mination of the true rate constant for the disproportionation of stibosobenzene awaits the preparation of pure samples of the compound.

Acknowledgment.—The authors wish to acknowledge the assistance by Claire T. Brooks and Joseph J. Holechek throughout the course of this work. The interest of Harry Eagle is also gratefully acknowledged.

Summary

1. The kinetics of the disproportionation of stibosobenzene were determined. From 20 to 100% completion the reaction was shown to obey a rate law: $-dx/dt = k_2x(1 - x)$, where x is the fraction of stibosobenzene remaining at time t.

2. Preparations of stibosobenzene hydrolyzed with aqueous ammonia obeyed a rate law: $-dx/dt = k_1x^2 + k_2x(1 - x)$ over the entire course of the reaction, and the ratio k_1/k_2 was found to be 0.02.

3. The reaction was shown to be catalyzed by the product, bis-(diphenylantimony)-oxide, and by bases such as sodium hydroxide, ammonia and pyridine.

4. Rate constants were reproducible for each preparation, but varied widely with different preparations, an effect which is probably due to traces of impurities.

5. The apparent energy of activation was found to be 23.5 kcal./mole.

6. As mechanism of the reaction a chain reaction is proposed which is initiated by the thermal dissociation of phenyl groups from stibosobenzene and bis-(diphenylantimony)-oxide.

RECEIVED[9] SEPTEMBER 29, 1948

(9) Original manuscript received May 5, 1948.

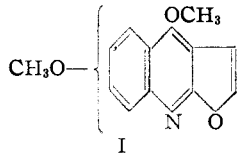
[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN, AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALCUTTA, INDIA]

On the Constitution of the Active Principles Isolated from the Matured Bark of *Aegle marmelos*, Correâ

BY ASIMA CHATTERJEE AND SUDHANGSU SEKHAR MITRA

The tree *Aegle marmelos*, Correâ (*Rutaceae*) commonly known as Bael, is indigeneous to India and found wild all over the Sub-Himalayan forests, in Central and South India. Its wood is yellowish-white with a strong aromatic scent. It is reputed to be a valuable Ayurvedic medicine for dysentery and various intestinal complaints. The bark as well as the fruits are used for this purpose. An examination of the fruits by various workers has revealed the occurrence of a coumarin[1] termed "marmelosin" which is identical with imperatorin,[2] a furocoumarin isolated from *Imperatoria ostruthium*[3] and *Angelica archangelica*.[4] The isolation of three crystalline constituents of the *Aegle marmelos* bark was described earlier.[5] We wish to report that one is an alkaloid identical[6] with γ-fagarine[7]; the second compound is marmesin, a coumarin which has not been isolated so far from other natural sources; and the third compound is umbelliferone.

Hydrochloric acid washing of ethereal bark extracts yielded a basic portion from which an alkaloid, m. p. 142.5–143°, was separated in 0.3% yield, which has been shown by Chakravarty[6] to be identical with γ-fagarine[7] (I).



I

The remaining ether extract upon concentration and standing in the refrigerator deposited crystals of marmesin, m. p. 189.5°, in a 0.6% yield. The mother liquor, after alkali washings and steam distillation, deposited umbelliferone m. p. 230° (yield, 0.06%).

The molecular formula of marmesin appeared to be $C_{14}H_{14}O_4$ which was confirmed by Rast's method and also by titration. Marmesin is optically active, $[\alpha]^{34}D$ +26.8° (in chloroform). This compound does not contain methoxy or methylenedioxy groups. It yields a monoacetyl derivative and readily undergoes dehydration producing anhydromarmesin. These facts indicate the presence of an hydroxyl group. Since the compound does not react with ferric chloride or diazomethane, it must contain an alcoholic group. Marmesin is neutral to litmus and is insoluble in aqueous alkali but readily dissolves in alcoholic alkali with a stable yellow color. This solution precipitated, on acidification, the original substance indicating a lactone structure. Marmesin dissolves in concentrated sulfuric acid with a yellow color and a deep violet fluorescence. When refluxed with aqueous alkali and a little mercuric oxide, marmesin passed into solution and, on acidification with hydrochloric acid, yielded an acid which did not undergo ring closure to give the

(1) B. B. L. Dikshit and S. Dutt, *J. Indian Chem. Soc.*, **7**, 759 (1930); **9**, 271 (1932).

(2) E. Späth, P. K. Bose, W. Grüber and N. C. Guha, *Ber.*, **70**, 1021 (1937).

(3) E. Späth and H. Holsen, *ibid.*, **66**, 1137 (1933).

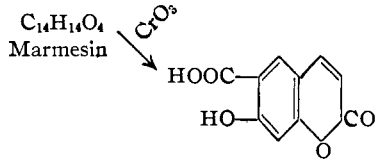
(4) E. Späth and F. Vierhapper, *ibid.*, **70**, 248 (1937).

(5) A. Chatterjee (née Mookerjee), *Current Science*, **12**, 209 (1943).

(6) K. K. Chakravarty, *J. Indian Chem. Soc.*, **21**, 401 (1944).

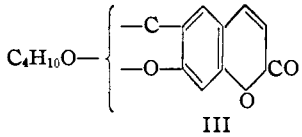
(7) V. Deulofeu, R. Labriola and J. Langhe, THIS JOURNAL, **64**, 2326 (1942).

original substance. Consequently, a corresponding *trans* coumaric (*trans*-marmesic acid) acid, $C_{14}H_{16}O_5$, must have been formed under the influence of mercuric oxide. All these reactions are indicative of a coumarin ring which was secured by the oxidation of marmesin with chromic acid to umbelliferone-6-carboxylic acid (II).



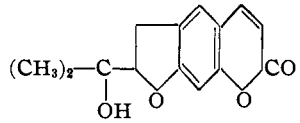
II

Consequently, the partial structure for marmesin can now be represented by (III).



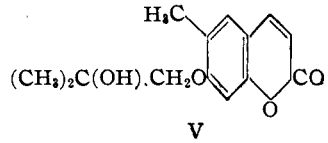
III

When fused with alkali, marmesin yields resorcinol, and, upon mild oxidation with chromic acid, acetone. The latter indicates that the group, $(CH_3)_2C(OH)$–, might be a part of the $C_4H_{10}O$-residue. The presence of a dimethylhydroxymethyl radical would also explain the easy dehydration of marmesin. One of the two phenolic hydroxyl groups which appears in resorcinol and umbelliferone-6-carboxylic acid is apparently involved in an ether linkage which in all probability leads to structure (IV) for marmesin.



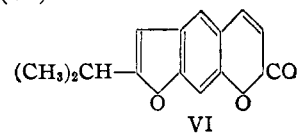
IV

By catalytic hydrogenation marmesin yields dihydromarmesin ($C_{14}H_{16}O_4$); however, anhydromarmesin adds four atoms of hydrogen ($C_{14}H_{16}O_3$). This observation eliminates structure (V).



V

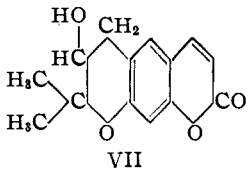
Formula (IV) represents a substituted dihydrofurocoumarin where the $(CH_3)_2C(OH)$-group is attached to the β-carbon atom in the dihydrofuran ring which has been also confirmed by the established identity of anhydromarmesin with desoxyoreoselone[8] (VI).



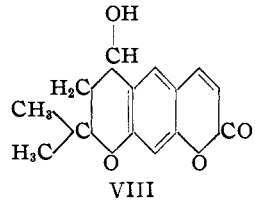
VI

(8) E. Späth, K. Klager and C. Schlösser, *Ber.*, **64**, 270 (1931); E. Späth and K. Klager, *ibid.*, **66**, 749 (1933).

The possibility of an alternate structure (VII) or (VIII) involving a chroman ring can be ruled out since anhydromarmesin is not identical with xanthyletin.[9] From the study of marmesin it ap-



VII



VIII

peared that it might be an optical isomer of L-nodakenetin,[10] the degradation product of the glucoside nodakenin, isolated from *Peucedanum decursivum*.[11] Therefore, our marmesin sample was compared with authentic nodakenetin obtained from Dr. W. Grüber (Vienna) to whom our thanks are due. Although the two compounds and their corresponding derivatives are very similar, they show a large melting point depression (35°). The mixture of the two samples in equal amounts shows no optical activity. It should be mentioned that free nodakenetin has not yet been found in nature but only as the glucoside mentioned[11]; however, its D-isomer, marmesin, occurs in the free state.

An interesting observation was made in connection with umbelliferone, *viz.*, that the latter was not present as such in the residual oil but could be obtained from it by steam distillation or saponification.[12] It is, therefore, probable that the bark of *Aegle marmelos* contains another as yet not isolated coumarin which can be readily hydrolyzed to umbelliferone.

Experimental

Extraction of the Matured Bark of Aegle Marmelos.—Two kg. of air-dried, powdered bark was extracted with ether for forty-eight hours in a Soxhlet apparatus. The deep-brown extract was shaken with 0.1% hydrochloric acid (300 ml.) to remove γ-fagarine. This was repeated (about 5 times) until the acid digest gave only an insignificant precipitate with Dragendorff's reagent. Then the brown ether solution (P) was washed with water, dried over sodium sulfate, concentrated to 500 ml. and kept in a refrigerator for four weeks.

Isolation of Marmesin.—The brown ethereal solution (P) deposited 12 g. of marmesin which was filtered off, and the mother liquor (Q) was kept for further investigation. Marmesin was purified by successive crystallizations from acetone, ethyl alcohol, benzene, and ethyl acetate when rhombic plates of a constant m. p. 189.5° were obtained. It sublimes unchanged in a 0.1 mm. vacuum at 150–160°. It is freely soluble in chloroform, fairly in acetone or alcohol, sparingly in benzene, ethyl acetate, ether, and is insoluble in petroleum ether or water; $[\alpha]^{34}D$ +26.8° (in chloroform).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.30; H, 5.69; mol. wt., 246. Found: C, 68.42; H, 5.74; mol. wt. (Rast), 252, 250.

Molecular Weight by Titration.—Marmesin (0.15 g.) was dissolved in 5 ml. of alcohol and refluxed for half an hour

(9) E. Späth, P. K. Bose, E. Dobrovolny and A. Chatterjee (née Mookerjee), *ibid.*, **72**, 1452 (1939).

(10) E. Späth and P. Kainrath, *ibid.*, **69**, 2062 (1936).

(11) J. Arima, *Bull. Chem. Soc. Japan*, **4**, 16 (1929).

(12) E. Späth and L. Socias, *Ber.*, **67**, 59 (1934).

with 25 ml. of 1 *N* aqueous potassium hydroxide. The pale yellow solution was cooled and the excess of alkali was back titrated with sulfuric acid (phenolphthalein). Found: mol. wt., 250, 253.

Action of Dilute Alkali on Marmesin.—Marmesin (0.25 g.) in 5 ml. of methyl alcohol was mixed with 40 ml. of 1% aqueous potassium hydroxide and refluxed for half an hour. The substance passed into solution and gradually became yellow. It was acidified with hydrochloric acid (congo red), allowed to stand overnight, and extracted with ether. The dry residue of this extract crystallized from acetone in colorless, rhombic plates which melted at 189–189.5°, alone or when mixed with a pure specimen of marmesin.

Acetylation of Marmesin.—A mixture of marmesin (0.25 g.), 5 ml. of acetic anhydride and 0.5 g. of freshly fused sodium acetate was refluxed for five hours. The mixture was poured into ice-cold water and stirred. The separated solids were collected, washed with ice-cold water and crystallized from hot water. The colorless flakes (0.25 g.), m. p. 130°, were washed with cold water and dried.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.55. Found: C, 66.91, H, 5.42.

Dehydration of Marmesin.—Marmesin (0.25 g.) dissolved in 50 ml. of dry benzene was refluxed with 2.5 g. of phosphorus pentoxide for five hours. The decanted, clear solution was concentrated to 5 ml. Transparent plates of anhydromarmesin separated which were filtered and washed with cold benzene; constant m. p., 138–140°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 73.69; H, 5.26. Found: C, 73.80; H, 5.60.

Catalytic Hydrogenation of Marmesin.—Marmesin (0.3 g.), dissolved in glacial acetic acid (10 ml.), was treated with hydrogen and Adams platinum oxide catalyst (0.1 g.) which had been saturated previously with hydrogen. The absorption of hydrogen (30.0 ml. at 30°, 760 mm.) corresponded almost exactly to 1 H_2. The solution was filtered, diluted with water and extracted with ether. The ethereal solution was washed successively with sodium bicarbonate and water, dried over sodium sulfate, concentrated to 5 ml., diluted with 1 volume of petroleum ether, and kept overnight. Colorless, rhombic plates separated, m. p. 135°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 67.75; H, 6.45. Found: C, 68.34; H, 6.20.

Catalytic Hydrogenation of Anhydromarmesin.—Anhydromarmesin (0.450 g.) in 10 ml. of glacial acetic acid was treated as above in the presence of 0.15 g. of catalyst. Within a few minutes 98.0 ml. of hydrogen was absorbed (30°, 760 mm.) corresponding to 4 gram atoms of hydrogen. The solution was treated as described in the previous section. The product crystallized from a mixture of benzene and petroleum ether in colorless flakes, m. p. 116–117°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.40; H, 6.90. Found: C, 72.70, H, 7.07.

***trans*-Coumaric Acid Derivative of Marmesin (*trans*-marmesic acid).**—A mixture of marmesin (0.39 g.), 30 ml. of aqueous 2 *N* sodium hydroxide and a little mercuric oxide was refluxed for two hours and filtered. The yellow filtrate was acidified with hydrochloric acid (congo red) and kept overnight. The precipitated yellowish-green flakes were recrystallized from dilute methyl alcohol and melted at 204° (dec.).

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 63.63; H, 6.02. Found: C, 63.95; H, 6.31.

Fusion of Marmesin with Potassium Hydroxide; Isolation of Resorcinol.—Marmesin (1.00 g.) was fused with potassium hydroxide (5.00 g.) in a nickel crucible and heated to 250° on a metal-bath for one hour. The product was cooled and digested with water. The brown solution was acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with 10% aqueous sodium bicarbonate and then with water, dried and concentrated. The separated crystals were recrystallized from alcohol and petroleum ether (b. p. 60°) and then from ethyl acetate (m. p. 109°). They gave a violet color with ferric chloride and reduced ammoniacal silver nitrate. The sample gave no melting point depression with resorcinol.

Anal. Calcd. for $C_6H_6O_2$: C, 65.45; H, 5.45. Found: C, 65.50; H, 5.61.

Oxidation of Marmesin with Chromic Acid.—A solution of marmesin (0.5 g.) in glacial acetic acid (8 ml.) was added to chromic acid (0.25 g. in 10 ml. of 50% acetic acid) and kept at room temperature for sixty hours in a closed flask. The mixture was cooled in ice and was slowly almost neutralized with strong sodium hydroxide. The solution was distilled until 15 ml. was collected in a receiver containing 4 drops of freshly distilled benzaldehyde and 4 drops of 10% sodium hydroxide. On keeping the mixture overnight in the refrigerator, a semi-solid separated that was extracted with ether. The dried extract was evaporated. The oily residue was treated with 2 drops of benzaldehyde (in dilute, acetone-free methyl alcohol) and cooled in ice when immediately glistening needles separated which were recrystallized from dilute methanol (acetone-free); pale yellow, shining needles, m.p. 112°. The substance was identified as dibenzal acetone by the mixed melting point test.

Isolation of Umbelliferone-6-carboxylic Acid by Oxidation of Marmesin.—Marmesin (1.5 g.) was treated with 300 ml. of 3% sulfuric acid and the mixture was heated. To the boiling mass, 5 g. of potassium bichromate (in 60 ml. of water) was slowly added and the brown-red solution was refluxed for six hours. Then the dark-green solution was cooled and shaken with ether to remove unchanged marmesin. The green aqueous filtrate was concentrated on a water-bath to 100 ml. and kept overnight at 0°. The separated pale yellow solid (0.5 g.) was washed with cold water. It crystallized from methyl alcohol in colorless needles, m.p. 260° (dec.). It gave a violet color with ferric chloride and dissolved readily in aqueous alkali or alkali bicarbonate (with effervescence) with a stable yellow color. The compound was identified as umbelliferone-6-carboxylic acid by m.p. and mixed m.p. tests.[13]

Anal. Calcd. for $C_{10}H_6O_5$: C, 58.27; H, 2.95. Found: C, 58.52; H, 3.23.

Methylation of Umbelliferone-6-carboxylic Acid.—The compound (0.05 g.) in methanol was treated with excess diazomethane (in ether). After two days, the solvent was removed, and the residue crystallized from a mixture of ether and methyl alcohol. The pale yellow needles melted at 165–166° and gave no depression with dimethyl-7-hydroxy-coumarincarboxylic acid (m.p. 168°).

Decarboxylation of 7-Hydroxy-coumarin-6-carboxylic Acid.—Umbelliferone 6-carboxylic acid (0.2 g.) isolated from chromic acid oxidation products of marmesin, was heated above its m.p. to 265–270° for thirty minutes. From the brown mass a colorless solid distilled at 150–160° (0.1 mm.). It crystallized from dilute methyl alcohol in needles, m.p. 230°. It had the same melting point when mixed with synthetic umbelliferone.

Anal. Calcd. for $C_9H_6O_3$: C, 66.64; H, 3.74. Found: C, 66.21; H, 3.98.

The methyl derivative of the decarboxylation product, prepared by the action of diazomethane, melted at 118–119° and showed no change when mixed with synthetic methyl-umbelliferone.

Isolation of Umbelliferone from the Fraction (Q).—The mother liquor, Q, left after removal of marmesin, was freed from the solvent, and the oil (R) obtained weighed 300 g. Two hundred grams of this oil was steam-distilled for twelve hours when an oil (6 ml.) was collected, having a bitter taste, and a pleasant smell, resembling that of a mixture of eucalyptus and lemon oil. After removal of this essential oil, the residue was cooled and a crystalline substance (0.80 g.) obtained. It was purified by crystallizations from methyl alcohol, ethyl acetate and

(13) H. von Pechmann, *Ber.*, **17**, 932 (1884).

water, yielding shining needles of umbelliferone, m.p. 230°.

Isolation of Umbelliferone from Oil (R) by Saponification.—To the oil (100 g.) (15°), 200 ml. of 20% methanolic potassium hydroxide was added with constant shaking. The mixture was allowed to stand for forty-five minutes, poured into 1.5 liters of ice-water and extracted five times with ether to remove unsaponifiable matter. The alkaline aqueous portion was acidified with hydrochloric acid (congo red) and distilled *in vacuo* to remove the greater portion of methyl alcohol. The next day the separated oil was extracted with ether and the extract was washed with 2 × 100 ml. of 25% potassium carbonate (W). The ethereal extract was washed with water, dried and distilled. Only a very small, gummy residue was left.

Isolation of Umbelliferone from Fraction (W).—The brown potassium carbonate washings (W) were acidified with hydrochloric acid (congo red) whereby the solution became turbid. It was extracted with 100 ml. of ether; the extract was twice washed with water, dried and distilled. A brownish, solid residue of umbelliferone (0.4 g.), mixed with a little viscous oil, was left, which crystallized from dilute methanol in silky, colorless needles; m.p. 230°.

Acknowledgment.—It is a pleasure to thank Professor L. M. Parks for suggestions and the laboratory facilities granted, and Professor A. H. Uhl, Professor S. N. Bose, Professor P. C. Mitter, and Dr. P. K. Bose for their interest in this investigation.

Summary

From the matured bark of *Aegle marmelos*, Correâ, three crystalline compounds have been isolated in pure state: 1, The alkaloid γ-fagarine; 2, A coumarin which had not been observed before in the free state in nature. It is an optical isomer of nodakenetin; and 3, Umbelliferone.

MADISON, WISCONSIN, AND
CALCUTTA, INDIA

RECEIVED JUNE 4, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF UTAH]

3,4-Dihydro-1,3,2H-Benzoxazines. Reaction of *p*-Substituted Phenols with N,N-Dimethylolamines

BY W. J. BURKE

Major attention in reactions involving phenol and formaldehyde has quite naturally been directed toward polymeric products in view of their wide industrial application. The marked reactivity of the intermediates involved, however, indicates the desirability of investigating further the possibility of isolating well defined monomeric compounds from such systems.

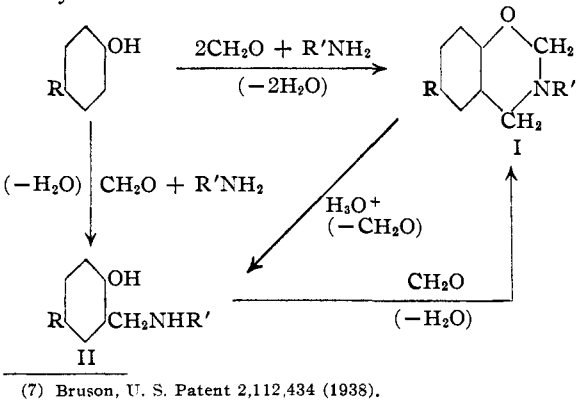
Interaction of secondary aliphatic amines and formaldehyde with phenols has been shown by Caldwell and Thompson,[1] and by Bruson and MacMullen[2] to result in the introduction of one or more dialkylaminomethyl substituents in positions ortho or para to the hydroxyl group. The reaction involved is shown as

$$C_6H_5OH + CH_2O + R_2NH \longrightarrow HOC_6H_4CH_2NR_2$$

Although generally considered to be a Mannich type of condensation, this and similar reactions involving the interaction of a secondary amine and formaldehyde with a compound containing active hydrogen were studied by others[3,4] several years before the initial related work of Mannich.[5]

Analogous studies involving primary rather than secondary aliphatic amines appear to have been limited to the use of 2-aminoethanol.[6] Reaction of equimolar quantities of this amine with formaldehyde and certain *o*- or *p*-substituted phenols resulted in crystalline compounds having *o*- or *p*-beta-hydroxyethylaminomethyl groups. Other phenols, such as the three cresols, gave resins containing nitrogen or sirups which could not be purified. The condensation of selected phenols and formaldehyde with sodium sulfanilate and related aminoaromatic sulfonic acid salts has also been reported[7] but the exact composition of the products was not determined.

The present work has been concerned with the reaction of *p*-substituted phenols with formaldehyde and primary amines in a molar ratio of 1:2:1, respectively. This procedure led to the formation in good yield of 3,4-dihydro-3,6-disubstituted-1,3-2H-benzoxazines (I), a new series of compounds.[8] In an alternate method, equimolar quantities of the *p*-substituted phenol, formaldehyde, and primary amine reacted to give as an intermediate an *o*-alkylaminomethyl-*p*-substituted phenol (II). Conversion of II to I took place readily by treatment with formaldehyde in the presence of a basic catalyst.



(1) Caldwell and Thompson, THIS JOURNAL, **61**, 765 (1939).
(2) Bruson and MacMullen, *ibid.*, **63**, 270 (1941).
(3) Bayer and Co., German Patent 92,309 (1897).
(4) Einhorn, Bischkopff and Szelinski, *Ann.*, **343**, 223 (1905).
(5) Mannich and Krosche, *Arch. Pharm.*, **250**, 647 (1912).
(6) Bruson, THIS JOURNAL, **58**, 1741 (1936).
(7) Bruson, U. S. Patent 2,112,434 (1938).
(8) The nomenclature employed in this paper follows that kindly suggested by Dr. Leonard T. Capell of *Chemical Abstracts*.