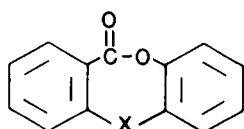


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Synthesis and Rearrangement of Dibenz[*b,e*][1,4]oxazepin-6(11*H*)-one, Depsazidone (I)

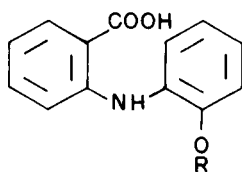
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A large number of naturally occurring compounds of the polysubstituted 2-hydroxyphenoxybenzoic acid lactone (depsidone) type were isolated by Asahina (2) from lichens. Noyce and Weldon and others (3) succeeded in the synthesis of the parent lactone, depsidone (Ia) and several simple homologs. Accordingly we became interested in the possibility of synthesizing a nitrogen analog, which we have termed depsazidone (Ib), and which does not occur naturally either as the parent or as derivatives.



Ia, X = O

Ib, X = NH



IIa, R = H

IIb, R = CH₃

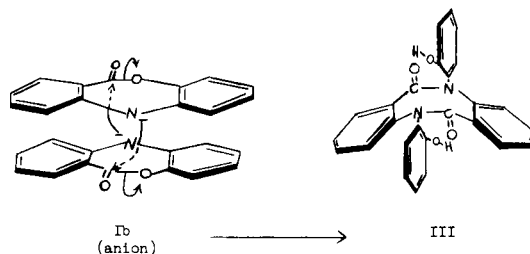
We therefore wish to report the synthesis of (Ib), and a novel rearrangement which it may be caused to undergo.

Since Ia was obtained by Noyce and Weldon (3) from 2-(2-hydroxyphenoxy)benzoic acid by lactonization, we followed a similar route to Ib. The intermediate, *N*-2-hydroxyphenylanthranilic acid (4) (IIa), was prepared from *o*-bromobenzoic acid and *o*-aminophenol by an Ullmann type condensation carried out in dimethylformamide with cuprous chloride catalyst and potassium carbonate as the base. Since only 38% yield was obtained in this procedure, we attempted to obtain a higher yield of IIa by blocking the phenolic hydroxyl group. Thus *N*-2-methoxyphenylanthranilic acid (IIb) was prepared in 79.1% yield from *o*-bromobenzoic acid and *o*-anisidine. However, we were unable to demethylate IIb (5a). Furthermore, *o*-benzyloxyaniline (5b) which on condensation with *o*-bromobenzoic acid and reductive debenylation was expected to give IIa, failed to condense with *o*-bromobenzoic acid.

N-(2-Hydroxyphenyl)anthranilic acid (IIa) was then lactonized to Ib by standing in ethereal thionyl chloride-pyridine for three days, followed by neutral-

ization and work-up. A pure product was obtained only after passage through a column of silica gel, and recrystallization from benzene. When stored in a dry amber bottle under nitrogen the compound gradually decomposed as indicated by the lowering of the melting point.

When this lactone was treated with sodium hydride in xylene, with or without an equivalent of DMF, a new substance was obtained the infrared spectrum of which was different from Ib. Whereas Ib showed strong absorption at 5.8 microns, the product now absorbed at 6.1 microns, which indicated the presence of a tertiary amide. The melting point changed from 160° to 275°. The new material was resistant to ordinary hydrolysis, but treatment with sodium hydroxide in propylene glycol gave recovered unreacted material and some IIa. The nmr spectrum suggested that the carbonyl group was not in the same plane as the benzene rings. In Ib, a peak in the nmr spectrum at 482 cps was assigned to the hydrogen *ortho* to the carbonyl group. In III, the *ortho* proton absorption was at higher field, under the other aromatic protons. A molecular weight determination by mass spectrography gave a value of 422, twice that of Ib, (211). Solvents were tightly bound and required drying at 200° at 5 microns for removal. From these data it was concluded that Ib rearranged to III. The dianthranilide, III, may have formed via a mechanism in which the nitrogenous anions attacked the carbonyl groups intermolecularly as shown:



Although III is described for the first time, dianthranilides are known (6), and by analogy to the salicylide series (7) they may exist in the *cis* form.

EXPERIMENTAL (8)

Dibenz[*b, e*][1,4]oxazepin-6(11*H*)-one, Depsazidone. A. *N*-(2-Hydroxyphenyl)anthranilic Acid, IIa (4).

A mixture of 321.6 g. (1.6 moles) of *o*-bromobenzoic acid, 800 ml. of dimethylformamide and 240 g. of anhydrous potassium carbonate was refluxed while approximately 610 ml. of the dimethylformamide was slowly distilled through a side arm. After cooling 32.0 g. of cupric oxide, 6.0 g. of cuprous chloride, 610 ml. of dimethylformamide and 192 g. (1.76 mole) of *o*-aminophenol (recrystallized from methanol with charcoal) were added. The mixture was again refluxed for 2 hours, with slow distillation of dimethylformamide and then it was cooled to room temperature. On dilution with 960 ml. of water, it was warmed to 50°, filtered, and the filtrate was boiled with 32 g. of charcoal and filtered. The filtrate was acidified to pH 2-3 with concentrated hydrochloric acid, cooled to 15° and filtered. The crude filter cake was dissolved in 2 liters of ethanol and re-filtered. The ethanol solution was then diluted with 6 liters of water, heated to boiling, filtered by gravity and allowed to cool overnight. The crystals, isolated by filtration, and dried in vacuum, weighed 164.7 g., m.p. 184-186°. When recrystallized from 1300 ml. of xylene (25 g. Norite A), 139.6 g., (38%) of *N*-(2-hydroxyphenyl)anthranilic acid, m.p. 190-191°, was obtained.

A sample recrystallized from aqueous ethanol, was analyzed.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.33; H, 4.98; N, 6.24. Infrared: 2.9 μ (-OH), 3.30 μ (-NH), and 5.90 μ (-CO).

B. Dibenz[*b, e*][1,4]oxazepin-6(11*H*)-one, Depsazidone, Ib.

To 6.5 liters of dry ether containing 162.6 g. (0.71 mole) of *N*-(2-hydroxyphenyl)anthranilic acid and 984 ml. of dry pyridine was added a solution of 59.6 ml. of thionyl chloride in 984 ml. of dry ether. The mixture was stirred for 3 days at room temperature. The pyridine was removed by extraction with five 1.4 l. portions of 1*N* hydrochloric acid and the solution was washed successively with two 250 ml. portions of water, three 340 ml. portions of 1*N* sodium bicarbonate and two 250 ml. portions of water. The ether solution was dried over magnesium sulfate, concentrated and the residue was recrystallized from 600 ml. of toluene with 13.6 g. charcoal. There was obtained 49.6 g. of vacuum dried material, m.p. 146-178°, which was boiled in benzene and filtered to remove 14.0 g. of insoluble matter which melted at 183-188°. From the cooled benzene filtrate there was obtained 30.2 g. of solid, m.p. 144-166°. An additional 2.1 g. of solid, m.p. 154-157°, was isolated by concentrating the benzene filtrate. The material, m.p. 144-166°, dissolved in 330 ml. of dry ethyl acetate, was passed through a column of 600 g. of silica gel which was eluted with dry ethyl acetate. Three 1 liter fractions were collected, which upon evaporation, gave the following residues: I - 10.5 g., m.p. 155-159°; II - 12.3 g., m.p. 144-150°; III - 2.3 g., m.p. 168-171°. Fraction II was dissolved in ether, extracted with sodium bicarbonate solution and reisolated to give 10.9 g., m.p. 153-156°. The total yield was 23.5 g., 15.7% of theory. A sample recrystallized from benzene, m.p. 161-162°, was analyzed.

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.92; H, 4.30; N, 6.63. Found: C, 73.72; H, 4.15; N, 6.65. Infrared: 2.96 μ (-NH), 5.8 μ (>C=O).

From the bicarbonate extracts, by acidification, 30.1 g. (18.5%) of *N*-(2-hydroxyphenyl)anthranilic acid, m.p. 189-190°, was recovered. Depsazidone must be stored under dry nitrogen. Even under these conditions the melting point gradually decreases and the range widens with the formation of *N*-(2-hydroxyphenyl)anthranilic acid.

5,11-Bis(2-Hydroxyphenyl)-5,11-dihydrodibenzo[*b, f*][1,5]diazocine-6,12-dione, III.

Into 90 ml. of dry benzene were placed 2.58 g. (0.058 mole) of a 53.5% mineral oil suspension of sodium hydride, 12.15 g. (0.058 mole) of depsazidone and, while warming and stirring, 4.21 g. (0.058 mole) of dry dimethylformamide was added. The mixture was refluxed 18 hours during which time a solid formed. Upon cooling to room temperature, 58 ml. of 1*N* hydrochloric acid was added, followed in 5 minutes by 100 ml. of 1*N* sodium bicarbonate solution. The solid was then isolated by filtration. After washing by shaking with 100 ml. of a mixture of 1:1 benzene-water, filtration and drying in vacuum at 50°, it weighed 7.9 g. and melted at 260-264°. Upon recrystallization from *n*-butyl acetate there was obtained 5.79 g. of product, m.p. 267-270°. This material contained butyl acetate which was removed by drying at 200° (0.030 mm.) for 2 hours (9). The yield was 4.9 g. (40.3%), m.p. 266.5-270°.

A sample, recrystallized from *n*-butyl acetate and dried at 200°/0.030 mm. for 2 hours, melted at 273-274°.

Anal. Calcd. for $C_{26}H_{18}N_2O_4$: M.W. 422.4; C, 73.92; H, 4.30; N, 6.63; O, 15.15. Found: C, 74.02; H, 4.62; N, 6.76; O, 15.73. Infrared: 3.05 μ (-OH) and 6.1 μ (O=C-N<). Mol. wt. Calcd. 422.2. Found (ms) 422, two fragments of mass 211 observed. Nmr. Eight

aromatic and one acidic protons. In the nmr spectrum of depsazidone, the *ortho* hydrogen appeared at 428 cps. In III the *ortho* proton absorption was at higher field, under the other aromatic protons.

The combined benzene phases were dried over magnesium sulfate and evaporated to dryness to give 2.6 g. of a yellow oil which was not investigated further. The bicarbonate washes were acidified to pH 1 with 6*N* hydrochloric acid to give 3.5 g. (26.5%) of *N*-(2-hydroxyphenyl)anthranilic acid, m.p. 180-183°.

Saponification of III.

Ten milliliters of propylene glycol containing 2.17 milli-equivalents of sodium hydroxide per ml. was diluted with water to a final volume of 25 ml. after addition of 0.827 g. of III. Acidification with dilute hydrochloric acid, after refluxing 3 hours, resulted in the isolation of 0.815 g. of material (97.5% recovery). Upon recrystallization from xylene (filtered insoluble material weighed 0.258 g., m.p. 232-239°) there was obtained 0.476 g. of *N*-(2-hydroxyphenyl)anthranilic acid, m.p. 183-185°, and 0.059 g., m.p. 166-208°. These quantities represent 96% recovery. The material with m.p. 232-239° was recrystallized from butyl acetate to give 0.163 g. of crystals, m.p. 277-279°. The infrared spectra were compared with those of authentic samples. The material melting at 232-239° was III, and that melting at 183-185° was *N*-(2-hydroxyphenyl)anthranilic acid.

N-(2-Methoxyphenyl)anthranilic Acid.

Into a 500 ml. 3-neck flask equipped with a reflux condenser with take off and a stirrer were placed 250 ml. of dimethylformamide, 75 g. of anhydrous potassium carbonate and 100.5 g. (0.50 mole) of *o*-bromobenzoic acid. The mixture was heated to reflux and a volume of 188 ml. of dimethylformamide and water was distilled. The residue was cooled and 188 ml. of dimethylformamide, 67.7 g. (0.55 mole) of *o*-anisidine, 10 g. of cupric oxide and 1.9 g. of cuprous chloride were added. The resulting mixture was refluxed for 2 hours with slow distillation and then cooled to room temperature. Water (300 ml.) was added, the mixture was warmed to 50° and filtered. The hot filtrate was treated with 10 g. of charcoal, filtered and on cooling to room temperature it was acidified with concentrated hydrochloric acid, cooled to 10°, and re-filtered. The brownish cake was recrystallized from aqueous ethanol and dried in vacuum. The yield of crude product was 96.1 g. (79.1%) m.p. 172.5-174°. Recrystallization from 800 ml. of toluene gave 84.7 g. of product, m.p. 175-176.5°.

A sample was recrystallized from benzene for analysis.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.13; H, 5.26; N, 5.58.

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- (8) All melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR 5 infrared spectrophotometer in chloroform or mineral oil. The nmr spectra were taken on a Varian A-60 spectrometer.
- (9) By comparison with synthetic mixtures of *n*-butyl acetate in mineral oil, the solvent content could be determined by infrared absorption at 5.75 μ .

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