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Structure of the *o*-Aminophenol–Adipoin Condensation Product

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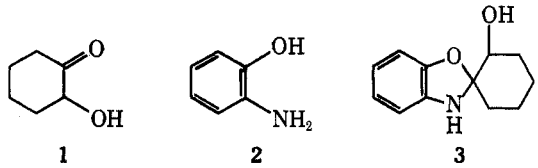
The thermal condensation product from adipoin and *o*-aminophenol is found to be 1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (**8**). This structure, which corrects an assignment in the earlier literature, is based on spectral data, chemical transformations, and a single crystal x-ray crystallographic study of 8 HI.

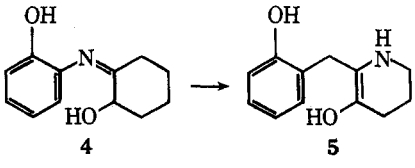
While studying the reactions of adipoin (**1**) with aromatic amines, Cummins and Tomlinson[1] found that heating **1** with *o*-aminophenol (**2**) at 135 °C produced a condensation product, $C_{12}H_{15}O_2N$, mp 171 °C, in unspecified yield. The spirocyclic structure **3** was tentatively assigned to this substance based largely on its infrared spectrum which displayed O–H



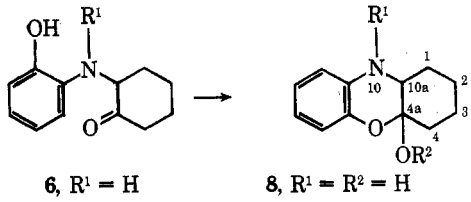
1 **2** **3**

and N–H but no C=O absorption. Our interest in spirocyclic systems prompted us to repeat this preparation so that the properties of the product might be explored. In our hands, heating an intimate mixture of **1** (as the dimer[2]) and **2** under nitrogen for 5 min gave the expected product in 57% yield. Its melting point and infrared spectrum were compatible with the reported data and it could be recrystallized unchanged from aqueous alkali in further agreement with the observations of Cummins and Tomlinson. However the NMR spectrum (in Me_2SO-d_6) of this condensation product ruled out the assigned structure **3** by failing to show a signal in the δ 3.5–4.0 region for the carbinol proton of a secondary alcohol.

At this point, an alternative formulation for the condensation product came to mind by very simple mechanistic



4 **5**



6, R^1 = H
7, R^1 = Ac

8, $R^1 = R^2$ = H
9, R^1 = Ac; R^2 = H
10, R^1 = Ac; R^2 = Ac
11, $R^1 = CH_2C_6H_5$; R^2 = H

reasoning. Initial reaction between **1** and **2** to give the Schiff base **4**, followed by successive proton shifts, would lead via enol **5** to the phenolic ketone **6**; the corresponding hemiketal structure **8** is compatible with all reported properties of Cummins and Tomlinson's condensation product and explains our failure to find a signal for a carbinol proton in its NMR spectrum. The formulation of this product as 1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (**8**) accounts for the observation of a 1 H multiplet at δ 3.0 ($-NCHCH_2-$) and the absence of any other signals (excluding exchangeable protons) in the region δ 2.5–6.8. The revised structure is further supported by the properties of several transformation products.

Brief heating with acetic anhydride at its boiling point (137 °C) converted **8** to the *N*-acetyl derivative **9**, mp 162–163.5 °C, whose infrared spectrum showed distinct hydroxyl and amide absorption as well as a weak carbonyl band at 1705 cm^{-1} reflecting a small fraction of the open form **7** in equilibrium with **9**. The 10a proton of **9** appeared as a four-line signal (X part of an ABC system) centered at δ 5.2. This 2 δ downfield shift on acetylation presumably reflects the diamagnetic anisotropy as well as the inductive effect of the acetyl substituent. Treatment of **9** with acetic anhydride at 90 °C in the presence of *p*-toluenesulfonic acid as catalyst provided the *O,N*-diacetyl derivative **10**, mp 126–127.5 °C, which showed bands in the infrared at both the amide and ester carbonyl stretching frequencies. Formation of the tertiary acetate presumably occurred by an alkyl–oxygen cleavage mechanism.

Alkylation of **8** with benzyl bromide yielded the noncrystalline 10-benzylhexahydrophenoxazine **11** which showed appropriate spectral characteristics; its NMR spectrum exhibited the nonequivalent benzylic protons as a widely separated (Δδ 0.36 ppm) AB quartet reflecting the proximity of nearby chiral centers.

The *o*-aminophenol–adipoin condensation product **8** was partly converted to a trideuterio derivative (46.5% d_3, 26.6% d_2) by heating a sample under reflux with NaOD in D_2O followed by H_2O washing of the product. Incorporation of one deuterium at C-10a and two at C-4, expected if **8** is in rapid equilibrium with fb6, is supported by the disappearance of appropriate proton signals in the NMR spectrum of 8-d_3 and its *N*-acetyl derivative.

Final support for the assigned structures was obtained by single-crystal x-ray crystallographic methods. Compound **8**

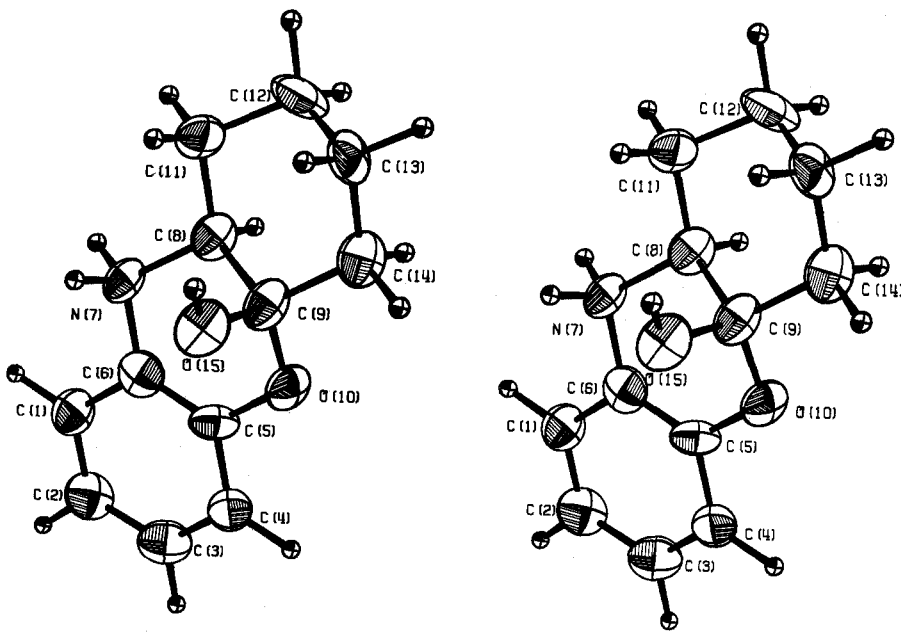
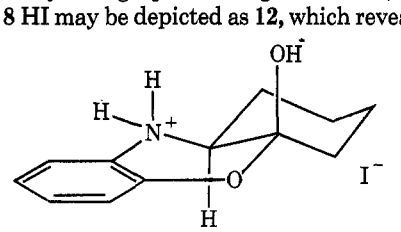


Figure 1. Stereoview of the hexahydrophenoxazine molecule.

gave a hydriodide which, by slow cooling of an aqueous 2-propanol solution, provided crystals suitable for x-ray analysis. Based on the crystallographic data given below, the crystal structure of 8 HI may be depicted as **12**, which reveals that the



12

tricyclic structure includes a trans fusion between the nonaromatic rings. Bond angles and bond lengths did not differ appreciably from the expected values.

The crystals were found to be of the monoclinic space group Cc with a = 17.834 (9), b = 8.831 (3), c = 10.534 (5) Å, β = 129.85 (3)°. The density was measured by flotation as 1.75 g/cm^3. Based on four molecules per unit cell, the calculated density was 1.737 g/cm^3. Because the molecule did not contain a center of symmetry or a twofold axis, space group $C2/c$ was eliminated. A 1-Å data set (maximum sin θ/λ = 0.5) was collected on a Syntex $P\bar{1}$ diffractometer using molybdenum radiation (λ = 0.71069 Å). The diffractometer was equipped with an incident beam monochromator. All diffraction data were collected at room temperature.

All crystallographic calculations were facilitated by the CRYM system.[3] A trial structure was obtained using conventional Patterson and Fourier techniques. This trial structure refined routinely to a final R index ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$) of 0.028. The final cycles of full matrix least squares contained all nonhydrogen coordinates, anisotropic temperature factors, and scale factor in one matrix. No corrections were made for absorption (μ = 25.3 cm^{-1}) or secondary extinction. Hydrogen positions were calculated wherever possible. The hydroxyl hydrogen was located by difference Fourier techniques. While the hydrogen parameters were added to the structure factor calculations during the final stages of refinement, they were not refined. A final difference Fourier revealed no missing or misplaced electron density. A stereoview of the molecule is given in Figure 1. Other pertinent crystallographic data will appear in the microfilm edition.

Experimental Section

Microanalyses were performed by Galbraith Laboratories, Inc., and Integral Microanalytical Laboratories, Inc., Raleigh, N.C. Melting points were determined on a Thomas hot-stage mounted on a Bausch and Lomb microscope and are uncorrected. Infrared (ir) spectra were recorded on a Beckman Acculab 1 or Beckman 33 spectrophotometer. Ultraviolet (uv) spectra were measured on a Perkin-Elmer 202 instrument. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Associates HA-100 instrument, and chemical shifts are given in parts per million (δ) downfield from an internal tetramethylsilane standard except where noted. The abbreviations s, d, t, q, m, and br stand for singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectra (MS) were determined on AEI MS 12 instrument. The abbreviation M$^+$ refers to the molecular ion. Analytical thin layer chromatography (TLC) was done on ICN silica gel F-254 and F-254/366 plates. Preparative thin layer chromatography was performed using Merck silica gel F-254 (20 × 20 cm × 2 mm thick) plates. Column chromatography employed Woelm alumina activity II or Bio-Sil A (100–200 mesh) silica gel.

1,2,3,4,4a,10a-Hexahydro-4a-hydroxyphenoxazine (8). Samples of 2-hydroxycyclohexanone (5.54 g, 48.6 mmol) and o-aminophenol (5.86 g, 53.8 mmol) were ground to an intimate mixture in a mortar and pestle, then heated in a flask under nitrogen at 129–130 °C for 5 min during which the mixture melted and then solidified. The product was taken up in hot ethanol, filtered through a cotton plug, and allowed to cool, giving 5.68 g (57%) of a beige, crystalline solid, mp 164–166 °C. Upon recrystallization from 80:20 ethyl acetate–n-hexane, colorless plates were obtained: mp 166.5–167.5 °C (lit.[1] 171 °C); ir 3580, 3480, 3390, 1610, 1590 cm^{-1}; uv max (CH_3OH) 208.5 nm (ϵ 29 300), 244.5 (7150), 295 (3810); max (0.0375 M NaOH in CH_3OH) 215.5 (11 400), 244 (5970), 295 (3060); NMR (Me_2SO-d_6 with external Me_4Si) δ 1.3–2.1 [br m, 8, $-(CH_2)_4-$], 3.0 (m, 1, NCH), 3.5 (br s, 1.4, OH), 5.7 (br s, 0.3, NH), 6.6 (m, 4, aromatic); MS m/e 205 (M$^+$).

1,2,3,4,4a,10a-Hexahydro-4a-hydroxyphenoxazine Hydriodide (8 HI). A sample of 8 (102 mg, 0.5 mmol) was dissolved in 2-propanol (3.0 ml) to which hydriodic acid (47% aqueous, 0.10 ml) had been added. Overnight cooling to 4 °C afforded 27.5 mg (17%) of colorless prisms, mp 169.5–171.5 °C with decomposition.

Anal. Calcd for $C_{12}H_{15}NO_2$·HI: C, 43.26; H, 4.84; N, 4.20. Found: C, 43.04; H, 4.51; N, 3.60, 3.81.

10-Acetyl-1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (9). A sample of 8 (2.03 g, 9.9 mmol) was dissolved in 10 ml of acetic anhydride and heated at 141–142 °C for 5 min. Solvent was removed under vacuum in the presence of added Celite to increase the surface area. Chloroform was added to the residue, Celite was removed by filtration, and the filtrate was concentrated under vacuum. The amorphous residue crystallized from ether (10 ml) giving 2.04 g (83%) of beige needles, mp 162–163.5 °C. Recrystallization from methylene chloride and n-hexane gave a colorless product: mp 164–165.5 °C; ir

($CHCl_3$) 3580, 3210, 1705, (weak), 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.7 [br m, 8, $-(CH_2)_4-$], 2.20 (s, 3, $NCOCH_3$), 5.19 (X part of ABX system, $J_{AX} + J_{BX}$ = 19 Hz, 1, $NCHCH_2$), 6.8–7.1 (br m, 4, aromatic), 9.24 (s, 1, OH); MS *m/e* 247 (M^+).

Anal. Calcd for $C_{14}H_{17}NO_3$: C,68.00; H, 6.93; N, 5.66. Found: C, 68.12; H, 6.87; N, 5.77.

4a-Acetoxy-10-acetyl-1,2,3,4,4a,10a-hexahydrophenoxazine (10). A sample of **9** (243 mg, 0.99 mmol) and *p*-toluenesulfonic acid (18 mg, dried by removal of water as a benzene azeotrope) were heated in 3.0 ml of acetic anhydride for 5 min at 80–90 °C. Solvent was removed in a manner similar to the method used in preparation of **9**. Preparative thin layer chromatography (silica gel, 20% EtOAc/$CHCl_3$, one development, R_f 0.49) gave 190 mg (66.4%) of colorless needles, mp 121–126 °C. Recrystallization from 50% ethanol–water gave colorless prisms: mp 126–127.5 °C; ir ($CHCl_3$) 1745, 1661 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.4 (br m, 8, aliphatic), 1.88 (s, 3, $NCOCH_3$), 2.26 (s, 3, $OCOCH_3$), 2.66 (br m, 1, NCH), 7.0 (m, 4, aromatic); MS *m/e* 289 (M^+).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N. 4.84. Found: C, 66.32; H, 6.92; N, 4.71.

10-Benzyl-1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (11). A solution of **8** (254 mg, 1.24 mmol) and benzyl bromide (1.0 ml) in 10 ml of acetone was heated under reflux with potassium carbonate (343 mg) for 13.5 h. After removal of solvent, the residue was partitioned between benzene and water. The organic phase was washed with water until neutral and the dried ($MgSO_4$) solution was filtered and concentrated. The residue was redissolved in benzene and filtered through an 8-cm column of alumina II. Removal of solvent afforded 150 mg (41%) of a colorless oil which appeared pure by TLC (R_f 0.40 on silica gel with chloroform): ir ($CHCl_3$) 3490, 2935, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.0–1.8 (m, 7, aliphatic), 2.20 [m, 1, $-OC(OH)CH$], 2.97 (m, 1, NCH), 3.64 (s, 1, OH), 4.18 and 4.54 (calculated shifts from AB quartet for benzylic protons), 6.8 (m, 4, aromatic), 7.3 (s, 5, aromatic); MS *m/e* 295 (M^+), 91 (tropylium).

4,4,10a-Trideuterio-1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (8-d_3). A sample of **8** (341 mg, 1.66 mmol) was added to a solution of sodium metal (0.2 g) in 10.0 ml of deuterium oxide and heated at reflux under nitrogen for 2 h. The reaction mixture was cooled to 10 °C, neutralized with glacial acetic acid, and extracted with 25 ml of chloroform. The organic phase was washed twice with water, dried ($MgSO_4$), and filtered through a column of silica gel (5 g) to remove traces of a polar contaminant. Removal of solvent gave 256 mg (74%) of a beige solid, mp 161–164 °C. Upon recrystallization from ethyl acetate and *n*-hexane, 128 mg of light pink crystals, mp 169–170 °C, were obtained: MS (14 eV) 4.4% d_5 (210), 13.9% d_4 (209), 46.5% d_3 (208), 26.6% d_2 (207), 4.7% d_1 (206), 3.9% d_0 (205).

4a-Acetyl-4,4,10a-trideuterio-1,2,3,4,4a,10a-hexahydrophenoxazine (9-d_3). A sample of 8-d_3 (111 mg, 0.53 mmol) was acetylated as for the undeuterated compound giving 71 mg (54%) of a pink, crystalline solid: mp 176–178.5 °C; NMR ($CDCl_3$) δ 1.0–2.2 [br m, 6, $-(CH_2)_3-$], 2.20 (s, 3, $NCOCH_3$), 6.8–7.1 (br m, 4, aromatic), 9.25 (s, 1, OH); MS (7 eV deuterated vs. 20 eV undeuterated) 8.5% d_4 (251), 51% d_3 (250), 32.5% d_2 (249), 5% d_1 (248), 3% d_0 (247).

Registry No.—**1**, 533-60-8; **2**, 95-55-6; **8**, 60349-94-2; **8** HI, 60349-95-3; 8-d_3, 60349-96-4; **9**, 60349-97-5; 9-d_3, 60349-98-6; **10**, 60349-99-7; **11**, 60350-00-7; acetic anhydride, 108-24-7; benzyl bromide, 100-39-0.

Supplementary Material Available. The following crystallographic data: coordinates and anisotropic temperature factors for nonhydrogen atoms, distances, and angles (1 page). Ordering information is given on any current masthead page.

References and Notes

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Notes

An Improved Synthesis of Sulfamoyl Chlorides

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Sulfamoyl chlorides are important intermediates in the synthesis of sulfamate esters and unsymmetrical sulfamides. These latter compounds are useful in the synthesis of azo compounds[1] as well as certain biologically active chemicals.[2] Although many processes have been published for the synthesis of alkyl sulfamoyl chlorides,[3] only one method of preparation[4,5] is frequently cited as being useful on a laboratory scale.[6] This involves direct treatment of an amine hydrochloride with sulfuryl chloride either with[5] or without[4] a Lewis acid catalyst. The method is limited to simple alkyl amines[4,5] and is often characterized by long reaction times,[4,5] large excesses of reagent,[4,5] and low yields.[4] In addition, this procedure precludes the synthesis of those compounds bearing functionality sensitive to sulfuryl chloride. Aryl and alkenyl sulfamoyl chlorides are thus unobtainable by this route.[5]

In view of the above limitations we have developed an alternative synthesis which not only provides for the facile preparation of simple alkyl sulfamoyl chlorides, but also allows, for the first time, synthesis of monoaryl sulfamoyl chlorides.

In 1953 Bieber reported that treatment of isocyanates with an excess of neat, anhydrous sulfuric acid resulted in evolution of carbon dioxide and concomitant formation of the corresponding sulfamic acid.[7] On a preparative scale this reaction has been rendered more convenient by use of a highly polar solvent such as nitromethane and 1 equiv of fuming sulfuric acid. The reaction is instantaneous and the product precipitates as a crystalline solid. Filtration and recrystallization (if necessary) affords pure sulfamic acids in good to excellent yields. (See Table I.)

These acids are then slurried in benzene and treated with phosphorus pentachloride. Gentle warming initiates a vigorous reaction which produces the sulfamoyl chlorides as well as phosphorus oxychloride and hydrogen chloride.[8] After concentration the product may be purified by distillation or crystallization, although in most cases removal of the final traces of phosphorus oxychloride at high vacuum provides a product adequate for continued use.

$$RNCO + H_2SO_4 \cdot SO_3 \rightarrow RNHSO_3H$$

$$RNHSO_3H + PCl_5 \rightarrow RNHSO_2Cl$$

While the above method is effective for simple alkyl compounds, there are certain cases (e.g., R = *tert*-butyl and phenyl, entries 6 and 7 in Table I) where the use of fuming sulfuric acid is precluded. An alternate procedure is then effective. The salt of the sulfamic acid may be prepared by treatment of chlorosulfonic acid with an excess of the corresponding