On the Structure of Pygmaein, a New Tropolone from *Cupressus pygmaea* Heartwood[1a]

EUGENE ZAVARIN AND ARTHUR B. ANDERSON

Received October 4, 1960

During the investigation of the tropolonic fraction of the steam-volatiles from *Cupressus pygmaea* (Lemm.) Sarg. heartwood,[1b] it was noticed that a part of the fraction reacted with 10% sodium hydroxide solution to form a salt of exceptionally low solubility. Paper chromatographic studies of this salt indicated that it was composed essentially of only one compound, previously designated as pygmaein. Regeneration of the parent tropolone from its salt, and crystallization from *n*-hexane produced crystals melting at 39–40°. The total yield of this material was 17% based on volatile oil and 0.34% on dry weight of wood.

The isolated substance gave positive copper acetate and ferric chloride tests for tropolones, and coupled readily with aromatic amines. It had an analysis corresponding to $C_{11}H_{14}O_3$ with one methoxyl. The molecular weight determination according to Rast (180 ± 20%) corroborated this formulation. The material was characterized by preparation of the copper chelate (1:2 molecular ratio), m.p. 211–212°, thallium · chelate (1:1 molecular ratio), m.p. 197–197.5°, dicyclohexylamine salt, m.p. 86–87°, and cyclohexylamine salt, m.p. 170.5–171°.

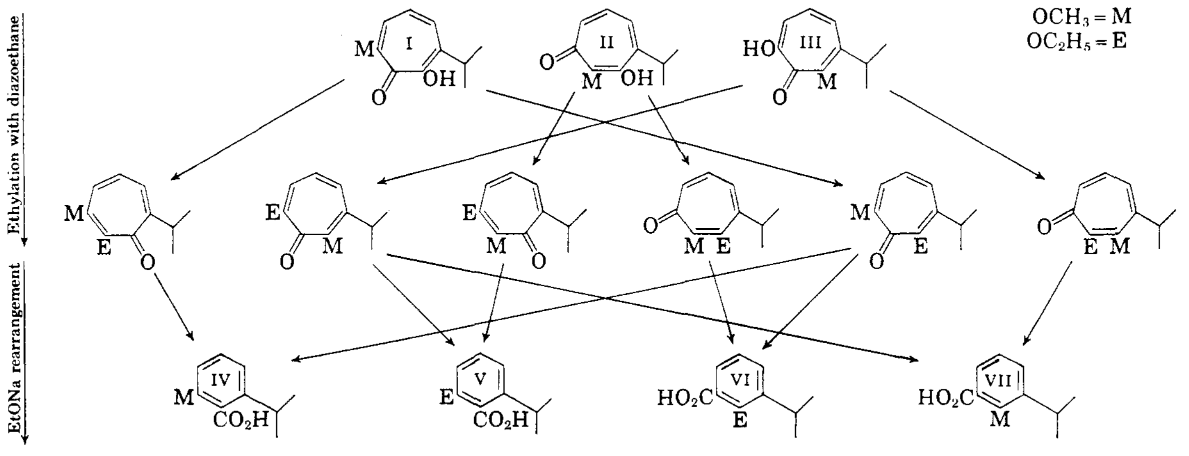
The ultraviolet and infrared spectra of pygmaein and its copper complex were characteristically tropolonic.[2] The infrared carbonyl band at 1612 cm.$^{-1}$ was surprisingly weak in pygmaein as compared to the bands exhibited by thujaplicins and nootkatin. In β-thujaplicinol, which has an additional *ortho* hydroxyl, this decrease in intensity has been attributed to the symmetrical placement of the two hydroxyls around the carbonyl.[3] The low intensity carbonyl absorption in pygmaein, which has only one hydroxyl next to carbonyl, seems to point out that this may not be the only reason.

In pygmaein copper chelate, as expected, the hydroxyl band was absent and the carbonyl band shifted to 1583 cm.$^{-1}$ with intensity somewhat increased.

The NMR spectrum of pygmaein exhibited, in addition to other peaks, a singlet corresponding to the methoxyl protons at +1.3 p.p.m. and a doublet at +3.8 and +3.9 p.p.m. stemming from the isopropyl methyl protons. The magnitude of J for the doublet (about 6.5 c.p.s.) as well as the intensity ratios of the peaks agreed with these assignments.[4]

This evidence seems to indicate that we are dealing with a tropolone type compound with methoxyl and isopropyl groups attached to the ring.

Refluxing pygmaein with a mixture of hydrobromic and acetic acids removed the methyl from the methoxyl to give an 89% yield of a tropolone indistinguishable from natural α-thujaplicinol.[1] Methylation with diazomethane, and refluxing the resulting methyl ethers with methanolic sodium methoxide gave a 31% yield of 2-methoxyl-3-isopropylbenzoic acid.[1] This seems to indicate that we are dealing with one of the three possible α-thujaplicinol monomethyl ethers. Of these, 2-methoxy-3-hydroxy-4-isopropyltropolone (II) does not seem to be a likely possibility since it is not a tropolone in the usual sense of the word and the compounds of its class have decidedly different physical and chemical properties.[5]



---

(1) (a) Presented before the Division of Cellulose Chemistry, American Chemical Society, New York, N. Y., September 12, 1960.

(1) (b) E. Zavarin, A. B. Anderson, and R. M. Smith, in press.

(2) P. L. Pauson, *Chem. Revs.*, **55**, 19 (1955).

(3) J. A. F. Gardner, G. M. Barton, and H. McLean *Can. Jour. Chem.*, **35**, 1039 (1957).

(4) J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 53. The chemical shifts in p.p.m. were calculated in relation to ethanol hydroxyl peak.

The structure of pygmaein was finally ascertained by ethylating the compound with diazoethane and refluxing the resulting mixture with sodium ethoxide to give a 26% yield of 2-methoxy-3-isopropylbenzoic acid. The above scheme depicts all of the possible ethyl ethers and rearrangement products that might arise, assuming all three possible structures for pygmaein. As can be seen, only structure III, 3-methoxy-4-isopropyltropolone, could give rise to 2-methoxy-3-isopropylbenzoic acid.

As far as is known, pygmaein has previously been neither synthesized nor isolated from a natural source. In addition, it has been chromatographically identified in *Cupressus goveniana* Gord., *Juniperus communis* L., and *Juniperus monosperma* (Englm.) Sarg.[1] It is presently being studied for toxicity to wood destroying fungi.

EXPERIMENTAL[6]

Isolation of pygmaein. The separation of 21.4 g. of the crude sodium salt of pygmaein from the volatile oil of *Cupressus pygmaea* heartwood has been described.[1] The parent tropolone was regenerated from the salt by treatment with 50 ml. of 10% hydrochloric acid, taken up in 150 ml. of *n*-hexane and precipitated at −5° with 10 g. of cyclohexylamine to give 21.3 g. of adduct, m.p. 164–170°. After decomposing the cyclohexylamine adduct with 100 ml. of 10% sulfuric acid by the usual procedure, the pygmaein was taken up in 50 ml. of *n*-hexane, treated with a teaspoon of charcoal, the solution filtered, and the tropolone crystallized from the same solvent at −5° to give 9.4 g. of crystals, m.p. 38–40° (yield 17% in oil; 0.34% of dry wood weight).

Characterization of pygmaein. An analytical sample of pygmaein was prepared by decomposition of its copper complex with hydrogen sulfide in chloroform solution, followed by sublimation and crystallization from iso-octane to give ill defined clusters of prisms, m.p. 39–40°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; mol. wt. (Rast), 194. Found: C, 67.69; H, 7.29; mol. wt. (Rast), 180 ± 20%.

The copper chelate of pygmaein was prepared by the usual procedure and purified by recrystallization from ethanol to give a mixture of needles and hexagons, m.p. 211–212°.

Anal. Calcd. for $C_{22}H_{26}O_6Cu$: C, 58.72; H, 5.82; Cu, 14.12; OCH_3, 13.79. Found: C, 58.59; H, 5.63; Cu, 14.64; OCH_3, 14.21.

Thallium chelate was prepared by dissolving 301 mg. of pygmaein, m.p. 38–40°, in 25 ml. of warm 5% ammonia and adding to it a solution of 742 mg. of thallium acetate in 5 ml. of water. Filtration and washing with water gave 575 mg. of yellow crystals, m.p. 195–198° (93% yield). Crystallization from chloroform/iso-octane gave long, characteristic plates, m.p. 197–197.5°.

Anal. Calcd. for $C_{11}H_{13}O_3Tl$: C, 33.23; H, 3.32. Found: C, 32.96; H, 3.24.

The preparation of the dicyclohexylamine salt, m.p. 86–87°, has been described.[7] The cyclohexylamine salt was obtained by the same procedure. Crystallization from hexane/chloroform gave elongated prisms, m.p. 170.5–171.5°.

Anal. Calcd. for $C_{17}H_{27}O_3N$: C, 69.59; H, 9.28. Found: C, 69.33; H, 9.01.

Spectral characteristics of pygmaein. Ultraviolet: λ_{max} 251 mμ (log ε 4.45); 325 mμ (log ε 3.75); 353 mμ (log ε 3.73); 366 mμ (infl.) (log ε 3.71); 310 mμ (infl.) (log ε 3.64)—(iso-octane). Pygmaein copper chelate (calculated on the basis of the molecular weight of the anion = 193): λ_{max} 264 mμ (log ε 4.53); 337 mμ (log ε 4.04); 381 mμ (log ε 3.79); 665 mμ (log ε 1.48)—(ethanol).

Infrared: 3160s, 2920s, 2840m, 1612w, 1575s, 1540s, 1500s, 1465s, 1450s, 1400s, 1390s, 1325m, 1286s, 1237s, 1205s, 1165s, 1120s, 1062s, 1035m, 975m, 940m, 917w, 890w, 865w, 805m, 795m, 685m, cm.$^{-1}$—(potassium bromide). Pygmaein copper chelate: no hydroxyl absorption between 4000 and 3000 cm.$^{-1}$—(Nujol). Carbonyl at 1582s—(potassium bromide).

NMR[4]: (60 mc, CS_2)—peak at −3.0 p.p.m., multiplet at −1.4 p.p.m., singlet at +1.3 p.p.m., doublet at +3.8 and +3.9 p.p.m. (J about 6.5 cps). Intensity ratios: 1.1:3.0; 2.8:6.0.

Reaction of pygmaein with hydrobromic acid. A 308-mg. portion of pygmaein, m.p. 38–40°, was refluxed with a mixture of 6.5 ml. acetic and 5 ml. of 42% hydrobromic acid for 100 min. The resulting mixture was diluted to 75 ml. with water, brought to *p*H 5 with ammonia and extracted with 30 ml. of chloroform. The extract was dried and the solvent evaporated. The residue was taken up in 15 ml. of iso-octane and the solution filtered from the small amount of impurities. The reaction product was precipitated at +5° by addition of 0.5 g. of dicyclohexylamine, giving 510 mg. of the adduct (89% yield), m.p. 130–130.5°, undepressed on admixture with the corresponding salt of naturally occurring α-thujaplicinol. The identity was further confirmed chromatographically as well as by comparing infrared spectra of the adducts and of the regenerated compounds themselves.

Rearrangement of the pygmaein ethyl ethers. Ethylation of 307 mg. of pygmaein, m.p. 38–40° was conducted using an excess of diazoethane, analogously to the diazomethane methylation. The resulting mixture of ethyl ethers was refluxed for 1 hr. with a solution of 0.5 g. of sodium in 15 ml. of absolute ethanol. The reaction products were degraded as described for the rearrangement of the methyl ethers[1] to give 153 mg. of dicyclohexylamine salt, m.p. 150.5–153.0° (26% yield). Regeneration of the parent acid gave crystals, m.p. 66.5–67.5°, undepressed on admixture with an authentic sample of 2-methoxy-3-isopropylbenzoic acid; preparation of the pure dicyclohexylamine salt from the regenerated acid gave crystals, m.p. 155.2–156°, undepressed on admixture with an authentic sample of the dicyclohexylamine salt of 2-methoxy-3-isopropylbenzoic acid.

Acknowledgment. We are indebted to Mrs. Rosalind M. Smith for some of the experimental work and to Alvin J. Berlin for running the NMR. spectra.

FOREST PRODUCTS LABORATORY
UNIVERSITY OF CALIFORNIA
RICHMOND, CALIF.

---

(5) R. B. Johns, A. W. Johnson, and M. Tisler, *J. Chem. Soc.*, 4605 (1954).

(6) All melting points are corrected; microanalyses by Microchemical Laboratory, University of California, Berkeley. Ultraviolet and infrared spectra were run on Beckman DK II and Perkin-Elmer Model 21 recording spectrophotometers, respectively, and NMR spectra on Varian Associates spectrometers.

(7) E. Zavarin, R. M. Smith, and A. B. Anderson, *J. Org. Chem.*, **24**, 1584 (1959).