posited white needles of XIIc (0.36 g., 19%), m.p. 144–145°. An analytical sample was obtained as fine white needles, m.p. 143–144°, by sublimation at 95° (0.5 mm.).

Anal. Calcd. for $C_{10}H_9O_2Cl$: C, 61.11; H, 4.62; Cl, 18.05. Found: C, 61.38; H, 4.87; Cl, 17.84.

3,6-Dimethylbenzocyclobutene-1-carboxylic Acid (XVIIIb).—A solution of 4,7-dimethyl-2-diazo-1-indanone (Xb) (1.00 g., 0.0054 mole) in tetrahydrofuran (170 ml.) and water (30 ml.) containing suspended sodium bicarbonate (1 g.) was irradiated at 50° for 16 hours. The solution was distilled until free of tetrahydrofuran and the tarry aqueous layer extracted with methylene chloride. The aqueous layer was acidified, extracted with ether, and the ether layer dried and evaporated. The residual yellow solid was sublimed at 78° (0.5 mm.) to give the acid XIIb as tiny white prisms (0.21 g., 22%), m.p. 107–109°.

Anal. Calcd. for $C_{11}H_{12},O_2$: C, 75.02; H, 6.87. Found: C, 75.12; H, 6.97.

1-Cyanobenzocyclobutene (XX). (a).—Monobromide XIX (5.00 g., 0.0273 mole) and sodium cyanide (2.0 g., 0.041 mole) were dissolved in dimethyl sulfoxide (30 ml.), heated at 50° for 30 minutes and finally at 95° for another 30 minutes. Water (150 ml.) was added and the solution was then extracted with 8:1 ether–petroleum ether (150 ml.). The ether solution was washed several times with water and then passed through anhydrous sodium sulfate. The solvent was evaporated and the residue distilled under reduced pressure. Three fractions, b.p. 88° (1.3 mm.), were obtained: (1) 0.615 g., $n^{25}D$ 1.5657; (2) 1.462 g. $n^{25}D$ 1.5492; (3) 1.204 g., $n^{25}D$ 1.5450; yield 3.28 g. (93%). Fraction 2 was analyzed.

Anal. Calcd. for C_8H_7N: C, 83.69; H, 5.46; N, 10.85. Found: C, 83.74; H, 5.48; N, 10.87.

(b).—A solution of monobromide XIX and sodium cyanide (excess) in methanol was refluxed for 11 hours and the reaction mixture worked up in the manner described above. A comparison of the infrared spectra of the product with those of the monobromide and nitrile indicated that only a 25–30% conversion to 1-cyanobenzocyclobutene took place under these conditions.

Hydrogen Peroxide Oxidation of 1-Cyanobenzocyclobutene (XX).—A mixture of the nitrile (1.00 g., 0.0078 mole), 30% hydrogen peroxide (2 ml., 0.017 mole) and 20% sodium hydroxide (2 ml.) reacted exothermically with evolution of oxygen. After 15 minutes of shaking, methanol was added carefully to sustain the reaction. If the temperature of the reaction mixture was allowed to increase above 60°, hydrolysis of the amide occurred as was evidenced by the evolution of ammonia. In all, 8–10 ml. of methanol was added; the use of less methanol led to incomplete reaction. When the addition of more methanol failed to increase the rate of evolution of oxygen, the mixture was warmed at 60° for 15 minutes longer. The reaction mixture was then transferred to a separatory funnel, diluted with water and extracted with methylene chloride (50 ml.). The methylene chloride solution, after filtration through anhydrous sodium sulfate, was diluted slowly with 30–60° petroleum ether, when benzocyclobutene-1-carboxamide (XXI) (0.835 g., 73%) precipitated in fine white needles, m.p. 158.5–159°. Recrystallization from methylene chloride–30–60° petroleum ether raised the melting point to a constant value of 159.5°.

Anal. Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.44; H, 6.31; N, 9.34.

Benzocyclobutene-1-carboxylic Acid (XVIIIa). (a).—The amide XXI (1.00 g.) was dissolved in hot 20% aqueous sodium hydroxide (15 ml.) and heated for 5 hours on the steam-bath. The solution was then cooled, made strongly acid with concentrated hydrochloric acid and extracted twice with 100-ml. portions of a 5:1 mixture of petroleum ether (30–60°) and ether. The organic extract was filtered through sodium sulfate, evaporated to dryness, and the residue dissolved in a small amount of petroleum ether (30–60°). On cooling the solution to −5° there was obtained, in two crops, benzocyclobutene-1-carboxylic acid (0.975 g., 97.5%), m.p. 74.5–76°. Several recrystallizations from petroleum ether (30–60°) raised the melting point to 76.5°.

Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44; neut. equiv., 148. Found: C, 72.60; H, 5.58; neut. equiv., 148.

(b).—A solution of 2-diazo-1-indanone (Xa) (2.0 g., 0.0126 mole) in tetrahydrofuran (200 ml.) and water (100 ml.) containing sodium bicarbonate (2.0 g.) was irradiated at the boiling point of the solution for 10 hours. Removal of the tetrahydrofuran by distillation left a tarry aqueous residue which, after extraction with methylene chloride, was acidified and extracted with ether. The ether layer was washed with water, dried over sodium sulfate and evaporated. The tan solid residue was sublimed at 90° (2 mm.) to yield small white prisms of benzocyclobutene-1-carboxylic acid (0.400 g., 21%), m.p. 71–74°. Recrystallization from petroleum ether gave white needles, m.p. 74–75°. The melting point of this material was not depressed upon admixture with a sample prepared by method a; in addition, the infrared spectra of both samples were identical.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA AGRÍCOLA, MINISTÉRIO DA AGRICULTURA]

The Chemistry of Rosewood. II. Isolation and Identification of Cotoin and Pinocembrin

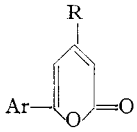
BY OTTO RICHARD GOTTLIEB AND WALTER B. MORS

RECEIVED OCTOBER 11, 1957

Two additional compounds—2,6-dihydroxy-4-methoxybenzophenone (cotoin) and 5,7-dihydroxy-flavanone (pinocembrin)—have now been isolated each from one of the commercially exploited species of South American rosewood trees (genus *Aniba*). Attention is again called to the chemical relationship between species in this plant genus.

The preceding article[1] described the isolation of two previously unknown substances from two species of South American rosewood trees: anibine (I) and 4-methoxy-paracotoin (II), found to be present in the wood of *Aniba rosaeodora* Ducke and *A. Duckei* Kostermans (family *Lauraceae*). Attention was called to the structural similarity of these two compounds with phenylcoumalin (III) and paracotoin (IV), which occur, respectively, in the barks of *Aniba coto* (Rusby) Kostermans and *A. pseudo-coto* (Rusby) Kostermans.[2] All these substances can be represented by substituted α-pyrones, with one aromatic substituent attached at position 6. Attention has now been directed to the acidic fraction of the original benzene extracts.

I, Ar = 3-pyridyl
R = OCH_3
II, Ar = piperonyl
R = OCH_3



III, Ar = phenyl
R = H
IV, Ar = piperonyl
R = H

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[1] Walter B. Mors, Otto Richard Gottlieb and Carl Djerassi, THIS JOURNAL, **79**, 4507 (1957).

[2] For historical and botanical background see ref. 1.

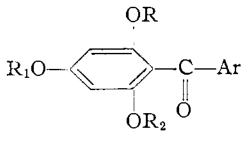
A. Duckei yielded as the main component of the acidic fraction cotoin (V) (2,6-dihydroxy-4-methoxybenzophenone), which is also the principal constituent of the true Coto bark, *A. coto*. It was isolated as yellow needles, m.p. 131–132°, empirical formula $C_{14}H_{12}O_4$. Its identity was immediately suspected and confirmed by direct comparison (mixture melting point and infrared spectrum) with an authentic specimen.

The principal acidic constituent of *A. rosaeodora* was isolated as colorless crystals, m.p. 201–203°, empirical formula $C_{15}H_{12}O_4$. It was identified as pinocembrin (X) (5,7-dihydroxy-flavanone), by mixture melting point and infrared and ultraviolet spectral comparison.

The similarity of this substance to cotoin is very striking. It becomes apparent, for instance, in the introduction of two acetyl groups, the obtention of benzoic acid on oxidation and the unsuccessful attempt of molecular weight determination apparently owing to the formation of a molecular addition compound with camphor (see Experimental Section). Another similarity is the high acidity of the two compounds. Both are soluble in bicarbonate solution and can be titrated with ethanolic potassium hydroxide to a phenolphthalein end-point. However, this acidity disappears upon acetylation.

The infrared spectra of the two compounds are also very similar. Owing to the existence of the particular conjugated chelate system which results from hydrogen bonding in compounds of the *o*-hydroxyacetophenone type[3] the carbonyl absorption is shifted considerably toward longer wave length (6.1–6.2 μ).

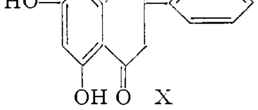
With the isolation of cotoin from one of the species of rosewood the relationship with the Coto barks again becomes apparent. *Aniba coto* is the only source from which cotoin had been isolated so far, whereas *A. pseudo-coto* contains a number of closely related derivatives (VI–IX).[4]



V, cotoin, R = R_2 = H; R_1 = CH_3; Ar = phenyl
VI, hydrocotoin, R = R_1 = CH_3; R_2 = H; Ar = phenyl
VII, methylhydrocotoin, R = R_1 = R_2 = CH_3; Ar = phenyl
VIII, protocotoin, R = R_1 = CH_3; R_2 = H; Ar = piperonyl
IX, methylprotocotoin, R = R_1 = R_2 = CH_3; Ar = piperonyl

The isolation of pinocembrin from the wood of a plant belonging to the *Lauraceae* may seem surprising. Pinocembrin is one of the more common components of the plant genus *Pinus*, where its occurence has been demonstrated in the heartwood of many species.[5] Up to now its presence in angiosperms was limited to a single known instance, namely, the wood of the cherry tree (family *Rosaceae*).[6] The fact that pinocembrin has now also been recognized in a species of the *Lauraceae* may suggest that this flavanone is more widespread outside the *Coniferae* than hitherto suspected.

Although at first sight this substance does not appear to be closely related to those previously found in *Aniba* species, direct comparison with the structure of cotoin clearly shows the common keto-phloroglucinol moiety, as well as the unsubstituted phenyl radical. According to Geissman and Hinreiner,[7] the naturally occurring benzophenones and flavonoids are closely related biogenetically. It is also of interest to recall Robinson's suggestion[8] of the role of polyketomethylene chains in the biosynthesis of many natural products, especially phloroglucinol derivatives and aryl-ketones, a hypothesis which easily applies to all the mentioned compounds from rosewood (I, II, V, X).



X

Experimental[9]

Extraction Procedure.—The general procedure followed was described in the previous communication.

Cotoin.—The benzene extract of the wood of *Aniba duckei*,[10] after removal of anibine, was extracted several times with 3% sodium hydroxide solution and the resulting precipitate removed by centrifugation. The aqueous basic solution was acidified with dilute hydrochloric acid and repeatedly extracted with benzene. The benzene layers were combined, washed with water and dried over anhydrous sodium sulfate. Crude cotoin crystallized after concentration in approximately 2% yield, and was purified by chromatography on alumina deactivated with 3% of 10% acetic acid, eluting with benzene. Recrystallization from benzene yielded pure cotoin as yellow needles, m.p. 131–132°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95; 1 OCH_3, 12.71. Found: C, 69.22; H, 4.94; OCH_3, 12.35.

Identity with an authentic specimen of cotoin was established by mixture melting point determination and infrared spectral comparison.

Attempted molecular weight determination by Rast's method: A portion of a mixture of 21.7 mg. of cotoin and 196.4 mg. of camphor melted in a capillary at 120°. On further heating the melt turned solid, melting again at 160°.

Acetylation of a sample with acetic anhydride–sodium acetate under reflux for 1 hr. followed by recrystallization from benzene led to cotoin diacetate, m.p. 91–92°.[11] Saponification of the acetate with ethanolic potassium hydroxide revealed two acetyl groups per molecule of 248 (molecular weight of cotoin, 244.24).

Oxidation of cotoin with aqueous alkaline potassium permanganate at room temperature yielded benzoic acid, m.p. 122°, identified by mixture melting point and infrared spectrum.

Pinocembrin.—The benzene extract of the wood of *Aniba rosaeodora*[10] was processed in the same way as described for *A. duckei*. The benzene solution of phenolic material, taken to dryness, yielded 0.37% crude pinocembrin. Sublimation *in vacuo* yielded slightly yellow crystals which, recrystal-

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(3) R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, THIS JOURNAL, **71**, 1068 (1949).

(4) For a complete review see J. Messner, *Pharm. Zentralh.*, **67**, 625 680, 696 (1926).

(5) H. Erdtman, "Progress in Organic Chemistry," Vol. 1, edited by J. W. Cook, Academic Press, Inc., New York, N. Y., 1952, p. 38.

(6) C. Mentzer and H. Pachéco, *Bull. soc. chim. biol.*, **34**, 956 (1952).

(7) T. A. Geissman and E. Hinreiner, *Bot. Rev.*, **18**, 210 (1952).

(8) R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, pp. 7–9.

(9) All melting points were determined on the Kofler block. Ultraviolet spectral measurements were performed with a Beckman model DU spectrophotometer. We are indebted to Mrs. Dolores Phillips, Spectrophotometric Laboratory, Wayne State University (Detroit, Mich.) for the infrared spectral measurements and to Dr. A. Bernhardt (Mühlheim, Germany) for the microanalyses.

(10) The same sample as used in the first investigation.

(11) G. Ciamician and P. Silber, *Ber.*, **27**, 411 (1894).

lized from benzene, yielded pure, optically inactive[12] pinocembrin, m.p. 201–203°.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.17; H, 4.80; OCH_3, 0.00.

Identity was confirmed by mixture melting point and infrared spectral comparison with an authentic specimen of pinocembrin.[13] The ultraviolet spectrum was in agreement with that published by Erdtman.[14]

Attempted molecular weight determination by Rast's method: A portion of a mixture of 13.7 mg. of pinocembrin and 163.5 mg. of camphor melted in a capillary at 120°. On further heating the melt turned solid, melting again at 164°.

Acetylation of a sample with acetic anhydride–sodium acetate under reflux for 1 hr. followed by recrystallization from boiling ethanol led to pinocembrin diacetate, m.p. 142–143°. The same treatment, prolonged for 5 hr., yielded the 2',4',6'-triacetoxychalcone, m.p. 117–119°. These constants are in agreement with those reported in the literature.[14,15]

Saponification of the pinocembrin acetate with ethanolic potassium hydroxide revealed two acetyl groups per molecule of 257 (molecular weight of pinocembrin, 256.25).

Oxidation of pinocembrin with aqueous alkaline potassium permanganate at room temperature yielded benzoic acid, purified by sublimation *in vacuo*, m.p. 122°, identified by mixture melting point (no depression) and infrared spectral comparison with an authentic sample.

Acknowledgment.—The authors wish to express their appreciation to the Conselho Nacional de Pesquisas, Brazil, for financial aid.

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[12] Pinocembrin from pine wood is optically active, $[\alpha]_D$ −56°, but racemizes on sublimation [G. Linstedt, *Acta Chem. Scand.*, **3**, 755 (1949)].

[13] The literature records variable melting points for pinocembrin. Racemization does not result in depression[14]; rather, the synthetic specimens (inactive) are recorded with the highest melting points.[15] We are indebted to Dr. Holger Erdtman, Royal Institute of Technology, Stockholm, for a specimen of levorotatory pinocembrin. Its infrared spectrum and that of our inactive preparation were superimposable.

[14] H. Erdtman, *Svensk Kem. Tid.*, **56**, 26 (1944).

[15] J. Shinoda and S. Sato, *J. Pharm. Soc.* (*Japan*), **48**, 109 (1928).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, YALE UNIVERSITY]

Imidazole Catalysis. IV.[1] The Reaction of General Bases with *p*-Nitrophenyl Acetate in Aqueous Solution

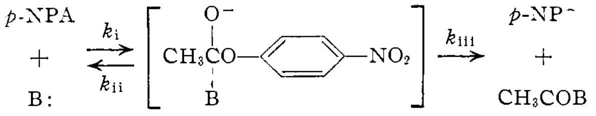
BY THOMAS C. BRUICE AND R. LAPINSKI

RECEIVED NOVEMBER 22, 1957

The second-order rate constant for the reaction of OH^-, CN^-, HPO_4^{--}, CH_3COO^-, H_2O, $C_6H_5O^-$, *p*-$ClC_6H_4O^-$, *p*-$CH_3OC_6H_4O^-$, $C_6H_5NH_2$, *p*-$CH_3C_6H_4NH_2$ and *p*-$CH_3CONHC_6H_4NH_2$ with *p*-nitrophenyl acetate have been determined. When the log k_2 values for the reaction of the bases studied herein as well as those for the imidazoles and pyridines of a previous study are plotted *vs.* pK_a', in the conventional Brönsted manner, it is found that the nitrogen bases are more efficient nucleophiles toward *p*-nitrophenyl acetate than are the negatively charged oxygen (or CN^-) bases.

As part of a program to study the base catalytic properties of imidazoles, the catalysis of the hydrolysis of *p*-nitrophenyl acetate (*p*-NPA) by imidazole and substituted imidazoles was investigated.[1a,1b] Certain observations made during these earlier studies indicated that the imidazoles were, as compared to other general bases, particularly reactive toward *p*-NPA. It has been the purpose of this study to compare the nucleophilicity of imidazoles and other general bases toward *p*-NPA.

In accord with present concepts of the mechanisms of $B_{AC}2$[2] displacement reactions at the ester carbonyl group the over-all reaction of *p*-NPA with a general base (B:) would be



$$CH_3COB \xrightarrow[H_2O]{k_{iv}} CH_3COOH + B:$$

In the instance where B: is OH^-, the ratio $[(k_i + k_{iii})/(k_i + k_{ii})]$ is probably quite large since, in the closely allied reaction of OH^- with phenyl benzoate in H_2O^{18} solvent, there is no back incorporation of O^{18} into ester.[3] For other bases it is possible that the ratio of forward to reverse rate constants are smaller as was shown by Bender for the alkaline hydrolysis of alkyl benzoates.[4]

In the reaction of *p*-NPA with imidazoles and pyridines the hydrolysis of the CH_3COB intermediates (acetylimidazole[5] and/or acetylimidazolium salt[1a] and acetylpyridinium salt[6]) is very rapid. Thus the catalytic constant for the reaction of imidazole with *p*-NPA is sufficiently large to give pseudo first-order kinetics even when the concentration of base was equal to or smaller than that of the substrate.[1a] In comparison, for bases such as phenolate and aniline the decomposition of CH_3COB would be rate limiting since the solvolyses of phenyl acetate and acetanilide proceed at much lower rates than for *p*-NPA. When a large excess of base is employed the accumulation of CH_3COB does not effectively lower the concentration of B:. Under these conditions the reaction of all bases with *p*-NPA may be treated by first-order kinetic expressions thus obviating the necessity of solving expressions for parallel first- and second-order reactions. The value of the second-order rate constant (k_2) for the displacement reaction [*i.e.*, B: + *p*-NPA → CH_3COB + *p*-NP^-) may then be obtained at any fixed *p*H and concentration of B: from the expression $(k_{obs} - k_w)/(B:) = k_2$, where k_{obs} is the observed *pseudo* first-order rate constant, k_w, is the solvolysis constant in the absence of B:,

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[1] For previous papers in this series see: (a) T. C. Bruice and G. L. Schmir, THIS JOURNAL, **79**, 1663 (1957); (b) **80**, 148 (1958); (c) G. L. Schmir and T. C. Bruice, *ibid.*, **80**, 1173 (1958).

[2] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 754.

[3] C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).

[4] M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

[5] M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1652 (1957).

[6] V. Gold, *et al.*, *J. Chem. Soc.*, 1406 (1953).