## Use of the Stenhouse Reaction for the Preparation of Mixed Dianils of 2-Hydroxyglutaconaldehyde

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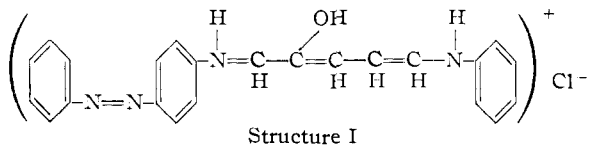
Previous studies have shown that the Stenhouse reaction[2] may be employed to form a wide variety[2a] of symmetrical dianils of 2-hydroxyglutaconaldehyde. A recent report from this Laboratory[3] discusses various proposals which have sought to explain the mechanism of the reaction and reviews much of the earlier literature.

One characteristic of many dianils of 2-hydroxyglutaconaldehyde is their instability.[3] In acidic solution 1-phenylimino-5-phenylamino-2-hydroxypenta-2,4-diene, a symmetrical dianil of 2-hydroxyglutaconaldehyde, undergoes ring closure with the formation of N-phenyl-3-hydroxypyridinium salts[2,4,5] and the elimination of aniline. The mechanism of this reaction is not entirely clear. The arylamine in either the 1- or 5-position of the dialdehyde could be cleaved during the formation of the pyridol. It occurred to us, therefore, that the reaction of various anils of furfural with aromatic amines other than those parent to the original anil might provide a source of useful unsymmetrical dianils. Ring closure of the latter should yield various N-aryl-3-pyridols and provide an insight into the mechanism of ring closure. The unsymmetrical dianils previously have not received systematic study although aniline and various other aromatic amines together with furfural and acid have been used to form resinous materials.[6,7] Schiff[8] studied reactions of furfural and mixtures of aromatic amines in the presence of acid but did not report details.

The preparation of 1-arylimino-5-arylamino-2-hydroxy-penta-2,4-diene salts where both aryl groups are the same in general offers no great difficulties other than those associated with the previously noted hygroscopic nature and instability of the products.[3] Boehm[9] has reported the affinity of these substances for many solvents of crystallization. In attempting to prepare 1-N-*p*-phenylazophenylimino-5-phenylamino-2-hydroxypenta-2,4-diene hydrochloride from N-*p*-phenylazophenylfurfurylideneimine and aniline hydrochloride some difficulties were encountered. After investigating various means, it was found that the product obtained directly from concentrated solution in methanol or ethanol melted at 157°, while that obtained by recrystallization from methanol melted at 174°. Both compounds gave the correct elementary analysis for the expected unsymmetrical dianil. Moreover, their absorption spectra were quite similar. The explanation may lie in simple polymorphism. An examination of structure I, however, reveals many opportunities for geometrical isomerization (*syn–anti*, *cis–trans*) as well as the possible existence of tautomeric forms. Tentatively, therefore, the higher melting product is called form A and the lower melting form B.



Structure I

For the preparation of 1-phenylimino-5-*p*-bromophenylamino-2-hydroxypenta-2,4-diene hydrochloride, stoichiometric amounts of N-*p*-bromophenylfurfurylideneimine and aniline hydrochloride were allowed to react in ethanol. The expected dianil could not be isolated readily from the reaction mixture. The product invariably gave carbon, hydrogen and bromine analyses, despite repeated recrystallization, which suggested contamination by the 1-*p*-bromophenylimino-5-*p*-bromophenylamino compound. When the reaction was carried out in the presence of three equivalents of the bromoanil and one mole of aniline hydrochloride, the isolated product was indeed 1-N-*p*-bromophenylimino-5-N-*p*-bromophenylamino-2-hydroxypenta-2,4-diene hydrochloride. Conversely, when three equivalents of aniline hydrochloride were employed with one mole of the bromoanil, the product obtained was, by analyses, virtually free of the bis-bromo derivative. These experiments serve to suggest the possibility of a redistribution reaction.

In the analogous preparation of 1-*p*-hydroxyphenylimino-5-phenylamino-2-hydroxypenta-2,4-diene hydrochloride from N-*p*-hydroxyphenylfurfurylideneimine and aniline hydrochloride no such difficulties were encountered, and the expected product was obtained readily. Rombaut and Smets[7] reported that *p*-aminophenol and *p*-anisidine are displaced from furfural by *p*-aminodiethylaniline and that *p*-nitroaniline is displaced by *p*-anisidine.

Furfurylideneimines, employed by us, were derived from *p*-aminoazobenzene, *p*-hydroxyaniline and *p*-bromobenzene. All these imines show absorption maxima in the range 325–370 mμ. The maximum for the unsubstituted phenyl compound, N-phenylfurfurylideneimine, lies at 320 mμ. The observed shifts of the maxima to longer wave lengths are in agreement with the generally observed shifts attributable to increased conjugation and introduction of nuclear substituents on the benzene ring which enhance the resonance possibilities.[10]

### Experimental

**N-*p*-Bromophenylfurfurylideneimine.**—*p*-Bromoaniline (17.0 g.) and 9.59 g. of furfural were placed in a small

(1) (a) Stauffer Chemical Co., Torrance, California. (b) Medical College of Virginia, Richmond, Va.

(2) J. Stenhouse, *Ann.*, **156**, 197 (1870), first described molecular reactions involved in the cleavage of the furan nucleus of 2-furaldehyde in the presence of acid and aromatic amines. (2a) T. H. Zincke and G. Mulhausen, *Ber.*, **38**, 3824 (1905).

(3) W. M. Foley, Jr., Guy E. Sanford and H. McKennis, Jr., THIS JOURNAL, **74**, 5489 (1952).

(4) J. C. McGowan, *J. Chem. Soc.*, 777 (1949).

(5) C. F. Koelsch and J. J. Carney, THIS JOURNAL, **72**, 2285 (1950).

(6) (a) M. Phillips and G. Mains, *Chem. and Met. Eng.*, **24**, 661 (1921); (b) H. F. Winterkorn, U. S. Patent 2,314,181, March 16, 1943.

(7) J. Rombaut and G. Smets, *Bull. soc. chim. Belg.*, **58**, 421 (1949), have investigated the reaction of furfural with aromatic amines in the absence of added acid. Bases were obtained with empirical formulas corresponding to free bases which might be expected from various unsymmetrical Stenhouse dyes. The reported stability of the former in acid, however, suggests that the compounds are isomeric with free bases of the type prepared by McGowan.[4]

(8) H. Schiff, *Ann.*, **239**, 349 (1887).

(9) T. Boehm, *Arch. Pharm.*, **267**, 129 (1929).

(10) G. N. Lewis and M. Calvin, *Chem. Revs.*, **25**, 273 (1939).

Claisen flask in a bath at 130°. The fraction, b.p. 89° (3.5 mm.), was collected (23.1 g., 92%). For analysis the product was recrystallized from *n*-hexane to yield pale yellow crystals, m.p. 62.5–63°. Absorption spectra were obtained on this and related azomethines at concentrations of approximately $10^{-4}$ *M* in absolute alcohol. $\lambda_{max.}$ 225, 287, 325 mμ; log ε 4.11, 4.27, 4.30; $\lambda_{min.}$ 250, 303 mμ; log ε 3.59, 4.26.

*Anal.* Calcd. for $C_{11}H_8NOBr$: C, 52.82; H, 3.22; N, 5.60. Found: C, 52.97; H, 3.22; N, 5.68.

**1-N-*p*-phenylazophenylimino-5-phenylamino-2-hydroxypenta-2,4-diene Hydrochloride.**[11]—N-*p*-Phenylazophenylfurfurylideneimine (2.75 g.[12]; $\lambda_{max.}$ 225, 240, 367 mμ; log ε 4.16, 4.15, 4.24; $\lambda_{min.}$ 233, 267 mμ; log ε 4.15, 3.85) was dissolved in a minimum amount of anhydrous ethanol, and 1.29 g. of aniline hydrochloride was added. The solution turned purple and deposited 3.29 g. (81%) of purple crystals, m.p. 157° dec. The product was washed with an excess of ether–alcohol (2–1) and then dried under diminished pressure. The melting point and color were unaltered. Fresh solutions[3] of the dianils were examined in absolute alcohol: form A, $\lambda_{max.}$ 245, 310, 395, 555, 590 mμ; log ε 4.24, 3.96, 4.65, 3.60, 3.58; $\lambda_{min.}$ 230, 290, 515, 580 mμ; log ε 4.22, 3.92, 3.51, 3.45.

*Anal.* Calcd. for $C_{29}H_{21}N_4OCl$: C, 68.2; H, 5.2; N, 13.84; Cl, 8.75. Found (cor. for ash): C, 67.6; H, 5.1; N, 13.85; Cl, 8.6.

**Conversion of Form A to Form B.**—The lower-melting form was dissolved in methanol at room temperature. The solution was chilled, and the purple crystals were washed with methanol–ether; m.p. 174° dec. Further recrystallization and drying under diminished pressure did not alter the melting point; $\lambda_{max.}$ 245, 295, 392, 540 mμ; log ε 4.24, 3.93, 4.54, 3.73; $\lambda_{min.}$ 230, 290, 320, 500, 610 mμ; log ε 4.19, 3.92, 3.91, 3.63, 3.61.

*Anal.* Found (cor. for ash): C, 67.8; H, 4.9; N, 13.8; Cl, 8.7.

**1-N-*p*-Bromophenylimino-5-phenylamino-2-hydroxypenta-2,4-diene Hydrochloride.**—N-*p*-Bromophenylfurfurylideneimine (0.83 g.) was dissolved in a minimum amount of anhydrous ethanol. A solution of aniline hydrochloride (1.3 g.) in anhydrous ethanol was added, and the mixture was allowed to stand. The purple crystals (0.5 g., 40%), m.p. 151° dec., were collected and washed with anhydrous ethanol. The melting point and color were unchanged upon repeated recrystallization and drying under diminished pressure at 76°. The compound was extremely hygroscopic and retains one molecule of water of crystallization upon exposure to moist air.

*Anal.* Calcd. for $C_{17}H_{16}N_2ClOBr \cdot H_2O$: C, 51.3; H, 4.56; N, 7.05; Br, 20.10; Cl, 8.92; $H_2O$, 4.53. Found: C, 51.6; H, 4.4; N, 6.99; Br, 20.01; Cl, 8.88; $H_2O$ (by loss of weight at 100° under diminished pressure), 4.51.

**1-N-*p*-Hydroxyphenylimino-5-phenylamino-2-hydroxypenta-2,4-diene Hydrochloride.**—To 7.0 g. of N-*p*-hydroxyphenylfurfurylideneimine[13] in 50 ml. of ethanol, a solution of 4.9 g. of aniline hydrochloride in 20 ml. of ethanol was added. On standing, the solution deposited 8.3 g. (70%) of purple crystals, m.p. 163–166° dec. For analysis the compound was recrystallized from ethanol and dried under diminished pressure. The purple product melted at 171–172° dec.; $\lambda_{max.}$ 250, 292, 520 mμ; log ε 3.93, 3.83, 4.18; $\lambda_{min.}$ 230, 272, 400 mμ; log ε 3.87, 3.78, 3.61.

*Anal.* Calcd. for $C_{17}H_{17}N_2O_2Cl$: C, 64.46; H, 5.41; N, 8.85. Found: C, 64.76; H, 5.71; N, 8.81.

**1-*p*-Bromophenylimino-5-*p*-bromophenylamino-2-hydroxypenta-2,4-diene Hydrochloride.**—To a solution of 1.72 g. of *p*-bromoaniline in 20 ml. of absolute alcohol was added 0.96 g. of furfural. The mixture was heated to 60° and then allowed to cool to room temperature. A solution of 2.09 g. of *p*-bromoaniline hydrochloride in 25 ml. of absolute alcohol was added with stirring. On standing, the solution deposited 1.4 g. of purple dianil hydrochloride, m.p. 159–160° dec. The crystals were collected and washed with alcohol–ether (1–1). For analysis the compound was dried under diminished pressure. Recrystallization from absolute alcohol did not affect the melting point of the crystals. An additional amount of product was obtained from the mother liquors to give a total yield of 3.92 g. (86%).

*Anal.* Calcd. for $C_{17}H_{15}N_2OClBr_2$: C, 44.5; H, 3.3. Found: C, 44.6; H, 3.3.

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(11) For simplicity of nomenclature it is assumed throughout this paper that no interchange has caused inversion of substituents between the 1- and 5-positions.

(12) M. Betti, *Gazz. chim. ital.*, **281**, 243 (1898).

(13) H. Schiff, *Ann.*, **201**, 355 (1880), prepared this compound, m.p. 180–182°. Our imine obtained by recrystallization from warm ethanol melted at 185–186°. *Anal.* Calcd. for $C_{13}H_9NO_2$: C, 70.6; H, 4.85; N, 7.48. Found: C, 70.8; H, 4.87; N, 7.56; $\lambda_{max.}$ 223, 286, 342 mμ; log ε 4.02, 4.19, 4.30. $\lambda_{min.}$ 226, 253, 306 mμ; log ε 3.87, 3.77, 4.03. Ronibaut and Smets reported m.p. 187–188°, and $\lambda_{max.}$ 285, 341 mμ; log ε 4.21, 4.33.

## Isomerization of Isospirostans to Furostenols with Pyridine Hydrochloride as the Catalyst

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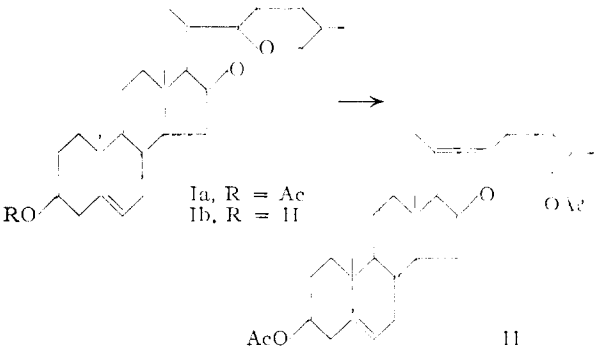
The isomerization of an isospirostan to a furostenol was studied by Gould, Staeudle and Hershberg[1] and they found that the conversion could be achieved at the boiling point of acetic anhydride in the presence of a Lewis acid such as aluminum chloride or acetyl chloride. Similar conditions, using acetyl chloride, also have been employed to convert $\Delta^{4,6}$-22-isospirostadiene-3-one to the corresponding 3-acetoxy-3,5,7-triene.[2] Although this latter reaction was complicated by the tendency of the starting ketone to form 3,26-diacetoxy-3,5,7,-20(22)-furostatetraene, the major product always contained the side-chain intact. In contrast, however, when the enol acetylation was conducted in the presence of one equivalent of pyridine (per mole of steroid), the enol acetate of furostatetraene was obtained in a yield of 40%. In view of the increased reactivity of the reaction system toward isospirostan ring isomerization when the pyridine was present, the role of this base in such a conversion has been evaluated.




It was found that when 22-iso-5-spirosten-3β-ol acetate (diosgenin acetate, Ia) was allowed to

(1) D. H. Gould, H. Staeudle and E. B. Hershberg, THIS JOURNAL, **74**, 3685 (1952).

(2) W. G. Dauben, J. F. Eastham, R. A. Micheli, K. H. Takemura, L. Mandell and J. M. Chemerda, *ibid.*, **75**, 3255 (1953).