THE STRUCTURES OF TWO SELF-CONDENSATION PRODUCTS FROM *o*-AMINOBENZALDEHYDE

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ABSTRACT

The nature of two self-condensation products of *o*-aminobenzaldehyde (one a bisanhydro trimer and the other a trisanhydro tetramer) formed under different conditions of acid catalysis has been reexamined Spectroscopic evidence is presented to support the assignment of structures V (R = H) and VIII (R = R' = H) to these.

There exists considerable literature on self-condensation products formed from o-aminobenzaldehyde (1 and references therein). The number and nature of these were considerably clarified by the work of Seidel (1), who isolated and characterized a bisanhydro trimer and trisanhydro tetramer of the parent compound. Chemical evidence was interpreted in terms of simple linear Schiff base formation among three or four molecules of o-aminobenzaldehyde to give structures I (n = 1) and I (n = 2). These were later amended to the cyclic formulae II and III (2). Melson and Busch (3) have described self-condensation products formed in the presence of certain metal ions. These are the macrocyclic tetramer IV and an analogous trimer in which the nitrogen atoms are coordinated around the cation in a planar array. The two condensation products described by Seidel have now been reexamined and new structures assigned on the basis of evidence detailed below.

According to Seidel's method the first of these was most conveniently prepared by weakly acidifying an aqueous solution of o-aminobenzaldehyde, from which it precipitated in a crystalline form. Its formulation as a bisanhydro trimer followed from a correct elemental analysis for $C_{21}H_{17}N_3O$. The infrared spectrum, with bands at 3 560 and 3 390 cm^{-1} , indicated the presence of a hydroxyl and at least one NH group. That there was only one NH group was shown by the preparation of an O,N-diacetyl derivative which possessed no further NH band in the infrared spectrum. The nature of the remaining 15 hydrogens was apparent from the nuclear magnetic resonance (n.m.r.) spectrum of a deuterated sample, which exhibited complex 12-proton absorption between τ 2.58 and 3.50, assigned to the aromatic hydrogens, and three closely spaced one-proton singlets between τ 4.43 and 4.60, assigned to hydrogens of the type (Ar, Y₂)CH (Y = N or O). The ultraviolet spectrum, with maxima at 241 m μ (ϵ 14 600) and 285 m μ (ϵ 2 300), resembled that of N-ethyl-o-toluidine, which has maxima at 244 m μ (ϵ 7 200) and 291 m μ $(\epsilon 2 450)$ (4). These data indicated that the three units of o-aminobenzaldehyde must be joined by bonds formed between the aldehyde and amino functions only, and that no aldimine groups (---CH==N--) were present in the product. It follows that, of the three original aldehyde carbons, one must carry the hydroxyl function and be linked to nitrogen, and the other two must each be bonded to two nitrogens. If the reasonable assumption is made that no aldehyde carbon is linked to the nitrogen of the same unit, this allows only one structure for the trimer, namely V (R = H).

When stirred with methanol containing a catalytic amount of p-toluenesulfonic acid, the trimer gave an O-methyl ether consistent with its formulation as a carbinolamine.

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Reaction of the monoacetylbisanhydro trimer V (R = COCH₃) with manganese dioxide yielded a dehydro derivative (VI, R = COCH₃), C₂₃H₁₇N₃O₂, in which the hydroxyl had been oxidized to a carbonyl function, $\nu_{max}^{\rm CCI_4}$ 1 714 cm⁻¹. Examination of a molecular model indicated that this compound belongs to the rare class of lactams in which steric requirements prevent overlap of the nitrogen lone-pair electrons with the carbonyl π bond. This results in their behaving more as aminoketones than as lactams. The position of the carbonyl band in the infrared spectrum is one consequence of this. The shift to higher frequencies than would be normal even for an aromatic ketone is probably caused by the inductive effect of the directly attached but unconjugated nitrogen atom. In the ultraviolet spectrum the band at longest wavelength, λ_{max} 333 m μ , lies between that of *o*-dimethylaminoacetophenone at 350 m μ and that of *o*-dimethylaminobenzamide at 315 m μ (5). In keeping with its behavior as a ketone, the lactam was reduced by sodium borohydride to the starting alcohol. Another example of such a "lactam" is oxohaemanthidine (VII), which has ν_{max}^{Nujol} 1 695 cm⁻¹ (6).

The second self-condensation product was obtained, according to Seidel's method, through the action of 50% sulfuric or hydrochloric acids on *o*-aminobenzaldehyde or on the bisanhydro trimer. This led to the formation of red crystalline salts, from which the free base was liberated by treatment with water. Analysis of this substance and a molecular weight determination on its monoacetyl derivative confirmed its formulation as a trisanhydro tetramer, $C_{28}H_{22}N_4O$. The most important observations from the infrared spectrum were two NH bands at 3 380 and 3 310 cm⁻¹, and a carbonyl band at 1 665 cm⁻¹. The nature of the carbonyl function as a formyl group was apparent from the presence in the n.m.r. spectrum of a one-proton singlet at τ 0.10, and from the preparation of an oxime of the monoacetyl derivative which underwent ready dehydration to

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a nitrile. In the n.m.r. spectrum of the tetramer there also appeared resonances for the two hydrogens attached to nitrogen, one a broad band centered at τ 5.1, and the other a doublet (J = 5 c.p.s.) at $\tau 0.93$ coupled to one of three one-proton resonances in the τ 4.3-4.7 region, all three ascribed, as in the trimer, to the system (Ar, Y₂)CH. A multiplet of weight 16 between τ 1.90 and 3.50 was also present for the aromatic hydrogens. It was apparent that the bonds joining the four units were once more between amino and formyl groups. By virtue of the presence of a formyl group one unit must be linked to the rest of the molecule by one or two bonds from its nitrogen atom. The former possibility requires that the molecule as a whole have two separate NH groups, whereas the latter requires either this or the presence of one NH₂ function. The very different positions of the NH resonances in the n.m.r. spectrum, the fact that the low-field NH exchanged much more slowly with deuterium, and its coupling to an aliphatic CH favored the presence of two separate NH groups. Under a variety of conditions, however, only a monoacetyl derivative of the tetramer could be obtained. A convincing answer came from nitrosation of this monoacetyl compound. This yielded an N-nitroso compound which had no NH absorption in its infrared spectrum. The absence in its ultraviolet spectrum of the long-wavelength band at $369 \,\mathrm{m}\mu$ characteristic of the *o*-aminobenzaldehyde chromophore suggested that the nitroso group was bonded to the nitrogen of this unit, which therefore was attached to the rest of the molecule by only one bond. The disappearance of this band or its appearance at shorter wavelengths on attachment of an electron-withdrawing substituent to the nitrogen is to be expected (7), and can be observed, for example, in N-acetyl-o-aminobenzaldehyde, which has its longest wavelength band at 330 m μ . The attachment of one of the four units by only a single bond from its nitrogen to the aldehyde carbon of a second, and the requirement that the aldehyde carbons of the remaining three units be linked each to two nitrogens permits, with the same assumption used in deriving the structure of the trimer, only one structure (VIII, R = R' = H) for the tetramer. The N-acetyl compound and its nitroso derivative are therefore VIII ($R = COCH_3$, R' = H) and VIII ($R = COCH_3$, R' = NO), respectively. Since, in the latter, the relationship of nitroso to aldehyde functions is critical for the deduction of structure, it was desirable to confirm this chemically. Reduction



of the nitroso group with zinc in acetic acid gave a substance, $C_{30}H_{23}ON_5$, which possessed no NH bands and no carbonyl band (other than that of the *N*-acetyl group) in the infrared spectrum. Its n.m.r. spectrum was similar to that of the parent nitroso compound, but in place of the signal assigned to the formyl proton at τ 0.10 there was a new one-proton doublet at τ 1.88 (J = 0.8 c.p.s.). The formula and spectra indicated that it was the desired indazole derivative IX. The lowest field signal at τ 1.88 in the n.m.r. spectrum is assigned to the C-3 hydrogen of the indazole ring and is in reasonable agreement with that reported for C-3 of indazole itself at τ 1.94 (doublet, J = 0.8c.p.s.) (8).

Although the ring systems of both the trimer and tetramer remain unaltered during

the mild chemical transformations described above, the inherent lability in protonic solvents is seen on treatment with cupric nitrate in refluxing ethanol. Under these conditions they give the macrocyclic tetramer IV (M = Cu) that was obtained directly from o-aminobenzaldehyde by Melson and Busch (3).

EXPERIMENTAL

General

Melting points were taken on a Kofler melting point apparatus and are uncorrected. Infrared, ultraviolet, and n.m.r data were obtained on Perkin-Elmer model 337, Perkin-Elmer model 202, and Varian Associates model A-60 spectrometers, respectively.

Bisanhydro Trimer (V, R = H)

Freshly prepared o-aminobenzaldehyde (9) (4.5 g) was dissolved in water (700 ml) at 50°. The solution was placed under a nitrogen atmosphere, cooled to 25°, and acidified with a solution of concentrated hydrochloric acid (6 ml) in water (50 ml). The mixture was seeded with the bisanhydro trimer and allowed to stand for 1 h until precipitation was complete. The product was collected, washed with 2% aqueous sodium bicarbonate solution, and dried. Crystallization from acetone-methanol gave the bisanhydro trimer (3.1 g). The analytical sample formed prisms when recrystallized from the same solvents, and had m.p. 233-237°.

Anal. Calcd. for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 76.85; H, 5.51; N, 13.09.¹ Ultraviolet spectrum: λ_{\max}^{MeoH} 241 m μ (ϵ 14 600), 285 m μ (ϵ 2 300), with a shoulder at 304 m μ (ϵ 1 400). Infrared spectrum: ν_{\max}^{MeoH} 23 560 (OH), 3 390 (NH) cm⁻¹; ν_{\max}^{Nujol} 3 300 (broad, NH and OH) cm⁻¹. Nuclear magnetic resonance spectrum of a deuterated sample in CD₃SOCD₃: τ 2.58-3.50 (12H, complex), τ 4.43 (1H, singlet), τ 4.45 (1H, singlet), τ 4.60 (1H, singlet).

N-Acetylbisanhydro Trimer (V, $R = COCH_3$)

The bisanhydro trimer (100 mg) was stirred with acetic anhydride (0.5 ml) at room temperature for 4 h. The monoacetyl derivative was collected by filtration and purified by crystallization from acetone. The analytical sample formed prisms when recrystallized from acetone, m.p. 227-229°.

Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.38. Found: C, 75.05; H, 4.97; N, 11.36. Infrared spectrum: $\nu_{max}^{CH_2 Cl} C^{1} 3 550$ (OH), 1 660 (NCOCH₃) cm⁻¹; $\nu_{max}^{Nujol} 3 200$ (broad), 1 660 cm⁻¹. Nuclear magnetic resonance spectrum on a deuterated sample in CD₃SOCD₃: 7 2.25-3.25 (12H, complex), 7 3.42 (1H, singlet), τ 4.40 (1H, singlet), τ 4.44 (1H, singlet), τ 7.40 (3H, singlet).

O, N-Diacetylbisanhydro Trimer

The bisanhydro trimer (100 mg) was acetylated in 1:1 pyridine-acetic anhydride (0.5 ml) for 12 h at room temperature. Addition of a few drops of water gave the diacetyl derivative in a crystalline form. The analytical sample formed needles when crystallized from dichloromethane-methanol, and had m.p. 222-225°.

Anal. Calcd. for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21. Found: C, 72.86; H, 5.12; N, 10.03. Infrared spectrum: $\nu_{max}^{CH_2Cl_2} 1$ 740 (OCOCH₃), 1 660 (NCOCH₃) cm⁻¹. Nuclear magnetic resonance spectrum (CDCl₃): τ 2.50–3.33 (14H, complex), τ 4.43 (1H, singlet), τ 7.48 (3H, singlet), τ 7.70 (3H, singlet).

O-Methylbisanhydro Trimer

The bisanhydro trimer (150 mg) was suspended in a solution of p-toluenesulfonic acid (10 mg) in methanol (5 ml), and the mixture stirred for 3 days at room temperature. After dilution with benzene it was washed with dilute aqueous sodium bicarbonate and water, and dried. Removal of the solvent and crystallization from dichloromethane-ether gave the product (105 mg). The analytical sample formed prisms when recrystallized from the same solvents, and had m.p. 228-230°,

Anal. Calcd. for C22H19ON3: C, 77.39; H, 5.61. Found: C, 77.15; H, 5.77.

The Lactam (VI, $R = COCH_3$)

A solution of the monoacetylbisanhydro trimer (89 mg) in dichloromethane (50 ml) was stirred at room temperature with manganese dioxide (3 g) for 4 h. After filtration through Celite the solution was evaporated to dryness in vacuo and the residue crystallized from dichloromethane-ether to yield the lactam (40 mg). The analytical sample separated from the same solvent mixture as prisms, m.p. 229-231°.

Anal. Calcd. for C23H17N2O2: C, 75.19; H, 4.66; N, 11.44. Found: C, 74.93; H, 4.90; N, 11.65.

Ultraviolet spectrum: λ^{MoOII} 210 mμ (ε 34 900), 238 mμ (ε 25 900), 333 mμ (ε 2 800). Infrared spectrum: $\nu_{max}^{CCl_4}$ 1714 (lactam C=O), 1678 (NCOCH₃) cm⁻¹. Nuclear magnetic resonance spectrum (CDCl₃): au 1.88 (1H, multiplet belonging to an aromatic hydrogen ortho to the lactam carbonyl), au 2.25–3.00 (12H, complex), τ 4.11 (1H, singlet), τ 7.46 (3H, singlet).

A sample of the lactam (30 mg) was dissolved in dioxane (1 ml) and water (0.2 ml), and reduced with sodium borohydride (11.5 mg) for 15 min at room temperature. The solution was poured onto ice and

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the product (19 mg) collected and dried. On examination by thin-layer chromatography (alone and admixed with monoacetylbisanhydro trimer) it showed one spot. It was crystallized once from acetone, and was found to be identical with the monoacetyl compound by comparison of their infrared spectra and melting points.

Trisanhydro Tetramer (VIII, R = R' = H)

A mixture of o-aminobenzaldehyde (2.5 g) and 1:1 sulfuric acid – water (10 ml) was stirred until solution was complete (ca. 0.5 h). Water (10 ml) was added and the solution was allowed to stand for 1 day until crystallization of the salt was complete. This was filtered off, washed with anhydrous ethanol, and dried, yield 2.05 g. It was converted quantitatively (as shown by thin-layer chromatography) into the trisanhydro tetramer by shaking it with water and chloroform. The free base was isolated from the chloroform solution and was crystallized once from chloroform-methanol. An analytical sample was obtained from the same solvent mixture, and had m.p. 235-236.5°.

Anal. Calcd. for C₂₈H₂₂N₄O: C, 78.12; H. 5.15; N, 13.02. Found: C, 77.92; H, 5.02; N, 12.83. Ultraviolet spectrum: $\lambda_{\text{max}}^{\text{McOH}} 210 \text{ m}\mu$ (ϵ 44 000), 237 m μ (ϵ 32 700), 267 m μ (ϵ 11 000), 286 m μ (ϵ 2 700), 369 m μ (ϵ 6 900). Infrared spectrum: $\nu_{\text{max}}^{\text{CH}_2Cl_2}$ 3 380 (NH), 3 310 (NH), 2 740 (aldehyde CH stretch), 1 665 (CHO) cm⁻¹; ν_{mus}^{Mus} 3 370, 3 555, 3 315 (NH), 1 665 (CHO) cm⁻¹. Nuclear magnetic resonance spectrum (CDCl₃): $\tau 0.10$ (1H, singlet), $\tau 0.93$ (1H, doublet, J = 5 c.p.s.), $\tau 1.90-3.50$ (16H, complex), $\tau 4.26$ (1H, doublet, J = 5 c.p.s.), $\tau 4.33$ (1H, singlet), $\tau 4.66$ (1H, singlet), $\tau 5.1$ (1H, broad band). Deuteration removed the doublet at τ 0.93 and the band at τ 5.1 from the spectrum, and collapsed the doublet at τ 4.26 to a singlet.

Similar results were obtained by using the bisanhydro trimer in place of o-aminobenzaldehyde.

Acetyltrisanhydro Tetramer (VIII, $R = COCH_3$, R' = H)

The trisanhydro tetramer (730 mg) was acetylated overnight in 1:1 acetic anhydride - pyridine (2 ml) at room temperature. Addition of a little water precipitated a crystalline product which, after one recrystallization from dichloromethane-methanol, gave the pure acetyl derivative. The analytical sample formed plates, m.p. 255-259°, when crystallized from the above solvent mixture.

Anal. Calcd. for C30H24N4O2: C, 76.25; H, 5.12; N, 11.86; mol. wt. 472. Found: C, 75.93; H, 5.11; N, 11.57; mol. wt. 469 (osmometric).

Infrared spectrum: $\nu_{\text{MDX}}^{\text{GO}14}$ 3 300 (NH), 1 668 (NCOCH₃) cm⁻¹; $\nu_{\text{MDX}}^{\text{Musol}}$ 3 325, 1 675 cm⁻¹. Nuclear magnetic resonance spectrum (CDCl₃): τ 0.05 (1H. singlet), τ 0.92 (1H, doublet, J = 5 c.p.s.), τ 2.0-3.25 (17H, complex), τ 4.20 (1H, doublet, J = 5 c.p.s.). τ 4.25 (1H, singlet), τ 7.5 (3H, singlet). Deuteration removed the doublet at τ 0.92, and collapsed that at τ 4.20 to a singlet.

An oxime was obtained by reaction of N-acetyltrisanhydro tetramer (150 mg) with hydroxylamine hydrochloride (145 mg) in pyridine (1 ml) for 12 h at room temperature. The analytical sample formed prisms, m.p. 248-250°, when crystallized from dichloromethane-ether.

Anal. Calcd. for C30H25O2N5: C, 73.90; H, 5.17; N, 14.37. Found: C, 73.76; H, 5.30; N, 14.20.

A sample of the oxime (115 mg) was dehydrated with toluenesulfonyl chloride (50 mg) in dry pyridine (1 ml) at 0° for 24 h. The solution was poured onto ice, and the product was collected by filtration and crystallized from dichloromethane-methanol to give the corresponding nitrile (107 mg). The analytical sample formed colorless prisms, m.p. 232-234°, when recrystallized from these solvents.

Anal. Calcd. for $C_{30}H_{23}ON_5$: C, 76.74; H, 4.94; N, 14.92. Found: C, 76.28; H, 5.08; N, 15.02. Infrared spectrum: $\nu_{\rm CHy}^{\rm CHyCl_2}$ 3 420 (NH), 2 225 (CN), 1 675 (NCOCH₃) cm⁻¹.

N-Acetyl-N'-nitrosotrisanhydro Tetramer (VIII, $R = COCH_3$, R' = NO)

Dry nitrosyl chloride was passed slowly during 4 min into a well-stirred ice-cold solution of acetyltrisanhydro tetramer (244 mg) in pyridine (6 ml). The solution was kept at $0-5^{\circ}$ for a further 30 min, and then poured onto ice to give the product. This was purified by crystallization from dichloromethanebenzene, giving 205 mg of the N-nitroso derivative. The analytical sample formed prisms when recrystallized from benzene, m.p. 192-195°.

Anal. Calcd. for C30H23N5O3: C, 71.86; H, 4.62; N, 13.96 Found: C. 71.95; H, 4.86; N, 14.24.

Ultraviolet spectrum: $\lambda_{\text{max}}^{\text{EtOH}}$ 209 m μ (ϵ 61 800), with shoulders at 240 m μ (ϵ 28 600), 275 m μ (ϵ 6 000), and 283 mµ (¢ 5 300). Infrared spectrum: v^{CC14} 1 704 (CHO), 1 675 (NCOCH₃). Nuclear magnetic resonance spectrum (CDCl₃): τ 0.10 (1H, singlet), τ 1.65–3.40 (18H, complex), τ 4.57 (1H, singlet), τ 7.50 (3H, singlet).

The Indazole (IX)

A mixture of zinc dust (460 mg) and N-acetyl-N'-nitrosotrisanhydro tetramer (210 mg) was added to a solution of anhydrous sodium acetate (750 mg) in glacial acetic acid (6 ml). The mixture was stirred for 0.5 h and poured onto ice; the crude product was filtered off and dried. It was purified by filtration through a column of grade III alumina (10 g) followed by crystallization from acetone to yield 155 mg of product. The analytical sample formed needles, m.p. 255-257°, when recrystallized from acetone.

Anal. Calcd. for C₃₀H₂₃ON₅: C, 76.74; H, 4.94; N, 14.92. Found: C, 76.22; H, 4.94; N, 14.97.

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Ultraviolet spectrum: λ_{max}^{EVB} 207 m μ (ϵ 61 500), 282 m μ (ϵ 5 800), 287 m μ (ϵ 5 750), and 300 m μ (ϵ 3 650), with shoulders centered at 245 m μ (ϵ 16 000) and 292 m μ (ϵ 5 000). Nuclear magnetic resonance spectrum (100 mCi in CDCl₃): τ 1.88 (1H, doublet, J = 0.8 c.p s), τ 2.1–3.4 (18H, complex), τ 3.27 (1H, singlet), 7 7.44 (3H, singlet).

Macrocyclic Tetramer (IV, M = Cu)

A solution of cupric nitrate trihydrate (53 mg) in ethanol (1 ml) was added to a refluxing suspension of trisanhydro tetramer (93 mg) in ethanol (2 ml). After 6 h at reflux temperature the solution was cooled and crystalline (IV, M = Cu) nitrate (121 mg, 93%) collected. The product was identical in its solidstate infrared spectrum with that obtained directly from o-aminobenzaldehyde by the method of Melson and Busch (3).

By using an equivalent amount of the bisanhydro trimer the same product was obtained in an 85%yield.

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