and 6.17 μ (vs); λ_{max}^{MeOH} 325 nm (plateau) (ϵ 5500), 291 (29,000), 235 (18,000), and 211 (23,000). **9a** was soluble in aqueous bicarbonate.

Anal. Calcd for $C_{16}H_{14}ClFO_6$ (356.73): C, 53.90; H, 3.96; Cl, 9.94; F, 5.33. Found: C, 53.56; H, 3.72; Cl, 9.77; F, 4.92.

5'-Tosyloxygriseofulvin (12).—A mixture (suspension) of 369 mg (0.001 mol) of 5'-hydroxygriseofulvin[4a,12] and 380 mg (0.002 mol) of tosyl chloride in 2.5 ml of dry pyridine was stirred at room temperature for 27 hr. An additional 190 mg (0.001 mol) of tosyl chloride was then added to the still heterogeneous reaction mixture and stirring continued for another 25 hr. A completely homogeneous reaction mixture formed which was poured into ice–water to precipitate the solid 5'-tosyloxy derivative. The aqueous mixture was made strongly basic (pH $\geq$ 13) with 2 *N* NaOH and stirred at room temperature for 20 min (to destroy excess tosyl chloride) before collecting the product, yield 410 mg (79%), mp 207–212°. Heating the mixture suspended in boiling methanol raised the melting point to 211–214°, λ_{max}^{KBr} 5.85 μ.

Anal. Calcd for $C_{24}H_{23}O_9SCl$ (522.95): C, 54.12; H, 4.43; Cl, 6.78; S, 6.13. Found: C, 54.45; H, 4.30; Cl, 7.08; S, 6.11.

Dehydrogriseofulvin (11) from 5'-Bromogriseofulvin and Silver Fluoride or Potassium Fluoride in Acetonitrile.—A solution of 0.59 g (0.0013 mol) of 5'-bromogriseofulvin in 10 ml of acetonitrile was heated under reflux (protected from light by wrapping the flask in aluminum foil) with 0.5 g (0.004 mol) of AgF (Alfa Inorganic Inc., Beverly, Mass.) for 17 hr and then filtered through Celite. The filtrate was evaporated and 200 mg of the residue obtained was thick-layer chromatographed (developing solvent PhH–EtOAc 1:1). Two somewhat overlapping zones were obtained which were eluted with acetone containing some MeOH. The faster of the two (37 mg) was identified as starting 5'-bromogriseofulvin by melting point and ir and tlc. The slower one (58 mg, mp 270–274° dec) was recrystallized from methanol to give material melting at 282–285° dec.

Anal. Calcd for $C_{17}H_{15}ClO_6$ (350.75): C, 58.17; H, 4.31; Cl, 10.10. Found: C, 57.49; H, 4.47; Cl, 10.36.

The infrared and nmr spectra of the compound were identical with those of authentic dehydrogriseofulvin.

Dehydrogriseofulvin was also the exclusive product obtained from the treatment of 5'-bromogriseofulvin with a large excess of potassium fluoride dihydrate in refluxing acetonitrile (18 hr).

Treatment of 5'-Bromogriseofulvin with Methanolic Methoxide. Formation of 2-Carbomethoxy-2',3,5-trimethoxy-4'-hydroxy-6-chloro-6'-methyldiphenyl Ether (10).—A suspension of 100 mg (0.23 mmol) of 5'-bromogriseofulvin in 1 ml of methanol was treated with 0.23 ml of *ca.* 1 *M* sodium methoxide in methanol (0.23 mmol), and the mixture was stirred at room temperature for 16 hr. Ice–water and methylene chloride were added and the mixture was extracted with dilute sodium hydroxide. Acidification of the basic extract gave 34 mg of a colorless solid A. Drying and evaporating the methylene chloride solution gave 24 mg of a yellow solid B.

Solid A melted at 195–199°. The analytical sample, obtained by recrystallization from methanol, melted at 194–199°: λ_{max}^{KBr} 3.0 (m), 5.75 (sh, m), and 5.85 μ (s); λ_{max}^{MeOH} 285 nm (ϵ 5400).

Anal. Calcd for $C_{18}H_{19}O_7Cl$ (382.79): C, 56.48; H, 5.00; Cl, 9.26. Found: C, 56.20; H, 4.82; Cl, 9.55.

The physical constants cited are in excellent agreement with those reported for **10** by Kyburz, *et al.*[3]

Solid B was identified as starting 5'-bromogriseofulvin (after recrystallization from MeOH) by melting point and mixture melting point, and tlc and infrared spectroscopy.

10 was also the exclusive transformation product when the reaction was conducted in refluxing methanol (1 hr).

Reaction of 5'-Bromogriseofulvin (6) and Sodium Thiophenolate.—To a solution of 0.46 mmol of sodium thiophenolate in 3 ml of methanol [prepared by adding 70 mg (0.64 mmol) of thiophenol to 0.46 ml of 1 *M* sodium methoxide in methanol] was added 0.2 g (0.46 mmol) of 5'-bromogriseofulvin **6**. The resulting suspension was stirred at room temperature for 26 hr and diluted with water, and the solid was collected, yield 110 mg, mp 120–197°. Tlc and nmr spectroscopy indicated the product to be mainly griseofulvin contaminated by some unreacted **6**.

(12) Prepared by Mr. M. Dann of these laboratories.

Registry No.—**2**, 25357-21-5; **3**, 25357-22-6; **4**, 25357-23-7; **5**, 25350-64-5; **6**, 25350-65-6; **7**, 25350-66-7; **8**, 25350-67-8; **9**, 25350-68-9; **9a**, 25350-69-0; **10**, 25357-24-8; **11**, 25357-25-9; **12**, 25357-26-0.

Acknowledgments.—We thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and staff for the ultraviolet and nmr spectra. We also thank Dr. R. B. Angier for his interest.

Structure of Kutkin, the Bitter Glucoside of *Picrorhiza kurroa* Royle ex Benth

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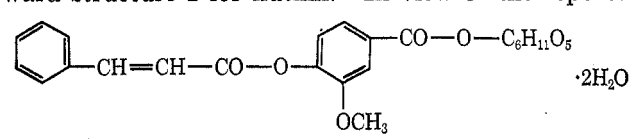
Received February 6, 1970

Picrorhiza kurroa Royle ex Benth (Scrophulariaceae)[1c] is a wild plant which grows from Kashmir to Sikkim at an altitude of 5000 to 10,000 ft. The roots are extremely bitter and extensively used in the indigenous system of medicine as an antiperiodic, stomachic, cathartic, and cholagogue. Rastogi, *et al.*,[2,3] previously isolated from the roots a bitter glucoside, kutkin, $C_{23}H_{24}O_{10}\cdot 2H_2O$, mp 211°, $[\alpha]^{41}D$ −165°, together with D-mannitol, vanillic acid, and several uncharacterised products. Kutkin, on hydrolysis, yielded vanillic acid, cinnamic acid, and glucose, on the basis of which they put forward structure I for kutkin. In view of the reported



I

uses of the drug in the indigenous and modern systems of medicine,[4,5] we became interested in the chemistry of kutkin which appeared to be the active principle of the drug. Moreover, the structure I proposed for kutkin by Rastogi, *et al.*, is not consistent with the biogenetic principles applicable to lignins,[6] known to be derived from C_6–C_3 and D-glucose precursors. Again, the facile hydrolysis of kutkin to glucose and other fragments in protic solvents, even at ordinary temperatures, also militates against the assumption[2] that the phenolic and sugar entities are joined in an ester linkage as shown in I.

Experimental Section

Kutkin, isolated from the roots of *Picrorhiza kurroa* (3 kg) following essentially the method of Rastogi, *et al.*,[2] crystallized

(1) (a) Department of Medicinal Chemistry, Post Graduate Institute of Indian Medicine; (b) Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-5, India; (c) R. N. Chopra, S. L. Nayar, and I. C. Chopra, "Glossary of Indian Medicinal Plants," CSIR, New Delhi, 1956, p 192.

(2) R. P. Rastogi, V. N. Sharma, and S. Siddiqui, *J. Sci. Ind. Res., Sect. B*, **8**, 173 (1949).

(3) R. P. Rastogi and M. L. Dhar, *ibid.*, **18**, 219 (1959).

(4) P. K. Das and M. K. Raina, *J. Res. Ind. Med.*, **1** (2), 213 (1967).

(5) H. S. Bajpai, S. S. Hospital, Banaras Hindu University, Varanasi-5, personal communication.

(6) W. J. Schubert, "Lignin Biochemistry," Academic Press, New York, N. Y., 1965, p 54.

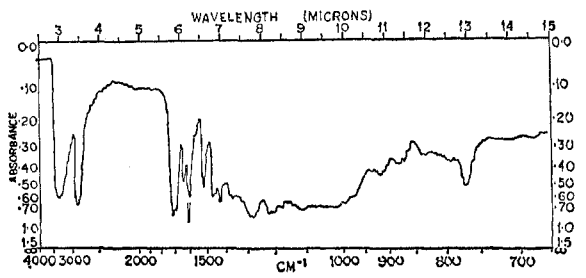


Figure 1.—Infrared spectrum of component A.

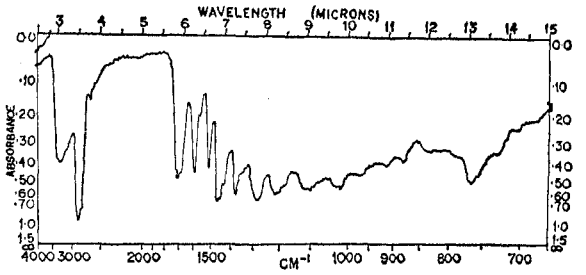


Figure 2.—Infrared spectrum of component B.

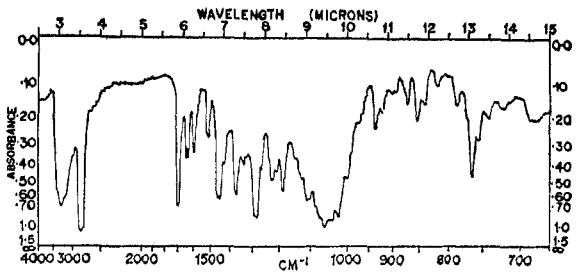


Figure 3.—Infrared specturm of kutkin.

from absolute alcohol as clusters of small needles: mp 214–216° (13 g); infrared λ_{max}^{Nujol} 3300 (OH), 1700 (-CH=CHCO-), 1650 (dissolved H_2O), 765 cm^{-1} (4 adjacent aromatic H).

Anal. Calcd for $C_{24}H_{28}O_{11}\cdot 2H_2O$: C, 54.54; H, 6.06. Found: C, 54.54, 54.81, 54.65; H, 5.55, 5.86, 5.81. Calcd for Rastogi's formula, $C_{23}H_{24}O_{10}\cdot 2H_2O$ (I): C, 55.6; H, 5.6. Found:[2] C, 55.0; H, 5.3.

Acid Hydrolysis of Kutkin to Glucose and Two Aglycones A and B.—Kutkin (1 g) in aqueous hydrochloric acid (2–3%, 30 ml) was kept at room temperature for 24 hr. Within 30 min the color of the solution changed to green which gradually faded away. The mixture was repeatedly extracted with chloroform and the chloroform extract was washed until free from acid and dried. On removal of solvent, a pale yellow amorphous compound B (0.1303 g) was obtained. Attempts to crystallize B from different solvents failed. It showed a single spot at R_f 0.87 (Whatman paper No. 1, *n*-butyl alcohol–pyridine–water, 30:15:22.5 v/v, Tollens reagent). The spot turned pink when sprayed with an alcoholic solution of 2,4-dinitrophenylhydrazine, followed by 10% KOH solution,[7] indicating its aldehydic character.

The acidic solution, after separation of B, was repeatedly extracted with isoamyl alcohol. The organic layer was processed in the above way, when another component A was obtained as a brown amorphous material (0.6188 g). On papergram, A showed two spots at R_f 0.77 (intense), no color with DNP reagent,[7] and R_f 0.87 (faint, due to B). The aqueous mother liquor left showed only one spot at R_f, 0.26 (D-glucose). Compound A was purified by repeated extraction with chloroform, followed by isoamyl alcohol. Attempts to dry a pure sample of A over dehydrating agents (concentrated H_2SO_4, P_2O_5) resulted in a mixture of A and B. On further hydrolysis, both A and B afforded a mixture of vanillic and cinnamic acids.

A fresh aqueous solution of kutkin did not exhibit any reducing spot on papergram, but on standing or warming exhibited only two spots at R_f, 0.26 (D-glucose) and 0.77 (A), but no spot at R_f, 0.87 (B), which appeared only in protic solvents along with the other two spots.

Periodic Acid Oxidation of Compound A.—A mixture of a yellow colored suspension of A (0.2 g) and periodic acid (1 g) in water (5 ml) was kept at room temperature for 20 hr. The product was steam distilled. The distillate was led to a saturated solution of dimedone in water. The resulting precipitate was filtered, washed with water, and dried, mp 189–190°, mixture melting point (with formaldehyde dimedone, mp 189–190°) remained undepressed.

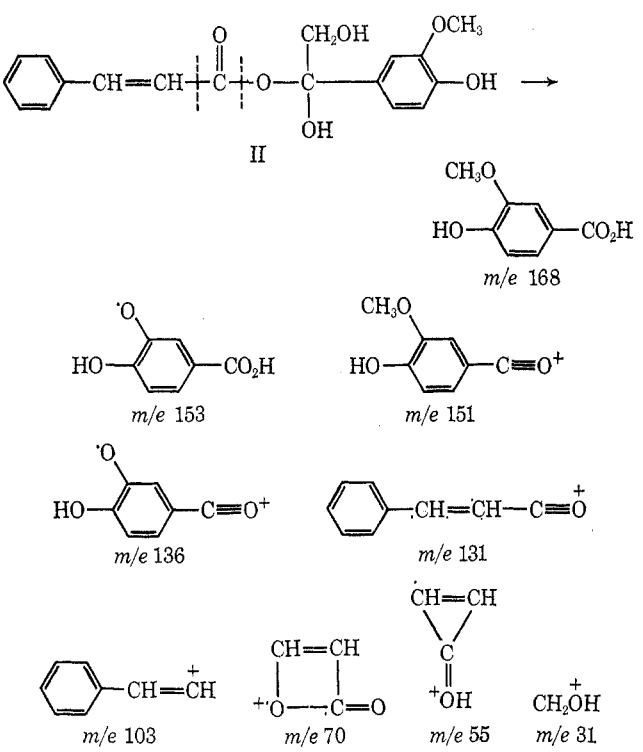
From the mother liquor, vanillin was isolated and characterized through the DNPH.

Results and Discussion

The compound A, $C_{18}H_{18}O_6$ (on the basis of integral proton count and by difference of the sugar component from the parent compound, $C_{24}H_{28}O_{11} + H_2O - C_6H_{12}O_6$), showed significant infrared absorption bands at 1700 (α,β-unsaturated ester carbonyl) and at 1650 cm^{-1} (due to dissolved water in polyhydroxy systems).[8] It did not show the molecular ion peak in its mass spectrum, but instead intense fragment ions appeared at *m/e* 168, 153, 151, 148, 147, 136, 131, 125, 103, 97, 77, 71, 70, 57, 55, and 31, consistent with structure II for A (Scheme I).

SCHEME I

MASS SPECTRAL FRAGMENTATION PATTERN OF A



In contrast to a one sharp band at 1700 cm^{-1} in the infrared spectra of kutkin and A, component B, $C_{18}H_{16}O_5$ (M^+, *m/e* 312), showed a twin peak at 1710 (CHO) and 1700 cm^{-1} (α,β-unsaturated ester). Again, the band at 1650 cm^{-1} ascribed to dissolved water in polyhydroxy systems[8] is completely absent in B. The location of the aldehyde function in B, associated with a OCH—CH= grouping, was confirmed from its nmr spectrum, which exhibited a doublet at δ 9.8 (J = 4

(7) E. Lederer and M. Lederer, "Chromatography," Elsevier, New York, N. Y., 1957, pp 169–170.

(8) G. Eglinton in "Physical Methods in Organic Chemistry," J. C. P. Schwarz, Ed., Olive & Boyd, Edinburg and England, 1964, p 106.

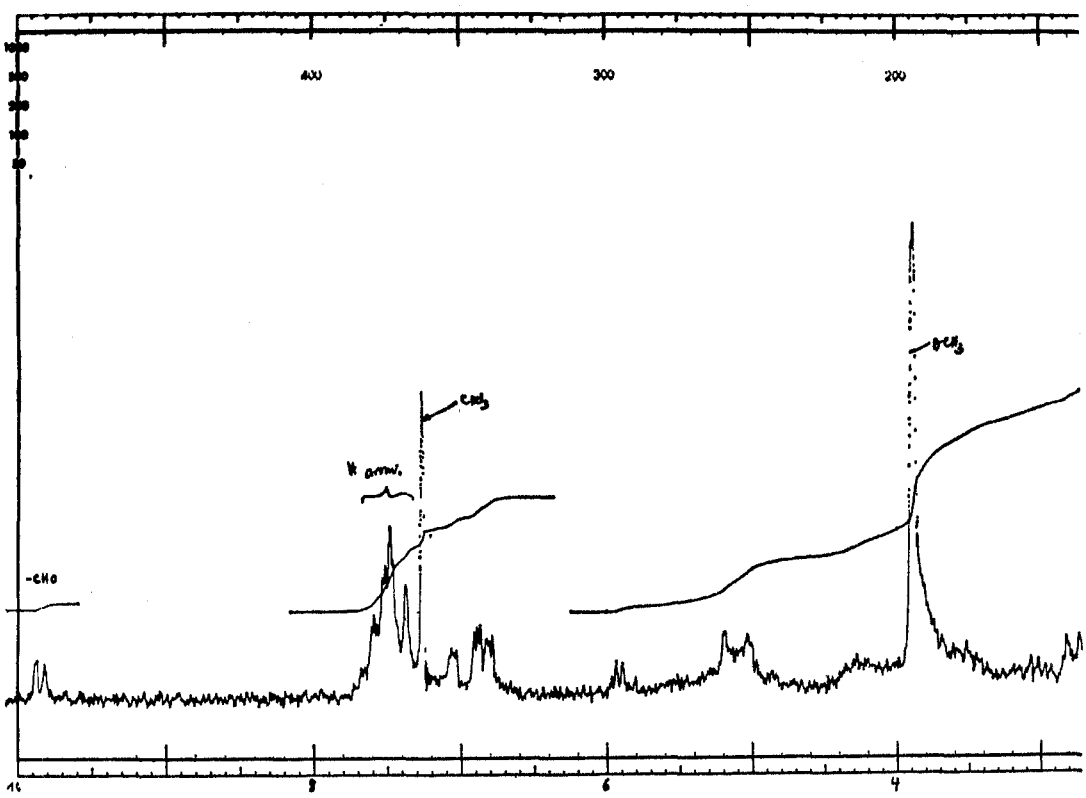
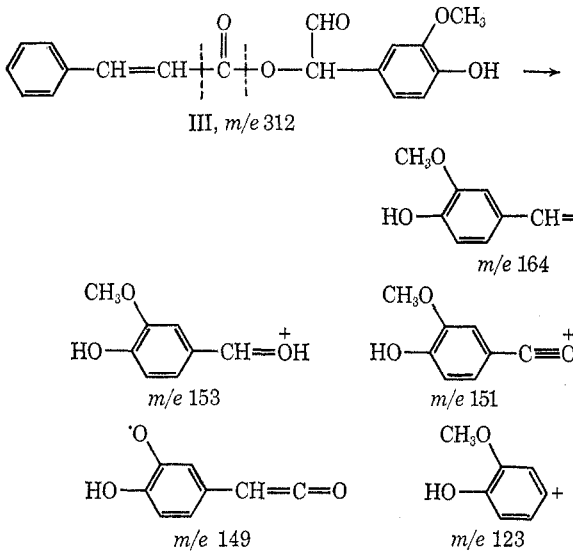


Figure 4.—Nmr spectrum of component B.

cps). These evidences together with the mass spectral fragmentation pattern (Scheme II), significant peaks at *m/e* 164, 153, 151, 149, and 123, indicate structure III for B.

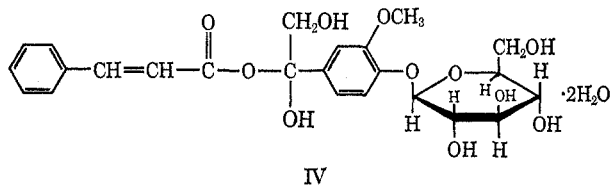
SCHEME II

MASS SPECTRAL FRAGMENTATION PATTERN OF B



See Figures 1–3 for infrared spectra of A, B, and kutkin. Figure 4 shows the nmr spectrum of B.

On the basis of structures II and III for the two major degradation products, we propose the following revised structure IV for the glucoside, kutkin. The physical data (nmr[9] and ir spectra, high optical rotation,[2] and analyses, *loc. cit.*) are consistent with the structure IV for kutkin. The observed hydrolysis of kutkin with emulsin indicates its β-glucosidic linkage.



IV

Registry No.—IV, 25356-80-3.

Acknowledgment.—K. B. is grateful to the Ministry of Health, Government of India, for the award of a Research Fellowship. Financial assistance from the ICMR (CDRS), New Delhi, is thankfully acknowledged.

(9) Dr. U. Scheidegger, Varian AG Research Laboratory, Switzerland, also opined, on the basis of nmr data, for the above structural assignments of kutkin and its two major degradation products, for which the authors are indebted.

Synthesis of 2-(2-Nitroalkyl)benzoates[1]

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Methyl 2-(2-nitroethyl)benzoate (**4**) was required for a synthesis[2] of 2-nitroindanone. A possible approach seemed to be selective hydrogenation of methyl 2-(2-nitrovinyl)benzoate (**3**). The latter compound was thought to be accessible by applying the β-nitro-

(1) Taken from the Ph.D. Thesis of S. R. Naik, University of Ottawa, 1967.

(2) H. H. Baer and S. R. Naik, *J. Org. Chem.*, **35**, 2927 1970.