A crystalline dihydrochloride was also isolated, but its extreme hygroscopicity prevented purification for analysis.

2-Diethylaminoethyl 4-heptylaminothiolbenzoate citrate, prepared from the base (reductive alkylation with *n*-heptaldehyde) and citric acid monohydrate in acetone, crystallized in rosets of tiny white needles from absolute alcohol–ethyl acetate, m. p. 123–124° (dec.).

Anal. Calcd. for $C_{26}H_{42}N_2O_8S$: N, 5.16; S, 5.91. Found: N, 4.70; S, 6.04.

2-Diethylaminoethyl 4-(5-hydroxyamylamino)-thiolbenzoate, from the 4-amino base[2] and 5-hydroxypentanal,[25,26] crystallized from benzene–Skellysolve B in large white prisms, m. p. 72.3–73.6°.

Anal. Calcd. for $C_{18}H_{30}N_2O_3S$: N, 8.28; S, 9.47. Found: N, 8.15; S, 9.53.

(25) Woods and Sanders, THIS JOURNAL, **68**, 2111 (1946); *Org. Syn.*, **27**, 43 (1947). Comparable yields were obtained when the preparation was modified by saturation of the neutralized hydrolysis mixture with ammonium sulfate, followed by a single ether extraction. This obviates the continuous ether extraction.

(26) The final reflux period, after the addition of the hydroxyaldehyde, was extended to two hours.

The **picrate** formed tiny orange-yellow needles from alcohol, m. p. 96.6–98.2°.

Anal. Calcd. for $C_{24}H_{33}N_5O_9S$: N,[22] 4.94. Found: N,[22] 4.79.

The **phosphate** crystallized from alcohol-acetone in rosets of white cottony needles, m. p. 163.6–164.4°.

Anal. Calcd. for $C_{18}H_{33}N_2O_6PS$: S, 7.35; H_3PO_4, 22.46. Found: S, 7.34; H_3PO_4, 22.51.

Summary

There has been described the preparation of a series of dialkylaminoalkyl thiol esters derived from the benzoyl, cinnamoyl, 4-aminobenzoyl, 4-alkylaminobenzoyl, 4-alkoxybenzoyl and 2-butyloxyquinoline-4-carbonyl nuclei. Modifications in the preparation of certain intermediates, leading to increased yields, have also been described.

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On an Alkaloid of *Kopsia Fruticosa*. I

BY A. BHATTACHARYA, A. CHATTERJEE[1] AND P. K. BOSE

Kopsia fruticosa, A.D. (*Apocynaceae*) is a large, evergreen shrub of the East Indies, which has been now naturalized in India. It was used as an arrow poison. All *Kopsia* species so far investigated have been found to contain alkaloids. Thus, a crystalline alkaloid has been isolated from the seeds of *K. flavida* Bl.[2]; the presence of three other alkaloids has been reported in *K. arborea* Bl., *K. albiflorum*, Bl., and *K. Roxburghii*[2] Bl. From *K. fruticosa* we have obtained a new alkaloid, kopsine, $C_{22}H_{26}N_2O_4$, m. p. 217–218° (dec.), $[\alpha]^{20}D$ +16.4° (in ethyl alcohol), and we wish to report its isolation and properties. Our mature leaves contained 0.12% kopsine and in the bark 0.06% was found (on the basis of dry weight). Thus, for large scale extraction, the leaves were preferred. Kopsine (in alcohol) is neutral to litmus. The solution shows green fluorescence. Its molecular extinction curve is represented in Fig. 1. The curve shows the maxima at 240 and 283 mμ and minima at 264, 279 and 286 mμ. The absorption spectra of kopsine are similar to those of indole alkaloids.[3,4] Kopsine does not show a coloration with ferric chloride but it gives the following reactions: concentrated sulfuric acid, colorless in the cold, pinkish upon heating; Erdmann reagent, gradual appearance of apple-green color; Fröhde reagent, solution slowly turns pink; Mandelin reagent, dissolves the alkaloid with permanganate-like color which gradually turns olive-green.

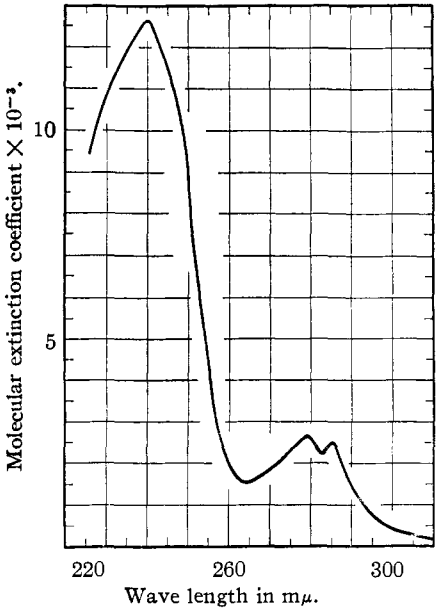

Fig. 1.—Molecular extinction curve of kopsine in alcohol.

A solution of kopsine in hydrochloric or sulfuric acid produces an orange precipitate with potassium bismuth iodide, a yellow precipitate with picric acid and a white precipitate with potassium mercuric iodide. (So far it has not been possible to prepare kopsine salts with some common mineral acids (HCl, HNO_3 and H_2SO_4, etc.) because of resinification). It forms, however, well defined

(1) Née Mookerjee.

(2) M. Greshoff, *Ber.*, **23**, 3537 (1890).

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

(4) W. A. Jacobs, L. C. Craig and A. Rothen, *ibid.*, **83**, 166 (1937).

salts with perchloric, picric, oxalic, chloroauric and chloroplatinic acids and then behaves as a monoacidic base. Both the base and its salts taste bitter. Kopsine contains one methoxyl. Dioxymethylene, carbonyl, hydroxyl and N-methyl groups are absent. The presence of two active hydrogens has been observed. On catalytic hydrogenation dihydrokopsine is formed. Kopsine readily yields a methiodide and gives negative tests for primary and secondary amino groups which suggests that the basic nitrogen atom is tertiary.

Kopsine is insoluble in cold alkali but is decomposed by hot ammonia to give a new base, kopsidine, $C_{20}H_{24}N_2O_3$, m. p. 142°, $[\alpha]^{25}D$ +30.2° (in alcohol), which yields a well crystallized picrate, m. p. 190° (dec.). Kopsidine dissolves in concentrated sulfuric acid and shows the following reactions: Erdmann reagent, olive-green; Fröhde reagent, the colorless solution slowly turns pink; Mandelin reagent, the purple solution gradually turns bottle-green.

Kopsidine contains the O-methyl group. On the basis of the empirical formulas kopsidine might be a deacetylation product of kopsine; however, kopsidine cannot be acetylated to kopsine.

Experimental

Isolation of Kopsine.—The coarsely powdered leaves (5 kg.) were extracted in a percolator with alcohol (10 liters, acidified with 10 ml. of glacial acetic acid) for four weeks. The deep green extract was concentrated to 100 ml. *in vacuo*. The viscous residue was poured into 0.5 liter of iced water. Overnight a thick, dark, tarry mass separated. The clear supernatant liquid was decanted and the tarry mass digested with 5 × 50 ml. of water (shaking). The filtrate was combined with the bulk of the decanted liquid, cooled in ice-water and basified with sodium bicarbonate. The separated kopsine was taken up in 200 ml. of chloroform; the extract was washed with water, dried over sodium sulfate and concentrated to 25 ml. This solution was diluted with 1 vol. of alcohol and kept overnight. Pale-yellow, glistening crystals of kopsine (6 g.), coated with a slimy mass, were thus obtained. On several crystallizations from acetone, alcohol, benzene and ethyl acetate, the m. p. increased from 198–220° to 208–210° (dec.). The base was dissolved in 100 ml. of 1% hydrochloric acid, filtered from the slimy mass and basified with sodium bicarbonate. The alkaloid crystallized from alcohol in colorless plates, m. p. 213–214° (dec.). By repeating this procedure thrice, it was obtained in the pure state, m. p. 217–218° (dec.). Samples regenerated from the picrate or oxalate showed the same m. p. Kopsine is freely soluble in chloroform, sparingly in methanol, ethanol, ethyl acetate, benzene and ether; it is insoluble in petroleum ether or water.

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.10; H, 6.80; N, 7.30; OCH_3, 8.11. Found: C, 69.35, 69.56; H, 6.43, 6.25; N, 7.47, 7.44; OCH_3, 8.28, 8.32.

Kopsine picrate was prepared by adding an ethereal solution of kopsine to picric acid (in ether). The yellow precipitate crystallized from alcohol in glistening yellow rods, m. p. 230° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot C_6H_3O_7N_3 \cdot 2C_2H_5OH$: N, 9.96. Found: N, 10.2.

Kopsine Oxalate.—An ethereal solution of anhydrous oxalic acid (0.2 g.) was added to 0.2 g. of kopsine (in ether). The colorless precipitate (0.15 g.) was washed acid-free and recrystallized from alcohol and acetone; prisms, m. p. 154° (dec.). It is highly soluble in water, acidic to litmus and liberates iodine from potassium iodide and potassium iodate.

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot C_2H_2O_4$: N, 5.93; Found: N, 6.1.

Kopsine Perchlorate.—One-quarter gram of powdered alkaloid was added slowly to perchloric acid (5 ml., 70%) diluted with 1 vol. of water. The colorless precipitate (0.27 g.) crystallized from water containing a little perchloric acid in needles, m. p. 284° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot HClO_4 \cdot 5H_2O$: Cl, 6.19. Found: Cl, 5.9.

Kopsine chloroplatinate was prepared by adding an aqueous solution of platinic chloride (5%) to a faintly acidic solution (HCl) of kopsine. Upon crystallization from water containing a little hydrochloric acid, glistening orange colored rods separated, which did not melt but decomposed above 150°.

Anal. Calcd. for $(C_{22}H_{26}N_2O_4)_2 \cdot H_2PtCl_6$: Pt, 16.6. Found: Pt, 16.12.

Kopsine Chloroaurate.—One-half gram of kopsine was dissolved in hydrochloric acid (2 *N*, 5 ml.) and an aqueous solution of auric chloride was added until precipitation was complete. The golden yellow rods were recrystallized from water containing a little hydrochloric acid; m. p. 203–205° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot HAuCl_4$: Au, 27.30. Found: Au, 27.30.

Kopsine Methiodide.—0.15 g. of kopsine was dissolved in dry acetone (8 ml.). Freshly distilled methyl iodide (1 ml.) was added and the mixture was kept overnight. The solution was concentrated *in vacuo* to a viscous residue which crystallized from alcohol; colorless plates, m. p. 200° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot MeI$: NMe, 5.54. Found: NMe, 4.83.

Determination of Active Hydrogen in Kopsine (Zerewitinoff).—0.05 g. of kopsine in 5 ml. of dry pyridine yielded 6 ml. of methane (0°, 760 mm.).

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: H, 0.526. Found: H, 0.53.

Catalytic Hydrogenation of Kopsine.—Kopsine (0.2736 g.), dissolved in glacial acetic acid (10 ml.), was treated with hydrogen and Adams platinum oxide catalyst (0.15 g.) which had been previously saturated with hydrogen. The absorption of hydrogen (17 ml. at 30°, 760 mm.) corresponded to two atoms of hydrogen per mole. The solution was filtered, diluted with water and basified with sodium bicarbonate. The base was taken up in 100 ml. of ether. The colorless ethereal digest was washed with water, dried over sodium sulfate and distilled. The residue was successively crystallized from acetone, ethanol, ethyl acetate and benzene; colorless crystals, m. p. 218° (dec.). Dihydrokopsine showed a m.p. depression of 26° when mixed with kopsine.

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.75; H, 7.29; N, 7.29. Found: C, 68.32; H, 7.50; N, 7.62.

Hydrolysis of Kopsine and Isolation of Kopsidine.—A half gram of kopsine in alcohol (5 ml.) was refluxed with 10% ammonia (2 ml.) for six hours. The clear solution deposited overnight colorless prisms, m. p. 140–142°. After recrystallizations from ethanol, ethyl acetate and acetone, the m. p. was found to be 142°. Kopsidine is soluble in methanol, ethanol, ether, ethyl acetate or benzene and is insoluble in petroleum ether and water; $[\alpha]^{25}D$ +30.2° (in alcohol).

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: C, 70.59; H, 7.05; N, 8.26; OMe, 9.12. Found: C, 70.28; H, 6.75; N, 7.92; OMe, 8.82.

Acknowledgment.—The authors wish to express their thanks to Professor L. Zechmeister for the laboratory facilities granted.

Summary

From *Kopsia fruticosa* a new alkaloid, termed kopsine, $C_{22}H_{26}N_2O_4$, m. p. 217–218° (dec.), has

been obtained. The isolation and properties of this alkaloid have been studied. On hydrolysis, it yields a base, kopsidine, $C_{20}H_{24}N_2O_3$, m. p. 142°; and on hydrogenation, a dihydro derivative, m. p. 218° (dec.).

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

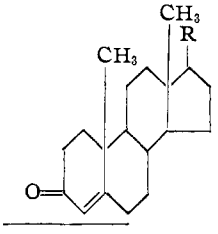
A New Series of Testosterone Esters

BY ARAM MOORADIAN, C. J. CAVALLITO, A. J. BERGMAN,[1] E. J. LAWSON AND C. M. SUTER

The literature is replete with attempts by workers in the field to prepare esters of testosterone which would show both more intensive and more prolonged androgenic action than testosterone itself. It was shown in early studies[2] that the lower aliphatic acid esters are most effective; as one increases the length of the carbon chain in the fatty acid residue, the effect becomes more prolonged but the intensity decreases rapidly. Ruzicka,[3] by his preparation and testing of the acetate and benzoate esters, initiated work which resulted in the general adoption of testosterone propionate as an activated form of testosterone. These workers[4] prepared a long series of aliphatic acid esters. Miescher's group[5] made a study of halogenated, aminated, and unsaturated aliphatic esters as well as carbonate esters. This latter group of workers[6] also studied the enol diesters of testosterone. Rabold and Dietrich[7] have made a study of the glucoside and tetraacetyl glucoside. The patent literature[8] describes a sulfonic acid and a phosphoric acid ester.

However, since it was felt that the field had not been combed thoroughly enough in view of the importance of the problem, there has been prepared a new series of esters several of which show activities surpassing testosterone propionate in rat tests where the weight increase of the seminal vesicles and the prostate was studied. A preliminary summary of the results obtained is shown in Table III. More complete biological results will be published[9] at a later date.

Esters of the general types



I, R = —OCOR′
II, R = —OCOR″—Y—R‴
III, R = —OCOR″OCOR‴

have been prepared (Table III) where R′ is of the carbocyclic or heterocyclic type, R″ and R‴ are various aliphatic or aromatic radicals and Y is oxygen or sulfur. Types I and III have been prepared from the acid chlorides and type II from the acid chlorides and anhydrides.

The acids shown in Table I were prepared by three methods. Method A involves the reaction of the appropriate sodium alkoxide or mercaptide with a halogenated acid. The second method, B, was used only to make ethyl or methylmercapto acids by the alkylation of the appropriate mercapto acid with ethyl or methyl sulfates. Method C involves hydrolysis of the corresponding nitrile.

In preparing the acid chlorides shown in Table II, both thionyl chloride (D) and phosphorus trichloride (E) were used. Phosphorus trichloride possesses the advantage that a colorless product almost always results. This is of decided advantage in the preparation of a color-free ester. Furthermore, in some instances in which thionyl chloride results in tar formation, phosphorus trichloride gives a fair yield of product. From the viewpoint of yield, however, thionyl chloride is usually to be preferred.

Some of the acids and acid chlorides described are old compounds but are included where the characterization is somewhat more complete than that described in the literature. Those acids which were obviously used but not described may be found elsewhere in the literature.

Experimental

***n*-Butylmercaptoacetic Acid (Method A).**—To 21.6 g. of *n*-butylmercaptan (0.24 mole) dissolved in 200 cc. of 18% sodium hydroxide solution was added 20.8 g. of chloroacetic acid (0.22 mole) dissolved in 100 cc. of 18% sodium hydroxide. The mixed solutions were heated for two hours on a steam-bath. The solution was then cooled and acidified and the product extracted with ether and distilled. Distillation gave 29 g. of product, b. p., 136–137° at 10 mm.

2-Ethylmercaptopropanoic Acid (Method B).—A solution of 43.5 g. (0.41 mole) of 2-mercaptopropanoic acid was prepared by dissolving it in a solution containing 36 g. (0.9 mole) of sodium hydroxide in 45 cc. of water. While this solution was being stirred and heated on a steam-bath 63.2 g. (0.41 mole) of diethyl sulfate was added dropwise. Heating was continued until a single phase resulted. The solution was cooled, acidified with dilute sulfuric acid, and extracted with ether three times. The ether was evaporated and the residue distilled, yielding 24.5 g. of product, b. p. 111–113° at 8 mm.

4-Methylmercaptobutanoic Acid (Method C).—Eighteen grams of methyl mercaptan (0.37 mole) was dissolved

(1) Present address, Quaker Oats Co., Rockford, Illinois.
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(9) By A. J. Bergman.