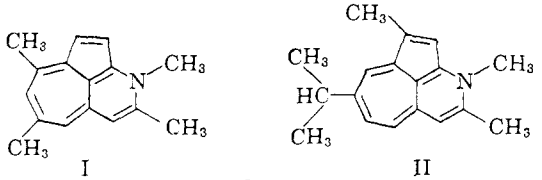
COMMUNICATIONS TO THE EDITOR

1*H*-CYCLOHEPTA[d,e]-1-PYRINDINE, A NEW CONJUGATE-UNSATURATED HETEROCYCLIC SYSTEM

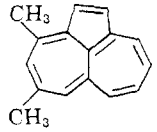
Sir:

In the course of studies on heterocyclic compounds which are iso-π-electronic with non-benzenoid aromatic hydrocarbons,[1] the synthesis of two derivatives (I and II) of the hitherto unknown 1*H*-cyclohepta[d,e]-1-pyrindine has been achieved. This new ring system is a π-excessive[2] heteroanalog of the interesting hydrocarbon (III) recently reported by Hafner.[3]



I

II



III

The 1,2,5,7-tetramethyl derivative (I) was prepared from 1-nitro-4,6,8-trimethylazulene.[4] Reductive acetylation[5] of this nitro compound afforded the corresponding 1-acetylamino derivative (IV) in nearly quantitative yield as blue needles, m.p. 178–181°. Found for $C_{15}H_{17}NO$: C, 78.76; H, 7.30; N, 6.46. Visible: λ_{max} 563 mμ (ϵ 524); infrared, 2.94 μ (NH); 5.93 μ.[6] Treatment of IV with sodium hydride followed by the addition of methyl iodide gave 95% of the N-methyl compound (V) as purple crystals, m.p. 162–164° (softening at *ca.* 155°). Found for $C_{16}H_{19}NO$: C, 79.70; H, 7.89; N, 5.82. Visible: λ_{max} 553 mμ (ϵ 525); infrared, 6.01 μ. As anticipated,[7] the intramolecular condensation of V was effected by reaction with sodium N-methylanilide and a 68% (93% net) yield of I[8] was obtained as green needles, m.p. 210–212° (evac. capillary). Found for $C_{16}H_{17}N$: C, 85.96; H, 7.43; N, 6.31. The infrared spectrum showed no peaks corresponding to NH or carbonyl groups. The ultraviolet and visible spectra were quite similar to those reported for III[3] and showed maxima in mμ (log ϵ) at 236 (4.52), shoulder at 243(4.47), 270(4.51), 290(4.26), 358(3.99), 387(3.74), 399(3.81), 423(3.56), shoulder at 630(2.56), 688(2.71), 766(2.72), and 869(2.43).

The pronounced basicity of I was evidenced by complete protonation in 10% sulfuric acid (maxima in mμ (log ϵ) at 238(4.33), shoulder at 253(4.20), 278(4.06), 292(4.04), 301(4.02), shoulder at 323-(3.87), 456(3.10), 481(3.10). and a shoulder at 510-(3.03)) and in formic acid to form red solutions.[9]

A parallel reaction sequence led to II. 3-Acetylaminoguaiazulene[10] was converted to the N methyl derivative (VI), obtained as blue crystals, m.p. 75–77.5°, in 56% yield. Found for $C_{18}H_{23}NO$: C, 80.31; H, 8.67; N, 5.26. Visible: λ_{max} 610 mμ (ϵ 490); infrared, 6.00 μ. Treatment of VI with sodium N-methylanilide gave 61% of II as red-brown needles, m.p. 179–180.5°. Found for $C_{18}H_{21}N$: C, 85.77; H, 8.51; N, 5.73. The ultraviolet and visible spectra of II showed maxima in mμ (log ϵ) at 238(4.47), 253(4.43), 270(4.49), shoulder at 300(3.84), 361(4.12), 398(3.69), 422-(3.62), 449(3.43), shoulder at 690(2.38), 763(2.50), 862(2.50) and 996(2.22). The infrared spectrum showed no absorption corresponding to NH or carbonyl groups.

I and II are fairly stable in crystalline form but decompose on alumina and slowly in solution. Their n.m.r. spectra were consistent with the proposed structures.

Acknowledgment.—We thank the National Science Foundation for support of this work under Grant G 7397.

(1) A. G. Anderson, Jr., W. F. Harrison, R. G. Anderson and A. G. Osborne, *J. Am. Chem. Soc.*, **81**, 1255 (1959); A. G. Anderson, Jr., and W. F. Harrison, *Tetrahedron Letters*, [2], 11 (1960).

(2) A. Albert, "Heterocyclic Chemistry," Essential Books, Fair Lawns, N. J., 1959.

(3) K. Hafner and J. Schneider, *Ann.*, **624**, 37 (1959).

(4) K. Hafner and C. Bernhard, *ibid.*, **625**, 108 (1959).

(5) A. G. Anderson, Jr., J. A. Nelson and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953).

(6) Ultraviolet, visible and near-infrared spectra were measured in cyclohexane solution and infrared spectra in carbon tetrachloride solution.

(7) The acidic nature of the methyl protons in 4-(8)methylazulenes is well established; *cf.* ref. 3.

(8) None of the presumed intermediate tricyclic hydroxy compound was isolated or detected in the reaction mixture.

(9) The basicity of I is in accord with the observation that 2-phenyl-2-pyrindine is appreciably more basic than azulene; A. G. Anderson, Jr., and W. F. Harrison, unpublished results.

(10) K. G. Scheibli, Doctoral Thesis, Eidgenössischen Technischen Hochschule, Zürich, Switzerland, 1952, p. 35.

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AGARITINE: AN IMPROVED ISOLATION PROCEDURE AND CONFIRMATION OF STRUCTURE BY SYNTHESIS

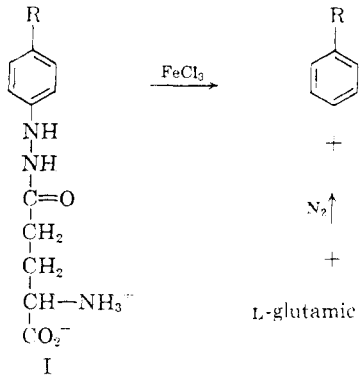
Sir:

In a recent communication[1] structure I (R = CH_2OH) was proposed for agaritine isolated from *Agaricus bisporus*. We have isolated agaritine in yields of *ca.* 1 g./10 lb. of mushrooms by a different process and have confirmed its structure as β-N-(γ-L(+)-glutamyl)-4-hydroxymethylphenylhydrazine by synthesis.

Buttons from two- to three-day old mushrooms[2] were homogenized in methanol (700 g. in 1350

(1) B. Levenberg, *J. Am. Chem. Soc.*, **83**, 503 (1961).

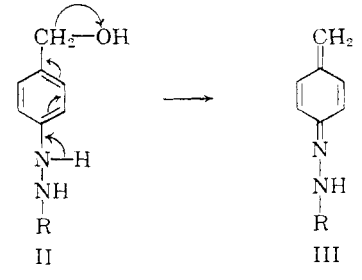
(2) Supplied by the Michigan Mushroom Co., Niles, Michigan.



ml.) at 4–10° for one minute in a large Waring Blendor. After filtration, the methanol was evaporated *in vacuo*. The aqueous concentrate (2 l.) was passed through a 7.5 × 43 cm. column of Dowex-2 (Ac^-), at the rate of 500–600 ml./hr. The column was eluted with deionized water and the effluent between 1350 and 3700 ml. was passed through a 4″ × 24″ column of Dowex-50 (NH_4^+) at a rate of 800 ml./hr. The column was eluted with deionized water and effluent volume from 8.4 to 10.4 l. was concentrated *in vacuo* to 50 ml. An equal volume of ethanol and 200 ml. of 1-butanol were added and the solution was evaporated *in vacuo* until it became hazy. After standing at 4° for two days 351 mg. of glistening white crystals was obtained; m.p. (dec.) 205–209°, (calcd. for $C_{12}H_{17}N_3O_4$: C, 53.9; H, 6.43; N, 15.7; O, 23.9; $-NH_2$, 5.2. Found: C, 53.9; H, 6.48; N, 15.5; O, 24.4; $-NH_2$, 5.5) pK_as in water: 3.4 and 8.86; λ_{max} 237 mμ (ε 12,000) and 280 mμ (ε 1400); $[\alpha]^{25}D$ + 7° (*c*, 0.8 in water).

N.m.r. spectral analysis indicated the presence of a *p*-disubstituted benzene ring and the possibility of the $-CH_2OH$ group in the ring. Degradation of agaritine with ferric chloride[3] yielded glutamic acid, nitrogen and benzyl alcohol.

The synthesis of substituted phenylhydrazides of glutamic acid (I) including agaritine (R = CH_2OH) was achieved by condensation of the γ-azide of N-carbobenzoxy-L-glutamic acid[4] with the appropriate hydrazine in ether solution. In the case of analogs such as I where R = H and CH_3 no particular difficulty was encountered and yields of *ca.* 60% were obtained. The protective group was removed by hydrogenolysis. However, the synthesis of agaritine itself presented special problems because of the instability of α-hydroxy-*p*-tolylhydrazine (II, R = H) and its derivatives. Apparently oxygen is eliminated readily in either acid or alkaline medium to yield reactive species III (R = γ-glutamyl or H) which can undergo various side reactions. For this reason it was necessary to devise experimental conditions whereby all steps were carried out under essentially neutral conditions. The α-hydroxy-*p*-tolylhydrazine required for the synthesis of agaritine was prepared by lithium aluminum hydride reduction of *p*-carboxymethylphenylhydrazine in boiling ether. A considerable portion of the ester was reduced to *p*-tolylhydrazine under these mild conditions. This was considered evidence for the elimination reaction (II → III).



Since no satisfactory method was found to isolate and purify α-hydroxy-*p*-tolylhydrazine, aqueous sodium chloride solution was added to the reduction mixture, the inorganic salts were removed by filtration and the γ-azide of carbobenzoxy-L-glutamic acid was added with stirring to the ether solution at 0°. The solvent was evaporated, the protecting group was removed by mild hydrogenolysis[5] and the product was purified by chromatography over Dowex-50 to provide a 6% yield of crystalline agaritine. On the basis of color reactions, R_f values, ultraviolet and infrared spectra, elemental analyses, m.p. and specific rotation the synthetic material was identical with that isolated from *A. bisporus*.

We are grateful to Dr. Bruce Levenberg, Department of Biological Chemistry, University of Michigan, for introducing this problem to us and for his handling of the biochemical aspects of it, to Wm. A. Struck and associates for analytical data, to Dr. George Slomp for the n.m.r. work and to John Woltersom for technical assistance.

(3) H. B. Milne, J. E. Halven, D. S. Ho and M. S. Mason, *J. Am. Chem. Soc.*, **79**, 637 (1957).

(4) S. G. Waley, *J. Chem. Soc.*, 517 (1955).

(5) Using 10% palladium-charcoal catalyst at 1 atm. at room temperature for one hour. However, using 10% palladium-barium sulfate catalyst at 1 atm. for 7 hours at room temperature, agaritine was converted quantitatively to the *p*-tolyl analog.

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OPTICAL ROTATORY DISPERSION STUDIES. LVII.[1] THE OCTANT RULE AND THE *t*-BUTYL GROUP. EVIDENCE FOR A TWIST FORM IN *cis*-2-*t*-BUTYL-5-METHYLCYCLOHEXANONE[2]

Sir:

From a consideration of the rotatory dispersion curves of (−)-menthone (I)[3] and (+)-isomenthone (II) it was suggested[4] that the energy difference between the axial and equatorial forms of 2-isopropylcyclohexanone is unexpectedly small (less than 0.9 kcal.). This was confirmed by direct

(1) Paper LVI, C. Djerassi and D. Herbst, *J. Org. Chem.*, in press.

(2) Supported by grant No. CRTY-5061 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. A portion of the experimental work was performed in 1959 at Wayne State University.

(3) All structural formulas in this communication represent correct absolute configurations according to the steroid notation.

(4) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., New York, N. Y., 1960, pp. 106, 187.