pale orange-yellow solution with a green fluorescence having a bluish tinge.

Anal. Calcd. for $C_{15}H_{10}O_5$: C, 66.7; H, 3.7. Found: C, 67.0; H, 4.1.

2-Methyl-3'-cyano-α-pyrono(7,8,6',5')chromone. Condensation of III (0.5 g.) with ethyl cyanoacetate (0.28 g.) in presence of piperidine gave the compound which appeared as pale yellow plates, m.p. 196–197° (dec.). In alcohol and concentrated sulfuric acid solutions, it exhibits a weak blue fluorescence.

Anal. Calcd. for $C_{14}H_7NO_4$: C, 66.4; H, 2.8. Found: C, 66.7; H, 3.1.

2-Methyl-3'-carbethoxy-α-pyrono(7,8,6',5')chromone. III (0.5 g.) was condensed with diethyl malonate (0.4 g.) in presence of piperidine and the resulting product crystallized from methanol when it appeared as colorless prisms, m.p. 205–206°. In alcohol, it gave a pale yellow solution with a pale greenish blue fluorescence and with alcoholic alkali deeper greenish blue was observed. In concentrated sulfuric acid it exhibits a weak violet fluorescence.

Anal. Calcd. for $C_{16}H_{12}O_6$: C, 64.0; H, 4.0. Found: C, 64.1; H, 4.2.

2-Methyl-α-pyrono(7,8,6',5')chromone-3'-carboxylic acid. Saponification of the above ester using methanolic alkali in the cold during 24 hr., followed by acidification gave the carboxylic acid, which on crystallization from methanol appeared as colorless rectangular prisms, m.p. 257–258° (dec.). It dissolved easily in sodium bicarbonate solution. In alcoholic solution, it exhibits a weak blue fluorescence.

Anal. Calcd. for $C_{14}H_8O_6$: C, 61.8; H, 2.9. Found: C, 62.0; H, 3.1.

2,2'-Dimethyl-3'-acetyl-γ-pyrono(7,8,6',5')chromone (XV). A mixture of XIV (1 g.), anhydrous sodium acetate (2 g.), and acetic anhydride (5 ml.) was boiled under reflux at 180–185° for about 6 hr. The product obtained after working up was crystallized from methanol when it appeared as colorless plates and prisms, m.p. 184–185° (dec.). A sublimed sample, however, melted at 185–186° (dec.). It gave no ferric coloration in alcoholic solution.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.2. Found: C, 67.8; H, 4.3. This compound readily gave its 2,4-dinitrophenylhydrazone which on crystallization from ethyl acetate–petroleum ether (b.p. 40–60°) appeared as deep yellow plates and prisms, m.p. 243–244° (dec.).

Anal. Calcd. for $C_{22}H_{16}N_4O_8$: C, 56.9; H, 3.5. Found: C, 56.8; H, 3.7.

2,2'-Dimethyl-γ-pyrono(7,8,6',5')chromone (XVI). 0.5 g. of XV was dissolved in aqueous sodium carbonate solution (2*N*, 50 ml.) and gently boiled under reflux for about 3 hr. The product when worked out was found to be a mixture of (XVI) and its corresponding diketone and hence the product was directly employed for complete cyclization. A solution of the mixture (0.25 g.) in absolute alcohol (5 ml.) containing concentrated hydrochloric acid (2 drops) was refluxed for 5 min. and the solvent removed by evaporation. The residue was then crystallized from methanol when it appeared as yellow prisms, m.p. 260–261°, having no positive reaction with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.4; H, 4.1. Found: C, 69.6; H, 4.3.

WALTAIR, INDIA

[CONTRIBUTION FROM UNIVERSITY COLLEGE OF SCIENCE AND TECHNOLOGY]

Studies on the Constitution, Stereochemistry, and Synthesis of Aegeline,[1] an Alkaloidal-Amide of *Aegle marmelos* Correa

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Aegeline, a neutral product of *Aegle marmelos* Correa, is shown to have the formula $C_{18}H_{19}O_3N$. It is proved to be *N*-β-hydroxy-β-*p*-methoxyphenylethylcinnamamide from the studies of its acid hydrolysis, hydramine fission, periodic acid oxidation, and other degradative experiments, and also by its synthesis. The stereochemistry and steric stability of the compound are discussed. The characteristic features observed in its ultraviolet and infrared spectra, particularly in the —C=C— stretching region and the "trans band region" at 990–965 cm.$^{-1}$ establish the *trans* configuration of aegeline.

The leaves of *Aegle marmelos* Correa were reported as a source of aegeline, m.p. 176° (yield, 0.09%) by Chatterjee and Bose.[2] The substance showed absorption in the ultraviolet region (λ_{max} at 217 mμ, log ε 4.5328, 223 mμ, log ε 4.5177, and 275 mμ, log ε 4.6053) and contained an alcoholic function. It was earlier believed to be a neutral non-nitrogenous compound from its elementary analysis but later a careful examination of its infrared spectrum (Table I) revealed that aegeline was a conjugated amide. This observation accorded with the ultraviolet spectra measurements which were closely similar to those of *trans-N*-methylcinnamamide (λ_{max} at 216, 222, and 273 mμ, log ε 4.2863, 4.2077, and 4.4038, respectively) thus indicating that the substance did contain nitrogen.[3] In further consonance with this fact, aegeline evolved a strong base having methylamine-like odor when fused with alkali. Thereby, serious doubt was raised as to the correctness of the formula $C_{18}H_{18}O_4$ originally proposed. Several elementary analyses now carefully performed clearly demonstrated that aegeline must possess the formula $C_{18}H_{19}O_3N$. The present communication concerns the studies on its constitution, synthesis, stereochemistry, and steric stability.

For the isolation of aegeline, the previous ether extraction method[2] was followed with some modification. The ethereal mother liquor left after the

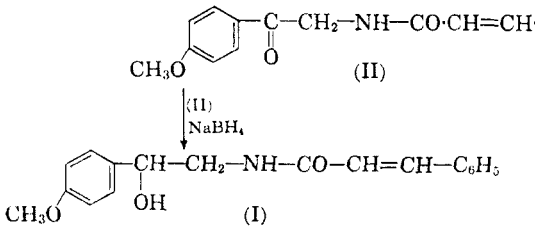
(1) Following the convention for terminology, the suffix *e* has been added to aegelin.

(2) A. Chatterjee and S. Bose, *J. Indian Chem. Soc.*, 29, 425 (1952).

(3) A. Chatterjee and S. K. Srimany, *Congress Handbook XVIth International Congress of Pure and Applied Chemistry*, Part II, p. 199 (1957).

removal of aegeline was freed from the solvent, taken up in benzene, and on subsequent chromatographic resolution on alumina using ethylacetate as the eluent yielded more aegeline, the over-all yield being 0.12%. The compound was freely soluble in chloroform, moderately in acetone, alcohol, and ethyl acetate, and sparingly in benzene, and contained a methoxyl group. It did not form salts with mineral or organic acids because of its insolubility in these reagents, thereby rendering alkaloid tests impossible with aegeline. Acetylation of the compound with acetic anhydride-pyridine yielded a monoacetate, m.p. 124°, with strong infrared alcoholic acetate absorption (λ_{max}^{Nujol} 1724 and 1235 cm.$^{-1}$). Microhydrogenation with Adam's catalyst in ethanol yielded a dihydro derivative, $C_{18}H_{21}O_3N$, m.p. 140°. Upon alkali fusion aegeline decomposed to give several products from which anisic acid and benzoic acid were isolated and identified. Prolonged alkali fusion demethylated anisic acid. With periodic acid aegeline formed benzaldehyde and anisaldehyde in a fairly good yield.

Upon hydrolysis with concentrated hydrochloric acid according to the method of Crombie[4] aegeline furnished anisaldehyde, cinnamic acid, and a mixture of two volatile bases. One of them formed a picrate, m.p. 208–209° which appeared to be the picrate of methylamine. Further characterization of the basic components is in progress. Simultaneous formation of anisaldehyde and the elimination of the nitrogen atom from aegeline during hydrolysis with hydrochloric acid emphasized that the compound had suffered hydramine fission and its basic fragment was β-hydroxy-β-*p*-methoxy-phenylethylamine derivative. Liberation of cinnamic acid coupled with the facts stated above made formula I[5] very probable. This unsaturated acylamido alcohol structure I for aegeline was finally substantiated by a simple and straightforward synthesis. ω-trans-cinnamoylamino-*p*-methoxy acetophenone (II) was synthesized according to the method of Lister and Robinson[6] with some modification. The latter upon reduction with sodium borohydride furnished aegeline (I).



It appeared of interest to study the geometrical configuration of aegeline because of its being a conjugated amide. Zechmeister[7,8] in his excellent work on the stereochemistry of carotenoids and diphenylpolyenes had shown that a definite correlation does exist between spatial configuration of organic molecules and their spectra (both ultraviolet and infrared). Similar observations were also made by Crombie[9–11] during the investigation of geometrical stereochemistry of unsaturated vegetable amides. Thereby, spectroscopic methods were applied by the present authors for the diagnosis of the configuration concerned. The spectral data were interpreted according to Zechmeister and Crombie.

The ultraviolet spectrum of aegeline, exhibited λ_{max} at 217, 223, and 275 mμ, log ε 4.5328, 4.5177, and 4.6053, respectively, which were indicative of trans-double bond to the carboxyamide grouping in I. This assignment was in agreement with the infrared spectrum of the compound. The latter showed a strong absorption at "trans-band region" (an intense band at 982 cm.$^{-1}$ with a shoulder at 990 cm.$^{-1}$, which was due to out-of-plane deformation vibration of the olefinic bond —CH=CH). Such stereochemically significant bands were found to be missing in dihydroaegeline. The facts stated above together with the absence of an absorption maximum of medium intensity at 818 cm.$^{-1}$ (for *cis*) in the infrared spectrum of the compound and the —C=C— stretching vibration discernible at 1665 cm.$^{-1}$ characteristic of trans α,β-unsaturated amides[10] clearly indicated the presence of α,β-trans linkage in aegeline. All the spectroscopical data cited here compared well with those of herclavin[12] (trans-*N*-2-*p*-methoxyphenylethyl-*N*-methylcinnamamide) and trans-*N*-methylcinnamamide (Table I) showing thereby that aegeline is indeed trans-*N*-β-hydroxy-β-*p*-methoxy-phenyl ethylcinnamamide. The amide (I) was found to exhibit considerable resistance to stereomutation. Thermal treatment and iodine-catalyzed irradiation with ultraviolet light for sixty-four hours failed to induce any stereochemical alteration in the molecule. This was in conformity with conclusions based upon molecular models. On a static model no inhibition of coplanarity was discernible with the *trans* configuration about the double bond, but with *cis* there was severe steric hindrance which forced the phenyl nucleus out of plane as observed with *cis*-cinnamic acid. This spatial conflict and the large amount of energy necessary for *trans-cis* rotation of the double bond appeared to be responsible for the steric stability of the compound.

(4) L. Crombie, *J. Chem. Soc.*, 995 (1955).

(5) When the structure determination of aegeline was complete, a preliminary note concerning its constitution was published (R. N. Chakravarty and B. Das Gupta, *Chem. & Ind. (London)*, 1632 (1955) confirming some of the results of the present authors.

(6) J. Lister and R. Robinson, *J. Chem. Soc.* 1297 (1912).

(7) L. Zechmeister, *Chem. Revs.*, **34**, 267 (1944).

(8) K. Lunde and L. Zechmeister, *Acta Chem. Scand.*, **8**, 1421 (1954).

(9) L. Crombie, *J. Chem. Soc.*, 1007 (1955).

(10) L. Crombie, *J. Chem. Soc.*, 4338 (1952).

(11) L. Crombie, *J. Chem. Soc.*, 2760, 2767 (1957).

(12) L. Crombie, *J. Chem. Soc.*, 995 (1955).

TABLE I

(Infrared data in cm.$^{-1}$)

Aegeline	Herclavin	Trans-*N*-methyl-cinnamamide
3250	1655	3280
3060	1610	3100
2830	1576	2860
1665	1509	1660
1627	1036	1625
1580	1027	1580
1520	991	1500
1062	982	983
1040		
990		
982		

Noteworthy was the behavior of aegeline toward polarized light. It contains an asymmetric carbon atom but is optically inactive. A review of the literature shows that when asymmetric carbon atoms are present, the rotatory power is obviously dependent on *cis-trans* isomerism.[7]

It therefore, seems that the linkage of the *trans*-cinnamoyl group to the optically active *N*-*β*-hydroxy-*β*-*p*-methoxyphenylethylamine causes an inversion at the asymmetric centre thereby producing racemic compound or it might be that the optically active bases (the enantiomorphs) themselves are unstable and readily racemise as observed in the case of vasicine.[13] Further investigation in this line is in progress.

EXPERIMENTAL

Isolation of aegeline from Aegle marmelos correa. Powdered sun-dried leaves (5000 g.) were extracted with ether (8000 ml.) in a Soxhlet apparatus for 72 hr. The deep green extract was concentrated to 500 ml, washed with 1% hydrochloric acid and 5% sodium hydroxide to remove bases, phenolic and acidic components. The ether solution after washing with water and drying over anhydrous sodium-sulphate was kept in the refrigerator for a fortnight when crude aegeline (3.6 g.) separated out. The adherent chlorophyll and gummy matters were removed by treating the crude mass with benzene and acetone (P). Fairly pure aegeline, m.p. 173–175°, thus obtained crystallized from ethanol in shining flakes. The mother liquor (P) was freed from the solvent, dissolved in benzene and chromatographed on 4000 g. of alumina. Elution with ethyl acetate (200 ml.) yielded homogeneous aegeline, m.p. 176° (2.4 g.) which upon crystallization from ethanol and ethyl acetate did not show any change in melting point.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.72; H, 6.39; N, 4.71; methoxyl, 10.44; active hydrogen, 0.34; mol. wt., 297. Found: C, 72.34, 72.40; H, 6.18, 6.26; N, 4.79; methoxyl, 10.46; active hydrogen, 0.31; mol. wt., 296.8 (Rast).

Monoacetylaegeline. A solution of 0.2 g. of aegeline in 2 ml. of acetic anhydride was refluxed with 2 drops of dry pyridine on water-bath for 4 hr. The reaction product was poured into water containing ice chips whereupon monoacetylaegeline separated out. It crystallized from ethyl acetate in colorless plates, m.p. 124°.

Anal. Calcd. for $C_{20}H_{21}O_4N$: C, 70.79; H, 6.19; N, 4.13; methoxyl, 9.14. Found: C, 70.59; H, 6.27; N, 4.11; methoxyl, 9.21.

(13) E. Späth, F. Kuffner, and N. Platzer, *Ber.*, **68**, 1384 (1935).

Dihydroaegeline. Aegeline (0.3 g.) upon hydrogenation with Adam's catalyst (0.09 g.) for 2 hr. in an aldehyde-free ethanolic solution (30 ml.) showed an uptake of one molar equivalent of hydrogen. The solution was freed from the catalyst and upon removal of the solvent dihydroaegeline (0.25 g.) was obtained. It crystallized from ethanol and ethyl acetate in colorless plates, m.p. 140°.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.24; H, 7.02; N, 4.68. Found: C, 72.30; H, 7.01; N, 4.58.

Ozonolysis of Aegeline. Ozonized oxygen was passed through aegeline (0.25 g.), dissolved in 10 ml. of ethyl acetate and 2 ml. of acetic acid, for 50 min., the solution being kept cooled to −75°. The ozonide thus formed was decomposed reductively by adding a mixture of magnesium powder (0.5 g.) and 10 ml. of aqueous acetic acid (1:1) and keeping it overnight. The decomposition product was diluted with water (50 ml.) and shaken with chloroform (30 ml. × 3).

The aqueous layer was removed and the organic layer was washed twice with HCl (2*N*) to remove the basic material. The chloroform layer was washed with water, dried over anhydrous sodium sulphate and distilled in an atmosphere of nitrogen. The residual oil was rapidly dissolved in 2 ml. of ethanol and treated with Brady's reagent. After 40 hr. the crude 2,4-dinitrophenylhydrazone of benzaldehyde was collected and dissolved in a mixture of benzene and ethyl acetate (1:1). The solution was chromatographed on Brockmann alumina. The faster running zone was eluted with benzene. The eluents upon evaporation and crystallization from ethanol yielded 45 mg. of DNPH, m.p. 233°. After two further crystallizations from the same solvent, it formed shining orange-red crystals, m.p. 234–35°, undepressed when mixed with benzaldehyde-2,4-dinitrophenylhydrazone, m.p. 235°.

Anal. Calcd. for $C_{13}H_{10}O_4N_4$: N, 19.58. Found: N, 19.72.

Periodate oxidation of the amide. Two grams of periodic acid was added to a methanolic solution (150 ml.) of 0.15 g. of neutral compound. After 4 hr. the mixture was steam-distilled. Benzaldehyde and anisaldehyde distilled over and they were extracted out from the distillate (800 ml.) with ether (250 ml. × 4) which was subsequently washed with a little sodium bisulfite to remove iodine. The ether extract on evaporation left anisaldehyde and benzaldehyde which with 2,4-dinitrophenylhydrazine gave orange-red crystals. These melted over a long range 225–247°. The crude derivative was dissolved in 15 ml. of benzene-ethyl-acetate (1:1) and chromatographed on alumina. Elution with benzene (45 ml.) yielded 80 mg. of 2,4-dinitrophenylhydrazone of benzaldehyde, m.p. 234°, and with ethyl acetate (30 ml.) 40 mg of DNPH of anisaldehyde, m.p. 250°.

Acid hydrolysis of aegeline. An ethanolic solution (5 ml.) of aegeline (0.5 g.) was heated at 120° in an oil bath for 60 hr. in a sealed tube with 5 ml. of concentrated hydrochloric acid. The product was diluted with 50 ml. of water and extracted with ether (A) (100 ml. × 3). Evaporation of the aqueous phase (B) gave a residue which upon decomposition with alkali liberated a gas. It was absorbed in 10 ml. of aqueous solution of 2*N* hydrochloric acid. The latter upon evaporation was dissolved in 1 ml. of water in which a few drops of aqueous solution of picric acid were added when a crystalline precipitate separated. It partly melted at 208–9° and decomposed when further heated. It did not depress the melting point of methylamine picrate, m.p. 209–10° when admixed but its further purification has not been possible.

The ether layer (A) was washed with water and shaken with an aqueous solution of sodium-bicarbonate from which cinnamic acid (0.159 g.) was isolated upon acidification with hydrochloric acid.

Anal. Calcd. for $C_9H_8O_2$: C, 72.97; H, 5.40. Found: C, 73.12; H, 5.32.

The ether layer (A) left after the removal of cinnamic acid was freed from the solvent, yielded anisaldehyde upon evap-

oration. The aldehyde was dissolved in 3 ml. of alcohol and gave 60 mg. of a derivative with 2,4-dinitrophenylhydrazine. An ethyl acetate solution (10 ml.) of the derivative was chromatographed on alumina and eluted with 45 ml. of benzene and with 30 ml. of ethyl acetate. The ethyl acetate eluents afforded deep-red crystals of pure anisaldehyde 2,4-dinitrophenylhydrazone, m.p. 250° which was crystallized from ethanol.

Anal. Calcd. for $C_{14}H_{12}O_5N_4$: N, 17.72. Found: N, 17.90.

Alkali fusion of the amide. Aegeline (1.0 g.) was fused with potassium hydroxide (6.0 g.) in a nickel crucible at 250° for 30 min. on a metal bath, when a base having a strong odor like methylamine was evolved. The mass was cooled and digested with 200 ml. of water in which 10.0 g. of solid ammonium chloride was added. The reddish brown solution was filtered and the aqueous alkaline filtrate was shaken up with ether (200 ml. × 5). The organic layer left no residue upon evaporation. The aqueous alkaline solution was cooled and acidified with hydrochloric acid. The turbid solution was subsequently extracted with ether (100 ml. × 3) which was washed with water and dried over anhydrous sodium sulphate. The ether solution upon evaporation yielded a mixture of anisic and benzoic acids (0.20 g.) which were separated by fractional sublimation and subsequent crystallizations from dilute ethanol. Anisic acid (30 mg.), m.p. 184° showed no depression in the mixture melting point with its authentic sample.

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.26; methoxyl, 20.39. Found: C, 63.29; H, 5.32; methoxyl, 20.45.

Benzoic acid melted at 121°. No change in m.p. was observed when mixed with an authentic sample of benzoic acid.

Anal. Calcd. for $C_7H_6O_2$: C, 68.85; H, 4.91. Found: C, 69.06; H, 4.86.

Synthesis of aegeline. The starting material for the synthesis was ω-amino-*p*-methoxyacetophenone hydrochloride, the latter being obtained by the prolonged hydrolysis (16 hr.) of ω-phthalimido-*p*-methoxyacetophenone[14] (crystallized from hot benzene) with concentrated hydrochloric acid at the reflux temperature. Hydrolysis in a sealed tube gave ω-amino-*p*-hydroxyacetophenone hydrochloride.

ω-amino-*p*-methoxyacetophenone hydrochloride (1.0 g.) obtained from acid hydrolysate was dissolved in minimum quantity of water (3 ml.) in which 3 ml. of an aqueous solution of hydrated stannic chloride (1.24 g.) containing 1 ml. of hydrochloric acid was added. The mixture was stirred when crystalline precipitate (2.0 g.) appeared. It was collected, dissolved in 20 ml. of hot water, cooled to about 37°, and stirred with 2.0 g. of molten cinnamoyl chloride. A cold aqueous solution of potassium hydroxide (25 ml., 10%) was added dropwise to the mixture. When the solution turned red, addition of alkali was stopped and stirring was continued until the solution became colorless. Further alkali was similarly added. The red coloration persisted when the addition of alkali was just complete. This procedure prevented the formation of pyrazine derivative.

ω-Cinnamoylamino-*p*-methoxyacetophenone separated, were collected after 2 hr., washed with water, and crystallized from ethylacetate in colorless shining flakes, m.p. 153–54°.

Anal. Calcd. for $C_{18}H_{17}O_3N$: C, 73.22; H, 5.76; N, 4.74. Found: C, 73.01; H, 5.58; N, 4.60.

Sodium borohydride (5.0 g.) was added to a methanolic solution (50 ml.) of ω-cinnamoylamino-*p*-methoxyacetophenone (0.5 g.). After 24 hr. the alcoholic solution was concentrated, treated with 100 ml. of water and shaken with ether (200 ml. × 3). The organic layer was washed with water, dried over anhydrous sodium sulfate, and distilled. The residue crystallized from ethylacetate in shining flakes, m.p. 176° (yield 60%), which were identical with natural aegeline in every respect.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 72.72; H, 6.39; N, 4.71; methoxyl, 10.44. Found: C, 72.38; H, 6.22; N, 4.80; methoxyl, 10.49.

Acknowledgment. Our grateful thanks are due to Dr. L. Marion, National Research Council, Ottawa, Canada, for the infrared spectra and Dr. A. Hofmann, Sandoz. AG., Switzerland, for valuable comments.

CALCUTTA 9, INDIA

(14) F. Tutin, *J. Chem. Soc.* 2508 (1910).