Base-Catalyzed Condensations of o-Phthalaldehyde with Urea and Thiourea

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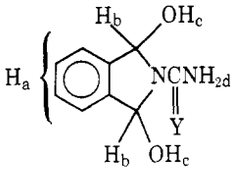
At room temperature o-phthalaldehyde reacts with thiourea in the presence of aqueous sodium hydroxide to form **1a** and/or **2a.** Analogous products (**1b** and **2b**) are produced in similar reactions with urea. Mechanism of formation and stereochemistry of these products are discussed. In methanolic or ethanolic solutions of the corresponding sodium alkoxides, o-phthalaldehyde reacts with urea or thiourea to yield monoalkoxy derivatives of **2a** and **2b** (**3a–d**); acidification of these alcoholic alkoxide reaction mixtures results in formation of dialkoxy derivatives (**4a–d**).

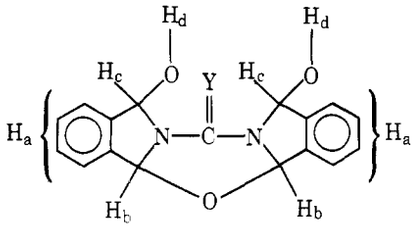
Base-catalyzed condensations of o-phthalaldehyde with primary amides have been shown to result in formation of *N*-acetyl-1,3-dihydroxyisoindolines or 1-hydroxy-3-amidylphthalans.[1] The determining factor in the type of product formed is the steric nature of the R group of the primary amide;[1b] products of the latter type have been isolated only when R is relatively large.

Similar reactions of o-phthalaldehyde with urea and thiourea have now been investigated. The relatively small size of the amino group led us to anticipate that products should be isoindoline derivatives.[2] At room temperature in dilute aqueous sodium hydroxide thiourea reacts smoothly with o-phthalaldehyde to yield *N*-thiocarbamyl-1,3-dihydroxyisoindoline (**1a**). When the basic filtrate from which **1a** was



1a, Y = S
b, Y = O

isolated is allowed to stand for 24 h, a second product, 2,3:5,6-dibenzo-1,7-dihydroxy-7a,8a-diaza-4-oxaoctahydro-*s*-indacene-8-thione (**2a**), is isolated. The product (**2a**) may



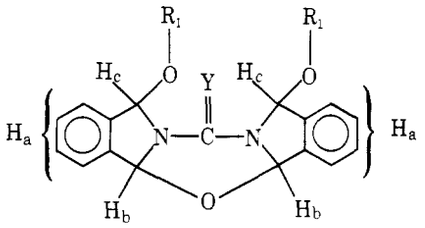
2a, Y = S
b, Y = O

also be prepared directly from o-phthalaldehyde (**1a**) and aqueous sodium hydroxide, and in poor yield, from **1a** alone in aqueous sodium hydroxide. o-Phthalaldehyde was detected in the filtrate of the last reaction. These facts indicate an equilibrium system in which the product obtained is dependent on reaction conditions (see Experimental Section).

Reaction of urea with o-phthalaldehyde under conditions used for the preparation of **1a** proceeds rapidly to yield only **2b.** In the presence of a large excess of urea and under the exact conditions described in the Experimental Section, pure **1b** is isolated in high yield. Again, an equilibrium system is obviously operating.

Chemically, **1a, 2a,** and **2b** behave as expected. Attempts to oxidize them or to use acid-catalyzed hydrolysis were unsuccessful. Base-catalyzed hydrolysis yields α-hydroxy-o-toluic acid.[1] All attempts to chemically characterize **1b** resulted in formation of **2b.**

Similar condensations of thiourea and urea with o-phthalaldehyde take place in methanolic sodium methoxide and in ethanolic sodium ethoxide. Primary products were shown to be **3a–d** (R_2 = H). Acidification of filtrates from such reactions or acidification of initial reaction mixtures results in formation of **4a–d.** That formation of the second azaacetal linkage in compounds **4a–d** is due to workup of reaction mixtures (i.e.,



3a, R_1 = CH_3; Y = S
b, R_1 = CH_3; Y = O
c, R_1 = C_2H_5; Y = S
d, R_1 = C_2H_5; Y = O

4a, R_1 = R_2 = CH_3; Y = S
b, R_1 = R_2 = CH_3; Y = O
c, R_1 = R_2 = C_2H_5; Y = S
d, R_1 = R_2 = C_2H_5; Y = O

acidification) was verified by allowing compounds of structure **3** to react with acidic methanol or ethanol; products were the corresponding compounds **4.** As expected, it is possible to form both azaacetal linkages by using acid catalysis. This was demonstrated by the conversion of **2b** to **4d** using dilute acid as catalyst.

Structural assignments for all compounds are strongly supported by infrared (see Experimental Section) and nuclear magnetic resonance spectra (Table I). The NMR spectra of the urea adducts, **1b, 2b,** and **3b,** are deceptively simple. They remain so even when run at 100 MHz. Fortunately, the thiourea analogues show much more complex spectra; it is even possible to observe coupling of H_b protons with H_c protons across the five-membered ring(s) in **2a, 3a,** and **3c.**

The NMR spectra of **2a, 3a, 3c,** and **4a–d** also provide important information about the stereochemistry of these compounds, since they indicate that the OH and/or OR groups have identical orientations with respect to the C=S or C=O groups. It is unlikely that **2b** or **3b** would differ in this respect. Further, the IR spectrum of **2b** shows very broad OH absorption, indicating strong hydrogen bonding with the >C=O. Models show that such a situation obtains only when the OH groups are cis to each other and in nearly the same plane as the >C=O.

If in the reasonable diadduct intermediate, **5,** the starred OH groups were in the transoid conformation, models indicate that formation of the tetrahydro-4*H*-1,3,5-oxadiazin-4-one (or thione) ring would require introduction of much strain in that ring system as well as much distortion of the five-mem-

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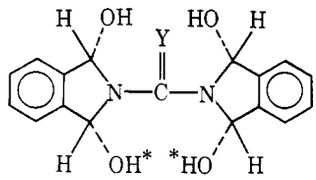
Table I. NMR Spectra of Reaction Products of o-Phthalaldehyde with Urea and Thiourea[a]

compd	registry no.	H_a	H_b	H_c	H_d	other
1a	67209-35-2	7.47 (s, 4)	6.38 (d, 2, 7.5)	5.83 (d, 2, 7.5)[b]	7.25 (s, 2)[b,c]	
1b	67209-36-3	7.42 (s, 4)	6.10 (s, 6)[b,d]	see H_b	see H_b	
2a	67209-37-4	7.52 (s, 8)	6.67 (d, 2, 2)	7.17 (2d's, 2, 2.2, 7.5)	6.62 (d, 2, 7.5)[e]	
2b	67209-38-5	7.48 (s, 8)	6.50 (s, 6)[d,e]	see H_b	see H_b	see H_b
3a	67209-39-6	7.58 (s, 8)	6.78 (d, 2, 1.5)	7.29 (d, 1, 1.5),[f] 7.25 (2d's, 1, 1.5, 7.5)[f]		–OH 6.73 (d, 1, 7.5),[g] OCH_3 3.44 (s, 3)
3b	67209-40-9	7.52 (s, 8)	6.55 (m, 5)[h]	see H_b		OCH_3 3.38 (s, 3)
3c	67209-41-0	7.52 (s, 8)	6.68 (m, 3)[i]	7.10 (m, 1, 1.5)[j] 7.25 (d, 1, 1.5)[j]		OCH_2 3.87 (q, 7), CH_3 1.19 (t, 3, 7)
3d	67209-42-1	7.50 (s, 8)	6.52 (s, 5)[h]	see H_b		OCH_2 3.78 (q, 2, 7), CH_3 1.17 (t, 3, 7)
4a	67209-43-2	7.42 (s, 8)	6.36 (d, 2, 1.5)	7.18 (d, 2, 1.5)		CH_3 3.65 (s, 6)
4b	67209-44-3	7.55 (s, 8)	6.49 (d, 2, 2)[k]	6.63 (d, 2, 2)[k]		CH_3 3.38 (s, 6)
4c	67209-45-4	7.41 (s, 8)	6.36 (d, 2, 1.8)	7.20 (d, 2, 1.8)		OCH_2 4.04 (q, 2, 7) CH_3 1.27 (t, 3, 7)
4d	67209-46-5	7.44 (s, 8)	6.39 (d, 2, 2)[k]	6.49 (d, 2, 2)[k]		OCH_2 3.57 (q, 4, 7) CH_3 1.08 (t, 6, 7)

[a] Data in table is given as chemical shifts in ppm (δ) downfield from Me_4Si (multiplicity, relative area, J in Hz); solvent used was Me_2SO-d_6 except for three compounds: **1a** cetone; **4a** and **4c**, CCl_4. [b] Signals for H_c and H_d disappear when D_2O is added. [c] Very broad absorption. [d] Absorption is for H_b, H_c, and H_d. [e] Signal for H_d disappears when D_2O is added. [f] Obviously, these two hydrogen atoms are nonequivalent; the higher field signal must be assigned to CHOH (cf. coupling constants). [g] Overlap of the OH signal with the H_b signal occurs; however, the splitting pattern is clear. [h] For H_b, H_c, and OH; addition of D_2O reduces relative area to 4. [i] For H_b and OH; addition of D_2O reduces relative area to 2. [j] Although all coupling constants could not be measured, the multiplicity of the higher field signal requires that it be assigned to CHOH. [k] Assignments were made by analogy to the corresponding thiourea derivative; run at 90 °C to effect solution.

bered rings. Conversely, were these groups in the cisoid conformation, the steric situation would be very favorable for ring closure. We postulate that **5** has the structure shown and that



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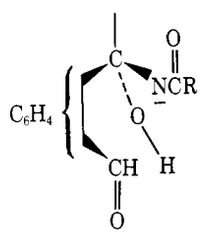
2a and **2b** have the cis-syn-cis configuration. Such a postulation requires that the monoadducts form stereoselectively and have cis OH groups.

Assuming that the mechanism of formation of the monoadducts involves attack of an amide anion on one formyl group of o-phthalaldehyde followed by proton loss and gain to yield an intermediate (**6**), it is possible to explain the ste-



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reochemistry of the monoadducts. As the amide ion in **6** attacks the remaining formyl group, the carbonyl oxygen must begin to move out of the plane of the benzene ring as both that atom and the carbonyl carbon begin to assume sp^3 character. Hydrogen bonding with the existing OH group, possible only if both oxygen atoms are oriented on the same side of the benzene ring, could well lower the energy of the activated complex. One should expect, then, that *cis*-1,3-dihydroxyisoindolines should be predominant products.[3]

The formation of **2a** and **2b**, **3a** and **3b**, and **4a–d**, as well as those compounds discussed in ref 1, must involve base-catalyzed azahemiacetal and/or azaacetal formation. While apparently rare, such reactions have previously been observed in methylol urea systems.[4]

Experimental Section[5]

Materials. Amides and o-phthalaldehyde were purchased from Aldrich Chemical Co., Milwaukee, Wisc., and purified by standard methods.

***N*-Thiocarbamyl-1,3-dihydroxyisoindoline (1a).** o-Phthalaldehyde (3.00 g, 0.0224 mol) and thiourea (1.80 g, 0.0224 mol) suspended in 300 mL of distilled water were treated with 5 mL of 5% aqueous NaOH added dropwise with stirring over a period of 10 min. After 4 h the product was suction filtered and recrystallized from an acetone–hexane mixture to yield 3.45 g (73%) of **1a:** mp 171–172 °C dec; IR 3300 (OH), 3200, 3400 (NH_2), 744 (CH out-of-plane deformation) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.42; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.47; H, 4.93; N, 13.46; S, 15.19.

2,3:5,6-Dibenzo-1,7-dihydroxy-7a,8a-diaza-4-oxaoctahydro-*s*-indacene-8-thione (2a). Method A. After 24 h of standing at room temperature, the filtrate from preparation of **1a** was filtered and recrystallized from acetonitrile to yield 0.25 g (7%) of **2a:** mp 201.0–201.5 °C dec; IR 3500 (OH), 748 (CH out-of-plane deformation) cm^{-1}.

Anal. Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58; S, 9.82. Found: C, 62.62; H, 4.31; N, 8.65; S, 9.89.

Method B. A mixture of pure **1a** (0.5 g, 2.38 mmol), 1 mL of 2.5% aqueous NaOH, and 50 mL of distilled water was stirred for 7 days. Suction filtration yielded 0.116 g of a mixture of **1a** and **2a.** Dissolution in hot methanol, addition of water until cloudiness developed, and suction filtration yielded 0.034 g of essentially pure **2a,** mp 200.5 °C dec. Removal of solvent by rotary evaporation gave 0.112 g of essentially pure **1a,** mp 170–172 °C dec. The filtrate showed a positive test for o-phthalaldehyde.[6]

Method C. o-Phthalaldehyde (1.00 g, 0.0075 mol) was added to 75 mL of distilled water. After solution was affected by heating, a solution of thiourea (0.57 g, 0.0075 mol) in 60 mL of distilled water was added; this was followed by addition of 12 mL of 2.5% aqueous NaOH. After stirring for 2 days at room temperature and suction filtration, the product was recrystallized from acetonitrile to yield 1.27 g (52%) of **2a.**

***N*-Carbamyl-1,3-dihydroxyisoindoline (1b).** A large excess of urea (2.69 g, 0.0448 mol) was added to 100 mL of distilled water. Stirring was begun, and 5 mL of 2.5% aqueous NaOH was added. o-Phthalaldehyde (3.00 g, 0.0224 mol) was added immediately and washed into the mixture with 50 mL more of distilled water.[7] After

5 days the product was suction filtered and recrystallized from acetonitrile to yield 3.51 g (81%) of **1b:** mp 172–173 °C dec; IR 3300 (OH), 3200, 3400 (NH_2), 1640 (amide I C=O), 744 (CH out-of-plane deformation) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.15; N, 14.43. Found: C, 55.85; H, 5.18; N, 14.30.

2,3:5,6-Dibenzo-1,7-dihydroxy-7a,8a-diaza-4-oxaoctahydro-*s*-indacen-8-one (2b). A stirred mixture of *o*-phthalaldehyde (3.15 g, 0.0235 mol), urea (0.67 g, 0.112 mol), and 100 mL of distilled water was treated with 5 mL of 2.5% aqueous NaOH; stirring was continued for 6 days. Recrystallization of the suction-filtered crystals from acetonitrile yielded 2.75 g (80%) of **2b:** mp 218–219 °C dec; IR 3333 (OH, v br), 1653 (amide I C=O), 720–780 (CH out-of-plane deformation)[8] cm^{-1}; mass spectrum *m/e* 310 (M), 309 (M − 1), 308 (M − 2), 307 (M − 3), aromatic cluster *m/e* 77, 78, 79.

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.81; H, 4.52; N, 9.03. Found: C, 65.92; H, 4.55; N, 8.97.

Monomethoxy, Monoethoxy, Dimethoxy, and Diethoxy Derivatives of 2a and 2b: 3a–d and 4a–d. All compounds were prepared by a modification of the method described in ref 1a. Urea or thiourea (0.015 mol), added to a solution of the sodium alkoxide (0.030 g at Na in 50 mL of the alcohol), was added dropwise over a period of 15 min to a rapidly stirred solution of *o*-phthalaldehyde (4.02 g, 0.030 mol) in 200 mL of the alcohol. In all cases, 24 h of stirring and standing for 2 weeks, a small amount of precipitate was evident. This was removed by suction filtration, and the filtrate was divided into two equal portions. One portion was immediately concentrated on a rotary evaporator. Resulting crystals were suction filtered, combined with the original precipitate, and recrystallized from acetonitrile. They were shown to be the monoalkoxy derivatives, **3a–d.** The second portion of filtrate was acidified with 6 N HCl until pHydrion paper showed a pH of ~1 when precipitation began. Dropwise addition of 6 N HCl was continued until reaction mixtures contained voluminous precipitates. Crystals were suction filtered, recrystallized from acetonitrile, and shown to be the dialkoxy derivatives **4a–d.** Further precipitation occurred for ~1 week. All derivatives gave positive Zeisel tests.

Yields (%) and melting points (dec): **3a,** 28, 180–182 °C; **3b,** 33, 205–206 °C; **3c,** 58, 192–193 °C; **3d,** 21, 218–219 °C; **4a,** 64, 173–174 °C; **4b,** 52, 227–228 °C; **4c,** 12, 179–180 °C; **4d,** 31, 229–230 °C. IR (cm^{-1}): OH 3400 (**3a**), 3440 3380 (**3c**), 3430 (**3d**); amide I C=O 1655 (**3b**), 1655 (**3d**), 1650 (**4b**), 1666 (**4d**); CH out-of-plane deformation 755 (**3a**), 754 (**3c**), 747 (**4a**), 750 (**4c**), see ref 8 for **3b, 3d, 4b,** and **4d.**

Anal. Calcd for $C_{18}H_{16}N_2O_3S$ (**3a**): C, 63.51; H, 4.74; N, 8.23, S, 9.42. Found: C, 63.40; H, 4.71; N, 8.24; S, 9.34. Calcd for $C_{18}H_{16}N_2O_4$ (**3b**): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.77; H, 5.06; N, 8.67. Calcd for $C_{19}H_{18}N_2O_3S$ (**3c**): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.44; H, 5.10; N, 7.82; S, 8.97. Calcd for $C_{19}H_{18}N_2O_4$ (**3d**): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.17; H, 5.36; N, 8.23. Calcd for $C_{19}H_{18}N_2O_3S$ (**4a**): C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.27; H, 5.00; N, 7.97; S, 9.12. Calcd for $C_{19}H_{18}N_2O_4$ (**4b**): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.32; H, 5.30; N, 8.24. Calcd for $C_{21}H_{22}N_2O_3S$ (**4c**): C, 65.95; H, 5.80; N, 7.32; S, 8.32. Found: C, 65.77; H, 5.81; N, 7.29; S, 8.30. Calcd for $C_{21}H_{22}N_2O_4$ (**4d**): C, 68.86; H, 6,01; N, 7.65. Found: C, 68.55; H. 6.25; N, 7.56.

Conversion of Compounds of Structure 3 to Compounds of Structure 4. These conversions were accomplished as described for formation of compounds of structure **4** above. Yields varied from 51 to 85%.

Conversion of 2b to 4d. After stirring for 10 days, a mixture of 300 mL of 95% ethyl alcohol, 3 mL of 6 N HCl, and 0.62 g (0.002 mol) of **2b** remained heterogeneous. Heating to 70 °C resulted in homogeneity. Cooling, suction filtration, and washing with acetone and 95% ethyl alcohol yielded product (0.70 g, 96%) shown to be identical with **4d** by undepressed mixture melting point (229–230 °C) and identical IR spectrum.

Registry No.—*o*-Phthalaldehyde, 643-79-8; thiourea, 62-56-6; urea, 57-13-6.

References and Notes

(1) (a) R. D. Reynolds and R. J. Conboy, *J. Org. Chem.*, **30,** 2251 (1965); (b) R. D. Reynolds, D. F. Guanci, D. L. Arendsen, and R. F. Wickman, *ibid.*, **35,** 3940 (1970).

(2) It has been shown (ref 1b) that *N*-methylurea reacts with *o*-phthalaldehyde to form a monoadduct of the isoindoline type. Secondary amides (acetanilide, *N*-methylacetamide, *N*-methylformamide) did not react.

(3) It should further be noted that trans OH groups in the monoadducts would result in chirality. Many attempts to resolve these compounds failed.

(4) F. D. Chattaway and E. J. F. James, *J. Chem. Soc.*, 109 (1934); *Proc. R. Soc. London, Ser. A,* **137,** 481 (1932); *ibid.*, **134,** 372 (1931).

(5) Melting points were taken on a Büchi melting point apparatus previously calibrated against standard substances; IR spectra were determined on a Beckman IR 8 spectrophotometer in KBr pellets. A Varian A60 spectrometer was used for 60-MHz NMR spectra; 100-MHz spectra were run on a Varian HA-100 spectrometer. Mass spectra were determined on a Perkin-Elmer-Hitachi instrument, Model RUM-GE, at 60 °C. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or determined on a Perkin-Elmer 240 C, H, N analyzer. All stirring was magnetic, and all products isolated were white crystals.

(6) J. D. Bill and D. S. Tarbell *Org. Synth.*, **34,** 82 (1954).

(7) Many variations of this procedure were attempted. All resulted in mixtures of **1b** and **2b.** Recrystallization of **1b** must be carried out very carefully; otherwise, contamination by **2b** occurs.

(8) Six strong peaks occur in this spectral range. This pattern is typical of all compounds isolated as products from 2 mol of *o*-phthalaldehyde/mol of urea.

Catalytic Hydrogenation of Some Acylguanidines

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The behavior of several acylguanidines toward low-pressure hydrogenation over PtO_2 catalyst was investigated. Creatinine (**3**) and alacreatinine (**7a**) gave cleanly the corresponding cyclic guanidines, iminoimidazolidines **4** and **8a.** β-Alacreatinine (**9**) also could be hydrogenated in aqueous acid to iminohexahydropyrimidine **10,** but the same reaction in water gave a mixture of products. Only guanidine itself could be isolated from the hydrogenation of acetylguanidine, while the simple amide analogue pyrrolidinone was not reduced under these conditions and gave γ-aminobutyric acid under forcing conditions. The glycocyamides alacreatinine (**7a**) and phenylalacreatinine (**7b**) were prepared by acid-catalyzed cyclization of the corresponding optically active α-guanidino acids. In both cases, the resulting glycocyamidines were racemic. When the hydrogenation of creatinine was carried out in D_2O, the product 2-imino-1-methylimidazolidine (**23**) contained two deuterium atoms at C-4 and two at C-5, thus suggesting that hydrogenation would also lead to racemization of an α-chiral center.

If the preparation of alkylguanidines could be effected by reduction of the corresponding acylguanidines, the process would be of considerable utility since a variety of acylguanidines is readily available.[1,2] We have recently[3] developed a procedure using lithium aluminum hydride which accomplishes this conversion. In pursuit of perhaps an alternative and more convenient process, we have investigated the catalytic hydrogenation of acylguanidines. Such reductions of acylguanidines have not been reported. Although amides can be so reduced, the conditions necessary invariably involve high

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