[2a] Their methods of isolation of the ester and its subsequent saponification were also used. In this way there was obtained 5.7 g. (26%) of pyrazinemethanol as a colorless oil, b.p. 59–60° at 0.23 mm. The n.m.r. and infrared spectra of the sample were indicative of a primary alcohol.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.85; H, 5.45; N, 25.47.

Separation of 2-Methylpyrazine 4-Oxide (II) from the Eutectic Melting at 44–45°.—A mixture of 22.0 g. of the eutectic and 58 ml. of acetic anhydride was boiled under reflux for 1 hr. The resulting dark oil was allowed to stand at room temperature for 5 days. Evaporation of the excess acetic anhydride and acetic acid on a steam bath under reduced pressure left a viscous black oil which, when vacuum distilled, yielded 22.7 g. of a yellow, partially crystalline oil. The crystalline portion was separated by dissolving the mixture in ether at a concentration of 25%, cooling the solution, and decanting the mother liquor. Final purification was performed by recrystallization from ether at room temperature, giving 8.3 g. (73% assuming the eutectic was 52% the lower melting isomer, as indicated by vapor phase chromatography) of 2-methylpyrazine 4-oxide as white crystals, m.p. 69–70°.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.56; H, 5.35; N, 25.51.

Terpenoids. XLV. Structure and Absolute Configuration of Canarone

A. D. Wagh, S. K. Paknikar, and S. C. Bhattacharyya

Contribution No. 574 from the National Chemical Laboratory, Poona, India

Received February 24, 1964

During the course of separation of the constituents of the Black dammar resin (*Canarium strictum* Roxb.),[1] we isolated a small amount of a new monoethynoid sesquiterpene ketone, canarone, $C_{15}H_{24}O$. On the basis of the results described below, it can be represented by structure I and its absolute configuration by the stereoformula IX.

The infrared spectrum of canarone exhibited bands at 1700 cm.$^{-1}$ characteristic of a 2,2-dialkyl cyclohexanone[2] and at 1420 cm.$^{-1}$ due to a –CO–CH$_2$– grouping. Bands at 3080, 1640, and 890 cm.$^{-1}$ indicated the presence of terminal methylene group. Ultraviolet spectrum showed the absence of a conjugation.

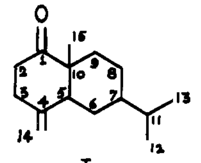
Canarone (I) on lithium aluminum hydride reduction gave canarol (IV), which on selenium dehydrogenation afforded eudalene (II). Canarone should therefore possess a eudalenic skeleton.

Hydrogenation of canarone (I) with Adams catalyst in acetic acid yielded a tetrahydro product, dihydrocanarol (VI), lacking the infrared bands due to ketone and terminal methylene groups, but instead showed an intense band at 3500 cm.$^{-1}$ due to a hydroxyl group.

Hydrogenation of canarol (IV) in acetic acid over Adams catalyst also afforded dihydrocanarol (VI), showing the presence of one double bond in canarol (IV) and hence in canarone (I). In conformity with this, quantitative hydrogenation of canarone over palladium–charcoal catalyst in methanol furnished the saturated ketone, dihydrocanarone (III). Canarone therefore should be a bicyclic ketone.

The position of the carbonyl function at C-1 was fixed by reacting canarone with methyl magnesium iodide and dehydrogenating the resulting tertiary carbinol to furnish 4-methyl eudalene (VII).[3]

Ozonolysis of canarol (IV) yielded formaldehyde as the only volatile component. The nonvolatile portion consisted of the hydroxy norketone (V), which gave a negative iodoform test. In its infrared spectrum, it showed strong absorption bands at 3400 (hydroxyl), 1710 (six-membered ring ketone), 1420 (–CO–CH$_2$), 1360 and 1375 cm.$^{-1}$ (isopropyl). This locates the position of the ethylenic linkage between C-4–C-14 and not in the isopropyl side chain. In further support for this, canarone and all the products derived from it exhibited a doublet (between 1360 and 1380 cm.$^{-1}$) in the methyl bending region, indicating the presence of a isopropyl group[4] in the hydroxy norketone (V), and hence the location of the exocyclic methylene group at C-4 in canarone (I).



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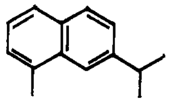

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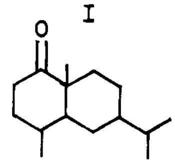

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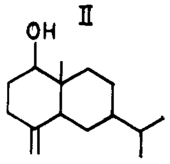

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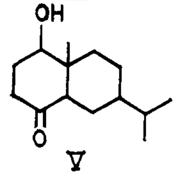

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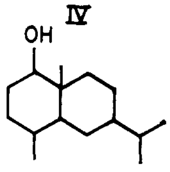

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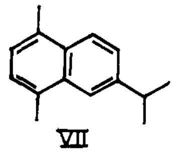

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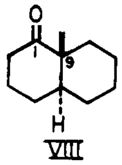
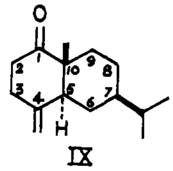


VIII



IX

The rotatory dispersion curve (Fig. 1A) of canarone (I) is the same type (+*ve* Cotton effect, *a* = +20), whereas the curve of the hydroxy norketone (V) (Fig. 1B)

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[1] Kirtikar and Basu, "Indian Medicinal Plants," Vol. 1, 1918, p. 287.

[2] E. J. Corey, T. H. Topie, and W. A. Wozhiak, *J. Am. Chem. Soc.*, **77**, 5415 (1955).

[3] G. Buchi, M. S. Wittenau, and D. M. White, *ibid.*, **81**, 1968 (1959).

[4] Infrared spectrum of canarone also showed the presence of bands at 1183 and 1160 cm.$^{-1}$, attributable to isopropyl group [*cf.* H. L. MacMurry and V. Thornton, *Anal. Chem.*, **24**, 318 (1952)].