Thebainone-2,4-dinitrophenylhydrazone.—A mixture of 924 mg. of thebainone and 660 mg. of 2,4-dinitrophenylhydrazine in 6 cc. of glacial acetic acid was heated on the steam-bath for 30 minutes, cooled, diluted with water, made basic with ammonia and extracted several times with chloroform. The chloroform extracts were washed, dried, concentrated and chromatographed on alumina. Development with alcohol-free chloroform gave a DNP fraction, passing into the filtrate, of 1.32 g. after removal of solvent. This residue crystallized directly from the chloroform during concentration and after several crystallizations from ethyl acetate orange prisms of m.p. 201.5–202.5°, $[\alpha]^{26}D$ −1375° (*c* 1.31, chf.), $[\alpha]^{26}D$ −1013° (*c* 0.460, acetic acid), were obtained.

Anal. Calcd. for $C_{24}H_{25}N_5O_6$: C, 60.13; H, 5.26. Found: C, 60.34; H, 5.49.

We have also sometimes obtained this substance as a solvate with alcohol of m.p. 120–145° with foaming, partial resolidification and remelting at 195–206°. Cleavage of this dinitrophenylhydrazone (187 mg.) to thebainone was achieved by refluxing in 8 cc. of acetone containing 1 cc. concentrated hydrochloric acid and a little mesityl oxide for two hours and 15 minutes. The mixture was diluted with water and extracted with chloroform to remove non-basic dinitrophenylhydrazones, and then made basic with ammonia. The precipitated thebainone (96 mg.) was removed by extraction with chloroform and purified through its hydriodide, m.p. 271–272°. On recovery from this salt, it melted at 130–150°, gas evolution at 152–154°, $[\alpha]^{25}D$ −48.1° (*c* 1.87, alc.) and gave a methiodide of m.p. 251–253°.

The Action of Acetic Acid on Thebainone-2,4-dinitrophenylhydrazone.—A solution of 54 mg. of thebainone-2,4-dinitrophenylhydrazone in glacial acetic acid was heated on the steam-bath for six hours, after which its specific rotation in this solvent had dropped to −728° (*c* 0.227). Processing as described above for the isomerization of β-thebainone-2,4-dinitrophenylhydrazone yielded a crude DNP fraction directly from the chromatographic column whose specific rotation was −1200° (*c* 0.423, chf.) and which gave only unchanged thebainone-2,4-dinitrophenylhydrazone on crystallization.

Thebainone from Phenolic Dihydrothebaine.—A solution of 549 mg. of phenolic dihydrothebaine in 4 cc. of 50% acetic acid was heated under nitrogen on the steam-bath for 45 minutes. The cooled solution was made basic with ammonia and extracted several times with chloroform. The chloroform extracts were washed, dried and concentrated and the residue therefrom was converted to its hydriodide, crystallized as such, reconverted to the free base and decolorized by chromatography on alumina using acetone as an elution solvent. The residue from the acetone solution on crystallization from wet benzene yielded a total of 248 mg. (47%) of thebainone half-hydrate m.p. 122–152°, gas evolution at the latter temperature, $[\alpha]^{30}D$ −45.5°.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE UNIVERSITY COLLEGE OF SCIENCE AND TECHNOLOGY]

Studies on the Degradation of Kopsine, the Alkaloid of *Kopsia fruticosa*. II

BY ANIL BHATTACHARYA

RECEIVED JUNE 2, 1952

Kopsine, $C_{22}H_{26}O_4N_2$, the alkaloid of *Kopsia fruticosa*, on mild degradation with aqueous and alcoholic alkali produces two new bases—kopsidine, $C_{20}H_{24}O_3N_2$, m.p. 142° (dec.) and kopsidinine, $C_{19}H_{22}O_2N_2$, m.p. 248° (dec.), which is free from methoxy. Their isolation, analyses, properties and ultraviolet absorption curves have been described. Kopsine produces 2-methylindole, C_9H_9N, m.p. 57°; indole-2-carboxylic acid, $C_9H_7O_2N$, m.p. 199°; and an uncharacterized base (in traces) on fusion with potassium hydroxide.

In a previous communication[1] the preliminary studies on the isolation and properties of kopsine, $C_{22}H_{26}O_4N_2$, m.p. 220° (dec.), the new alkaloid of *Kopsia fruticosa*, have been reported. It was also recorded that with ethanolic ammonia, Kopsine suffers mild hydrolysis and produces a new base, kopsidine, $C_{20}H_{24}O_3N_2$, m.p. 142° (dec.), containing a methoxy group. The same base, kopsidine, has been obtained by hydrolysis of the original base, kopsine, with a dilute aqueous sodium hydroxide solution (0.4%). It forms a crystalline hydrochloride, $C_{20}H_{24}O_3N_2 \cdot HCl$, m.p. 340° (dec. at 290°), produces a rose-red coloration with perchloric acid and responds to all the tests for alkaloidal reagents. A comparative study of the molecular formula of kopsine and kopsidine suggested that kopsidine might be a deacetylation product of kopsine, but on acetylation under various conditions kopsidine failed to produce kopsine or its acetylation product.

On hydrolysis with a strong ethanolic solution of potassium hydroxide (20%) kopsine yields a methoxyl free base, kopsidinine, $C_{19}H_{22}O_2N_2$, m.p. 248° (dec.) (yield 10%). It forms light brown needles which are highly soluble in methanol, ethanol, acetone, ethyl acetate and chloroform, moderately soluble in ether and benzene but insoluble in petroleum ether. Kopsidinine forms a crystalline hydrochloride, $C_{19}H_{22}O_2N_2 \cdot HCl$, which does not melt but decomposes at 295°. It produces an orange-red precipitate with potassium–bismuth iodide, a yellow precipitate with picric acid and a white precipitate with potassium mercuric iodide. Kopsidinine gives characteristic color reactions with alkaloidal reagents, as shown in Table I.

TABLE I

	Reagents	Color reactions
1	Concd. H_2SO_4	Colorless in cold, but gradually changes to pink
2	Erdmann reagent	Color changes from purple to red
3	Fröhde reagent	Color gradually changes to light pink

The same base, kopsidinine, has been isolated though in poor yield (1.0%), by the hydrolysis of the base, kopsine, with strong ethanolic or amyl alcoholic potassium hydroxide (60%) solution.

A comparative study of the absorption curves (Fig. 1) of both kopsine and kopsidinine shows that the curves are very similar to that of indole,[2,3] thus indicating the presence of an indole nucleus in both kopsine and kopsidinine. The physical evidence of the presence of the indole nucleus in kopsine has been established by chemical evidences which are put forward in the present communication.

(1) A. Bhattacharya, A. Chatterjee and P. K. Bose, THIS JOURNAL, **71**, 3370 (1949).

(2) M. S. Kharasch, D. W. Stanger, M. A. Bloodgood and R. R. Legault, *Science*, **83**, 36 (1936).

(3) W. A. Jacobs, L. C. Craig and A. Rothen, *ibid.*, **83**, 166 (1936).

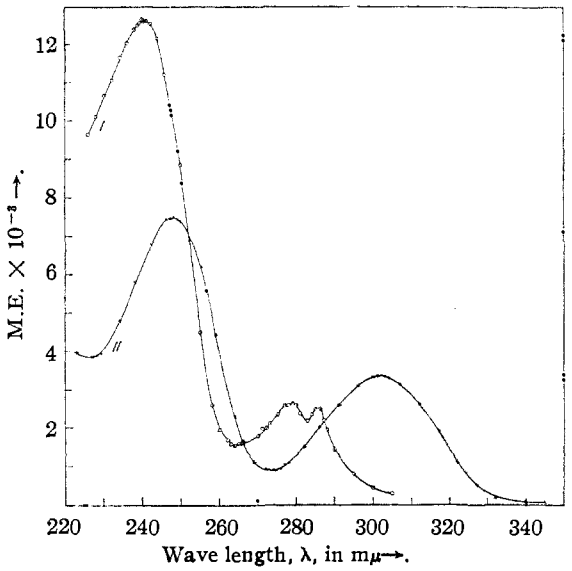
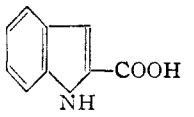
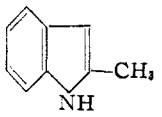


Fig. 1.—Molecular extinction curves of: I, kopsine in alcohol; II, kopsidinine in alcohol; using Beckmann Quartz Spectrophotometer, Model DU: length of the cell, 1.0006 cm.; concentration of kopsine, 15 mg./10^3 cc.; concentration of kopsidinine, 33 mg./10^3 cc.

From the fusion of kopsine with potassium hydroxide two products have been isolated, namely, indole-2-carboxylic acid m.p. 199° (I), golden yellow picrate, m.p. 178°, and 2-methylindole, m.p. 57° (II), scarlet red picrate, m.p. 134°. Also a base has been obtained in traces, the characterization of which is in progress. The identity of indole-2-carboxylic acid was shown by the mixed m.p. determinations with the synthetic sample prepared by the method of Ciamician and Zetti[4] as also its picrate. 2-Methylindole was identified by mixed m.p. determinations with the synthetic sample prepared according to the method of Fischer[5] and its picrate.



I



II

The presence of an indole nucleus in the kopsine molecule has been further confirmed by the isolation of indole and its derivatives from selenium dehydrogenation and zinc dust distillation products which will be described later.

Experimental

Hydrolysis of Kopsine and Isolation of Kopsidine.—Kopsine (0.1 g.) was refluxed with 20 ml. of 0.1 *N* aqueous sodium hydroxide solution for two hours. Colorless crystals appeared on cooling, m.p. 135–140° (dec.); on crystallization from ethanol (95%) the melting point of the substance was raised to 142° (dec.). Further crystallizations did not change in melting point and the substance was found to be identical with kopsidine.[1]

Kopsidine hydrochloride was prepared by passing dry hydrochloric acid gas through a cooled solution of kopsidine (0.2 g.) in ether–chloroform mixture (2:1, 80 ml.) when a colorless solid precipitated. The supernatant solution was decanted and the solid residue was refluxed with absolute ethanol (10 ml.) for 8 hours when crystalline hydrochloride appeared. It was twice crystallized from absolute ethanol in colorless shining needles (0.2 g.) decomposing at 290° and melts at 340°. The hydrochloride is highly soluble in water, sparingly soluble in absolute ethanol but insoluble in most of the organic solvents.

Anal. Calcd. for $C_{20}H_{24}O_3N_2 \cdot HCl$: Cl, 9.43. Found: Cl, 9.78.

Hydrolysis of Kopsine and Isolation of Kopsidinine.—Kopsine (1.0 g.) in aldehyde-free ethanol (95%, 10 ml.) was refluxed with 20% ethanolic (95%) potassium hydroxide solution (20 ml.) for 9 hours. The clear, colorless solution became turbid and reddish-brown. The excess of ethanol was removed in vacuum. The residue was dissolved in water (30 ml.). The aqueous alkaline solution was thoroughly extracted with chloroform (150 ml. in five portions). The chloroform solution containing the base was washed with water and then extracted with aqueous hydrochloric acid (5%). The deep red aqueous acidic solution containing the base was well cooled and then basified with strong ammonia, when a flocculent precipitate of kopsidinine appeared. This precipitate on keeping in a frigidaire for 8 hours became light brown needles (0.1 g.), m.p. 235° (dec.). On several crystallizations from dilute ethanol (5%) the m.p. could be raised to 248° (dec.). Kopsidinine is highly soluble in ethanol, acetone, chloroform and ethyl acetate but sparingly soluble in benzene and ether.

Anal. Calcd. for $C_{19}H_{22}O_2N_2$: C, 73.55; H, 7.10; N, 9.03. Found: C, 73.58; H, 7.09; N, 9.52, 9.33.

The aqueous alkaline solution left after the removal of the base, was cooled in ice and acidified with hydrochloric acid when the solution became turbid. The turbidity was extracted with ether (100 ml.). The ethereal extract containing the acid was washed with water and then repeatedly extracted with an aqueous solution of sodium bicarbonate (2 *N*). The aqueous alkaline extract was cooled in ice and then acidified. The turbidity thus obtained was extracted with ether. The ethereal solution was well washed with water and dried over anhydrous sodium sulfate. The gummy residue left on the removal of ether was very small, further isolation of which is in progress.

Strong Hydrolysis of Kopsine and Isolation of Kopsidinine.—Kopsine (5.0 g.) was refluxed separately with 150 ml. of aldehyde-free ethanolic (95%) and amyl alcoholic potassium hydroxide solution (60%) for 6 hours. Following the same procedure for isolation (*vide supra*) a basic product of m.p. 232° (dec., 0.05 g.) and an acidic gum in traces were obtained. The basic product on treatment with charcoal and several crystallizations from dilute ethanol (50%) gave light gray needles, m.p. 247.5° (dec.), which was found to be identical with kopsidinine.

The hydrochloride of kopsidinine was prepared and purified by following the same method as for the kopsidine hydrochloride (*vide supra*). Kopsidinine hydrochloride is highly soluble in water and the water solution is rose-red in color. It is sparingly soluble in absolute ethanol but insoluble in almost all organic solvents. It does not melt but decomposes at 295°.

Anal. Calcd. for $C_{19}H_{22}O_2N_2 \cdot HCl$: Cl, 10.25. Found: Cl, 10.31.

Alkali Fusion of Kopsine.—Kopsine (10.0 g.) was fused with potassium hydroxide (60.0 g.) in a nickel crucible at 300–320° for 30 minutes on a metal-bath. On cooling, the mass was digested with water (300 ml.) and solid ammonium chloride (20 g.). The turbid solution was filtered. This aqueous alkaline filtrate (A) was shaken with ether (360 ml. in 6 portions). The ether solution containing the basic portion was washed with water, dried over anhydrous sodium sulfate and evaporated. The gummy residue left was obtained in very small quantity, further work on which is in progress.

The aqueous alkaline solution (A, *vide supra*) freed from the base was acidified with hydrochloric acid in the cold when a yellow precipitate appeared. The precipitate was taken up in ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. The dry ether solution on evaporation left a solid residue which on sublimation *in vacuo* at 0.01 mm. gave two different products (a) and (b) which could be separated by fractional sublimations.

(a) The product distilled at 80° (0.01 mm.) as a colorless oil which slowly solidified on keeping. It was purified by

(4) G. Ciamician and C. Zetti, *Ber.*, **21**, 1930 (1888).

(5) E. Fischer and H. Hess, *Ann.*, **236**, 126 (1886); E. Fischer, *Ber.*, **19**, 1563 (1886).

further sublimation and collected as colorless crystals (0.02 g.), m.p. 57°. It has a faecal smell and turns pine chip soaked in concentrated hydrochloric acid cherry red. It produces a scarlet-red crystalline picrate, m.p. 134°.

Anal. Calcd. for C_9H_9N: C, 82.44; H, 6.87; N, 10.69. Found: C, 82.65; H, 6.85; N, 10.75.

It was proved to be identical with synthetic 2-methylindole, m.p. 57°, by a mixed m.p. determination and also the mixed m.p. determination of its picrate, m.p. 134°—with the picrate (which melts alone at 134°) of synthetic 2-methylindole.

(b) This fraction was separated from the adhesive gum by several fractional sublimations in higher vacuum (0.01 mm.) and was finally obtained as a colorless solid at 110° (0.01 mm.). It is an acid as it dissolves in sodium bicarbonate solution with an effervescence and the alkaline solution on acidification regenerates the original substance. It crystallizes from benzene in glistening flakes, m.p. 199° (yield 0.15 g.). The acid, when treated with soda lime, produces an oil, which has an offensive odor like skatole and responds to the pine chip test for indole. The acid produces a violet-red coloration with isatin and concentrated sulfuric acid. It decomposes at 230° producing indole, C_8H_7N, m.p. 51°. The acid and its picrate did not depress the m.p. of synthetic indole-2-carboxylic acid and its picrate (golden yellow), m.p. 178°, when mixed.

Anal. Calcd. for $C_9H_7O_2N$: C, 67.09; H, 4.35; N, 8.70. Found: C, 67.07; H, 4.34; N, 8.73.

Acknowledgment.—In conclusion, the author expresses his thanks to Dr. Asima Chatterjee (née Mookerjee) for the valuable suggestions and the laboratory facilities given. The author is also grateful to Prof. L. Zechmeister and Prof. A. J. Haagen-Smit, California Institute of Technology, for micro-analyses of the compounds.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Condensations of Cinchoninaldehyde. VI.[1] With the Quaternary Alkiodides of Some Heterocyclic Active Methyl Compounds

BY ARTHUR P. PHILLIPS

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Cinchoninaldehyde has been condensed with a series of alkiodides of 2- and 4-methylpyridine and with the methiodides of 2- and 4-methylquinoline and of 2,4-dimethylthiazole. Some observations have been made concerning the relationship between structure and reactivity of the methylpyridine and quinoline alkiodides.

In a continuation of the study of the chemical reactivity of cinchoninaldehyde it has been condensed with a number of alkiodides of 2-methylpyridine and 4-methylpyridine, and with the methiodides of 2-methylquinoline, 4-methylquinoline and 2,4-dimethylthiazole. The reactions were run in methanol solution using piperidine as the catalyst. Yields were moderately good varying between 50 and 90%. Although cinchoninaldehyde belongs to the type of aldehyde for which high carbonyl reactivity is expected,[2] the reactive methyl components are of that class which gives best yields with those aldehydes such as *p*-dimethylaminobenzaldehyde and *p*-methoxybenzaldehyde, bearing strong electron release substituents, even though the carbonyl reactivity of the latter aldehydes is of a low order.[2-4]

Two points in connection with the relationship between structure and reactivity were explored semi-quantitatively: (1) The comparative reactivities of the 2- and 4-methyl groups in the methiodides of the pyridine and quinoline series using cinchoninaldehyde as the common carbonyl reactant. (2) The possible variation in the steric hindrance to the condensation depending upon the size of the N-alkyl group in the 2-methylpyridine alkiodides.[5] Any such manifestation should be more prominent with cinchoninaldehyde than with benzaldehyde because of the ortho substituent, the 5-position on the benzene ring, of the former.

Although the reactions had not been run uniformly at first, the key condensations were repeated under identical conditions employing a two-hour reaction time which gave less than optimal yields in each case. Comparison of the yields of I[6] (33%) and V[6] (22%) and of VIII (41%) and IX (27%) seems to indicate a greater reactivity for the 2-methyl methiodides with *this particular type*[2] of aldehyde. This is in spite of the fact that any hindrance to the reaction by the N-alkyl of the alkiodide should make the 2-methyl derivatives less favorable sterically than their 4-methyl analogs. It must not be overlooked that in some cases side reactions may have complicated the picture. Thus in the preparation of IX from cinchoninaldehyde and 4-methylquinoline methiodide about 25% of a highly colored by-product was obtained. This was deep greenish-black and probably is a cyanine dye, of structure as yet undetermined.

Further work is planned to compare the reactivities of the 2- and 4-methyl heterocyclic derivatives both as the tertiary bases and as their methiodides with several aldehydes of different types.[2] It is felt that the apparent "reactivity" of the methyl may depend not only upon its position on the ring (2- or 4-) but upon both the state of the hetero nitrogen and the type of aldehyde under consideration.

Comparison of the yields of I (33%, quaternizing alkyl is CH_3) and IV (25%, quaternizing alkyl is $(CH_3)_2CH$) indicates that steric interference between the aldehyde and quaternizing alkyl cannot be a very significant factor in the reaction, for changing the alkyl from methyl to isopropyl resulted in only a small decrease in the yield of product.

(1) Paper V, THIS JOURNAL, **74**, 5230 (1952).

(2) A. P. Phillips and J. G. Murphy, *J. Org. Chem.*, **16**, 954 (1951).

(3) A. P. Phillips, *ibid.*, **12**, 333 (1947).

(4) A. P. Phillips, *ibid.*, **14**, 302 (1949).

(5) Any steric factor associated with the N-alkyl groups should be insignificant for the 4-methylpyridine alkiodides.

(6) See Table I for the structures of the compounds indicated here by numbers.