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COMMUNICATIONS

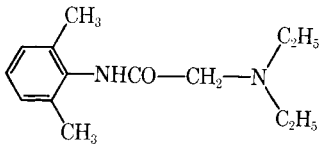
Disproportionation of Lidocaine Sulfate Dihydrate in Certain Organic Solvents

Keyphrases ☐ Lidocaine sulfate dihydrate—synthesis ☐ Disproportionation, organic solvents—lidocaine sulfate dihydrate ☐ IR spectrophotometry—identity

Sir:

The disproportionation of lidocaine[1] sulfate dihydrate into the bisulfate and amine base has been observed.

$$[XYLH]_2SO_4 \cdot 2H_2O \longrightarrow XYL + [XYL]HSO_4 + 2H_2O$$

where XYL = lidocaine 

It was this reaction that presented difficulty in the preparation of lidocaine sulfate. Such a disproportionation was suspected when attempts to prepare the sulfate in the presence of acetone yielded only the bisulfate. The sulfate was ultimately synthesized utilizing a suitable mixed organic solvent system, namely, 95% ethanol and ethyl ether.

Lidocaine Sulfate Dihydrate—Fifty-two grams (0.22 mole) of lidocaine base was dissolved in 125 ml. of ether. To 50 ml. of 95% ethanol previously cooled in an ice-water bath was added slowly, 5.3 ml. (9.8 g.; 0.1 mole) of concentrated sulfuric acid. The acid-alcohol mixture was added dropwise to the ether solution of the base under vigorous magnetic stirring. After complete addition, the precipitate was isolated by filtration and washed with several portions of ether. A yield of 56.8 g. (93%) was obtained. Recrystallization from 15% ethanol in benzene by cooling from 30 to 10° gave colorless crystals, m.p. 106–108°.[2] IR spectrum[3] showed S-O str. at 1125 cm.$^{-1}$ [lit. 1125–1080 cm.$^{-1}$ (1)].

Anal.[4]—Calcd. for $C_{28}H_{50}N_4O_8S$ (602.80): C, 55.79; H, 8.36; N, 9.30; S, 5.32; XYL, 77.75; H_2O, 5.97%; mol. wt., 603. Found: C, 55.99; H, 8.61; N, 9.07; S, 5.60; XYL, 77.52; H_2O, 6.09%; mol. wt., 618.

Supplementary Data—Assay (2) of lidocaine bisulfate, m.p. 218–220° [lit. 210–212° (3)], for lidocaine base gave the following results: Calcd., 70.50%; Found, 70.22%. IR spectrum showed S-O str. at 1180 and 1070 cm.$^{-1}$ [lit. 1190–1160 and 1080–1015 cm.$^{-1}$ (1)]. The pH of a 2% solution in saline of lidocaine sulfate dihydrate and lidocaine bisulfate was 5.5 and 2.7, respectively. Melting point determination on lidocaine base gave the value of 67–69° [lit. 66–69° (4, 5)].

Disproportionation Reaction Procedure—The solvents used were absolute ethanol, acetone, benzene, carbon tetrachloride, chloroform, ether, and water. Five grams (0.0083 mole) of lidocaine sulfate dihydrate was placed in 200 ml. of solvent contained in a 500-ml. stoppered flask and mixed well. After 3 days at room temperature the mixture was filtered. In the case of the solvents acetone and chloroform, in which a visible reaction had taken place, the weight and melting point of the precipitate formed was obtained. In the case of the other solvents in which no visible reaction appeared, the filtrate was evaporated to dryness over a steam bath. The weight and melting point was obtained on the residue. Further confirmation of the recovered sulfate and the reaction products lidocaine base and bisulfate was obtained by IR spectra.

Results—The sulfate was completely soluble in absolute ethanol and water. No precipitation occurred upon standing for 3 days. Upon evaporation of the filtrate the unreacted sulfate was recovered in both cases, m.p. 106–108°; recovery 4.8 g. (96%).

In benzene, carbon tetrachloride, and ether there was no visible evidence of a reaction taking place. The sulfate appeared to be insoluble in these solvents. Evaporation of the filtrates gave a 5–11% yield of lidocaine base indicating a limited disproportionation.

[1] Xylocaine (Lidocaine USP), Astra Pharmaceutical Products, Inc., Worcester, Mass.
[2] All melting point values corrected, using a Mel-Temp apparatus.
[3] Perkin-Elmer model 137B, KBr.

[4] Microanalyses involving C, H, and N were performed by Schwarzkopf Laboratories, Woodside, N. Y. All other analyses were performed by our Analytical Laboratories. Sulfur, gravimetric as barium sulfate; lidocaine base, alkaline (NH_4OH) chloroform extraction, nonaqueous perchloric acid titration (2); water, Karl Fischer method; molecular weight, classical method with Fisher apparatus, Beckman thermometer.

The solvents acetone and chloroform produced a different and distinguishable precipitate. The sulfate dissolved at a moderate rate in acetone yielding, simultaneously, a light voluminous precipitate. In chloroform, the sulfate dissolved immediately followed by a slow but continuous precipitation. Isolation of the precipitate gave a 96% and 57% yield of lidocaine bisulfate in acetone and chloroform, respectively.

Thus over a 72-hr. period at room temperature a substantial disproportionation of lidocaine sulfate dihydrate to yield bisulfate and base was observed in acetone and chloroform.

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Occurrence of Bis-Noryangonin in *Gymnopilus spectabilis*

Keyphrases ☐ *Gymnopilus spectabilis*—analysis ☐ Bis-Noryangonin, occurrence—*Gymnopilus spectabilis*

Sir:

Gymnopilus spectabilis (Fr.) Singer has been reported to elicit hallucinogenic responses (1–3). Experimental pharmacologic data for confirmation or explanation of these reports are lacking for both the mushroom and known constituents of *Gymnopilus* species. However, bis-noryangonin [4-hydroxy-6-(4-hydroxystyryl)-2-pyrone], a styrylpyrone related to those occurring in kava root, has been isolated from *G. decurrens* Hesler (4), and the presence of indole derivatives other than psilocin and psilocybin has been suggested in *G. spectabilis* on the basis of thin-layer chromatographic examination (3).

Carpophores of *G. spectabilis* were collected near Tenino, Washington, on November 12, 1968, and freeze-dried. The powdered mushroom (50 g. of a 20-mesh powder) was extracted by shaking for 24 hr. at room temperature with 2 l. of ethyl acetate. TLC of the extract using a silica gel adsorbent and ethyl acetate–*n*-hexane–glacial acetic acid (5:3:1), chloroform–methanol (3:1), and 95% ethanol solvent systems revealed a constituent which was indistinguishable from bis-noryangonin. When the chromatograms were sprayed with 2% *p*-dimethylaminobenzaldehyde in acidic ethanol (concentrated HCl–95% ethanol, 1:3), this constituent formed a green chromophore which changed to purple with heat, a characteristic feature of bis-noryangonin.

The constituent suspected of being bis-noryangonin was isolated using the dry-column chromatographic procedures previously established for this compound (4). The IR spectrum (KBr pellet)[1] of the isolated material was consistent with this tentative identification showing characteristic peaks at 3200 cm.$^{-1}$ (OH); 1650 cm.$^{-1}$ (C=O of lactone ring); 1600, 1510 cm.$^{-1}$ (C=C). The UV spectrum[2] λ_{max}^{EtOH} 354 mμ (log ϵ 4.22) and 224 mμ (log ϵ 4.33) was also comparable to that observed with reference bis-noryangonin.

The methyl derivative of the isolated constituent was prepared by a proven method (4). No depression in the 156–157° m.p. of the derivative was noted upon admixing with known yangonin [4-methoxy-6-(4-methoxystyryl)-2-pyrone]. The mass spectrum[3] showed a parent and base ion peak at *m/e* 258.0892, both observed and calculated for $C_{15}H_{14}O_4$. The next most abundant peak was at *m/e* 230.0943 (28%), as anticipated from the known fragmentation pattern of yangonin (4, 5). The IR spectrum of the methyl derivative was identical in all respects with that of authentic yangonin, and the UV spectrum λ_{max}^{EtOH} 356 mμ (log ϵ 4.49) and 218 mμ (log ϵ 4.33) was in agreement.

The experimental observations establish the occurrence of bis-noryangonin in the fruiting bodies of *G. spectabilis*. No evidence of indole constituents was noted during the investigation, and it is presumed that the purple chomophore developing upon treatment of this styrylpyrone with *p*-dimethylaminobenzaldehyde explains the earlier suggestion of indole metabolites (3).

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[3] Picker-AEI MS-9 mass spectrometer, Picker Nuclear Division, White Plains, N. Y.