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## The Formation of Dihydropyridazines from Succinaldehyde bis (diethyl acetal) and Phenylhydrazines

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Succinaldehyde bis (diethyl acetal) and phenyl-, or ring substituted phenyl-hydrazines cyclize in 25% acetic acid into the corresponding 1-*N*-aryl-dihydropyridazines I—IV. On the basis of spectral and chemical evidence the structure of I—IV was established, and the conditions leading to dihydropyridazine formation were investigated.

It has been shown<sup>1-4</sup> that phenylhydrazine hydrochlorides bearing an electron releasing group in the *p*-position condense smoothly with various aliphatic acetals in 25% acetic acid at 50—80° into the corresponding indole derivatives. In order to check whether such an indolization could be achieved also with succinaldehyde bis (diethyl acetal) as the aldehydic moiety, the acetal was brought into reaction with equimolar amounts of *p*-benzyloxy- and *p*-methoxy-phenylhydrazine hydrochloride respectively. Crystalline products I and II deposited from the reaction mixture in high yield; however, their microanalyses and IR spectra ruled out the indolic structure for these compounds.

It was found<sup>4</sup> that under the above conditions, phenylhydrazine hydrochloride and *m*-benzyloxyphenylhydrazine hydrochloride fail to condense with the acetals of aliphatic monoaldehydes, into any defined product. However, with succinaldehyde bis (diethyl acetal) both the hydrazines give high yields of compounds III and IV respectively. As the microanalytical data of I—IV supported either a dihydropyridazine or a *N*-aminopyrrole structure, the spectral and chemical properties of these compounds were investigated.

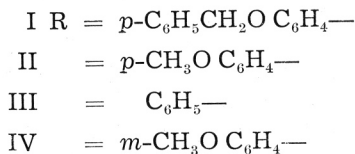
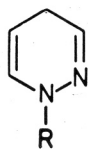
It is known<sup>5</sup> that 3-keto- and 3-aldehydo-acid arylhydrazones can undergo cyclodehydration to give pyridazinones, and that this route may be the competing reaction with the indole formation. In addition, reactions of succinic esters with unsubstituted and substituted hydrazines leading to dihydropyridazines and *N*-aminopyrroles are described in the literature<sup>6</sup>; in most cases when the reaction was performed in acetic acid, the product was recognized as *N*-aminopyrrole. Recently, Lemal and Rave<sup>7</sup> in a study on the tosylhydrazine-2,5-diethoxyfuran reaction found that the formation of the corresponding *N*-aminopyrrole, dihydropyridazine and bishydrazone respectively, is highly dependent upon the choice of the reaction conditions.

The IR spectra of I—IV show the absence of N—H stretching absorption at 3  $\mu$ , excluding thus a *N*-aminopyrrole structure. There is a strong absorption in the 6.25—6.30  $\mu$  region (C=N stretching vibration) but the presence of the

aromatic ring in the molecule makes an assignment of this frequency difficult. The presence of two peaks in the 3.45—3.55  $\mu$  region, attributed to saturated  $\text{CH}_2$  stretching vibrations, supports a 1,4- and/or 1,6-dihydropyridazine structure. The UV spectra of I—IV, measured in ethanol, are very similar and show two strong absorption maxima in the 210—228 and 280—285  $m\mu$  region. A comparison with the UV spectra of some known *N*-aminopyrroles and dihydropyridazines also points to the latter structure.

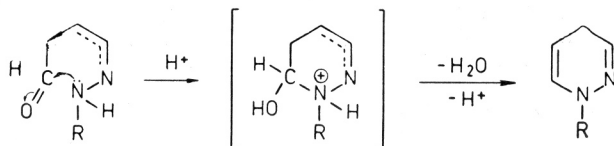
Compounds I—IV behave as very weak bases; they are soluble in concentrated and insoluble in dilute hydrochloric acid. On paper chromatography they develop a blue-green colour with Ehrlich reagent, while they fail to give the pine-splinter test for pyrroles. The final evidence for their structure was obtained when III proved to be identical with 1-phenyl-1,4-dihydropyridazine prepared already by Ciamician and Zanetti<sup>8</sup> by treating succinaldehyde bis (phenylhydrazone) with cold concentrated hydrochloric acid. To our knowledge III is the only 1-*N*-aryl dihydropyridazine described so far in the literature.

Dihydropyridazines I—IV can be presented in two tautomeric forms: as 1,4- and 1,6-dihydro derivatives. According to the available data in the literature,<sup>6,9</sup> the more stable 1,4-dihydro structure should be preferred. It is interesting that I was resolved by fractional crystallization into isomers Ia (m. p. 173—175°) and Ib (m. p. 150—152°); however this fact was not further investigated.



The ease with which the formation of I—IV takes place is remarkable, even at room temperature high yields of I and III were obtained. In addition, the yields of III were found to be unaffected if instead of phenylhydrazine hydrochloride the free base, or instead of the acetal the aldehyde was used. In order to find out whether the bishydrazones are the intermediates in this reaction, succinaldehyde bis (phenylhydrazone)<sup>10</sup> (V) was treated with 25% acetic acid, as well as with dry hydrogen chloride in benzene. Indeed, in both cases the conversion of V into III took place extremely easily<sup>8</sup>. Nevertheless, according to the following results the bishydrazones appear not to be the intermediates in the examined reaction: 1) Identical yields of III were obtained when one or two molecular proportions of phenylhydrazine hydrochloride were used. 2) As expected<sup>4</sup>, attempts to prepare from *p*-benzyloxy- and *p*-methoxy-phenylhydrazine the corresponding succinaldehyde bishydrazones failed. 3) Addition of succinaldehyde acetal to an equimolar amount of phenylhydrazine hydrochloride in 25% acetic acid caused almost immediately the separation of a thick yellow oil which gradually solidified into III. However, when succinaldehyde was added at room temperature to a tenfold excess of phenylhydrazine in 25% acetic acid, the separation of a crystalline solid identified as the bis-hydrazone V took place.

Hence, it appears that in the case of succinaldehyde and its acetal, the second aldehydic group is so favourably located that in an acidic medium the internal cyclodehydration of the already formed monohydrazone (or enhydrazine) precedes the attack of a second molecule of arylhydrazine:



Evidence for the electronic effect of the substituents on the aromatic ring was obtained in the reaction with 2,4-dinitrophenylhydrazine: here the electron withdrawing nitro groups prevent the cyclization to the corresponding dihydropyridazine, and the bishydrazone, together with some *N'*-acetyl-*N*-(2,4-dinitrophenyl)-hydrazine are the only reaction products.

#### EXPERIMENTAL

Melting points are uncorrected. The IR spectra were determined on a Perkin-Elmer 137 infracord spectrophotometer. The UV spectra were measured in absolute ethanol solutions ( $10^{-5}$  mole/l.) on a Perkin-Elmer 137 UV spectrophotometer. Descending one-dimensional chromatography was performed on Whatman No. 1 paper in 1. *n*-butanol-acetic acid-water (60 : 15 : 25) and 2. isopropanol-ammonia-water (10 : 1 : 1).

#### 1-(*p*-Benzyloxyphenyl)-1,4-dihydropyridazine (I)

*p*-Benzyloxyphenylhydrazine hydrochloride (0.627 g., 2.5 mmole) was dissolved in 25 ml. of 25% acetic acid at 80° and succinaldehyde *bis* (diethyl acetal)<sup>11</sup> (0.586 g., 2.5 mmole) was dropped in under stirring; the stirring and heating was then continued for 2 hours. From the reaction mixture 0.553 g., 84% of crude I was deposited (m. p. 140–147°). After two recrystallizations from acetone, the compound melted in the range from 154–164°, and was analytically pure.

*Anal.* C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O (264.31) calc'd.: C 77.24; H 6.10; N 10.60%  
found: C 77.27; H 6.37; N 10.51%

IR spectrum (KBr) in  $\mu$ : 6.25 w, 6.40 vw (C = N and C = C); 7.63 m (PhN <); 8.14 s, 9.70 m (C—O—C); 12.23 s (1,4-di-subst. benzene), 13.45 s, 14.30 m (monosubst. benzene). UV spectrum:  $\lambda_{\text{max}}$ , 212 m $\mu$  ( $\epsilon = 15,300$ ) and 282 m $\mu$  ( $\epsilon = 11,300$ );  $\lambda_{\text{min}}$ , 230 m $\mu$  ( $\epsilon = 4,680$ ). *R<sub>f</sub>* values: solvent 1. 0.92; solvent 2. 0.88; blue-green spot with Ehrlich reagent (2% *p*-dimethylaminobenzaldehyde in 5% hydrochloric acid).

When the above condensation was performed at room temperature, 76% of crude I (m. p. 149–153°) was deposited from the reaction mixture in 2 hours.

Fractional crystallization of I. Analytically pure I was subjected to five successive recrystallizations from ethyl acetate; the less soluble isomer *Ia* crystallized as shiny plates, m. p. 173–175°, while on the concentration of the mother liquors the more soluble isomer *Ib* crystallized in the form of needles, m. p. 150–152°.

*Anal.* C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O (264.31) calc'd.: C 77.24; H 6.10; N 10.60%  
*Ia* found: C 77.34; H 6.10; N 10.32%  
*Ib* found: C 77.39; H 5.81; N 10.90%

#### 1-(*p*-Methoxyphenyl)-1,4-dihydropyridazine (II)

From *p*-methoxyphenylhydrazine hydrochloride (0.437 g., 2.5 mmole) and succinaldehyde *bis* (diethyl acetal) (2.5 mmole) as described for I. From the reaction

mixture 0.365 g., 77% of crude II with m. p. 168—182° deposited. After two recrystallizations from benzene the compound melted at 232—234° (decomp.), white needles.

*Anal.* C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O (188.22) calc'd.: C 70.19; H 6.43; N 14.88%  
found: C 70.55; H 6.53; N 15.09%

IR spectrum (KBr) in  $\mu$ : 6.30 m, 6.40 m (C = N and C = C); 7.62 m (PhN <); 8.10 s, 9.65 m (C—O—C); 12.12 s (1,4-disubst. benzene). UV spectrum:  $\lambda_{\max}$ . 214 m $\mu$  ( $\epsilon = 8,370$ ) and 285 m $\mu$  ( $\epsilon = 12,800$ );  $\lambda_{\min}$ . 229 m $\mu$  ( $\epsilon = 1,220$ ).  $R_f$  values: solvent 1. 0.91; solvent 2. 0.86; blue-green spot with Ehrlich reagent.

### 1-Phenyl-1,4-dihydropyridazine (III)

From phenylhydrazine hydrochloride (0.362 g., 2.5 mmole) and succinaldehyde bis (diethyl acetal) (2.5 mmole) as described for I. From the reaction mixture an oil separated which gradually solidified; after 2 hours III (0.336 g., 85%, m. p. 171—175°) was filtered off. Two recrystallizations from ethyl acetate afforded the analytically pure substance; white needles, m. p. 182—183°, reported<sup>8</sup>: 184—185°.

*Anal.* C<sub>10</sub>H<sub>10</sub>N<sub>2</sub> (158.20) calc'd.: C 75.92; H 6.37; N 17.71%  
found: C 75.63; H 6.22; N 17.99%

IR spectrum (KBr) in  $\mu$ : 6.30 s, 6.40 m (C = N and C = C); 7.62 m (PhN <); 13.35 s, 14.40 m (monosubst. benzene). UV spectrum:  $\lambda_{\max}$ . 209 m $\mu$  ( $\epsilon = 15,300$ ) and 279 m $\mu$  ( $\epsilon = 16,800$ );  $\lambda_{\min}$ . 232 m $\mu$  ( $\epsilon = 3,730$ ).  $R_f$  values: solvent 1. 0.93; solvent 2. 0.88; blue-green spot with Ehrlich reagent.

When the equimolar ratio phenylhydrazine hydrochloride: succinaldehyde acetal was changed to 2 : 1, the yield of III (m. p. 178—180°) was 86%. When the reaction with equimolar amounts of reagents was performed at room temperature, 86% of III (m. p. 170—172°) was obtained after 2 hours.

### 1-(*m*-Benzyloxyphenyl)-1,4-dihydropyridazine (IV)

*m*-Benzyloxyphenylhydrazine hydrochloride (0.627 g., 2.5 mmole) was dissolved in an acetic acid — water — ethanol mixture (1 : 1 : 2, 40 ml.) and treated with 2.5 mmole succinaldehyde bis (diethyl acetal) at 80° as described for I. An oil separated almost immediately; after cooling the reaction mixture was evaporated *in vacuo* to one third of the volume and extracted with benzene. The combined extracts were washed with a saturated solution of sodium hydrogen carbonate, dried over potassium carbonate and evaporated *in vacuo*. The remaining dark oil was chromatographed over an alumina (Lachema, after Brockmann) column (25 × 1 cm.), using benzene as the eluting agent (25 ml. fractions). Fractions No. 3 and 4 gave on evaporation 0.367 g., (55%) of a yellow oil which could be crystallized from ethyl acetate. After two recrystallizations from the same solvent, IV with m. p. 169—170° was obtained.

*Anal.* C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O (264.31) calc'd.: C 77.24; H 6.10; N 10.60%  
found: C 77.56; H 5.85; N 10.87%

IR spectrum (KBr) in  $\mu$ : 6.25 s, 6.40 s (C = N and C = C); 7.60 m (PhN <); 8.25 s, 9.50 m (C—O—C); 13.35 s, 14.45 s (monosubst. benzene). UV spectrum:  $\lambda_{\max}$ . 228 m $\mu$  ( $\epsilon = 12,600$ ) and 283 m $\mu$  ( $\epsilon = 10,300$ );  $\lambda_{\min}$ . 252 m $\mu$  ( $\epsilon = 857$ ).  $R_f$  values: solvent 1. 0.94; solvent 2. 0.86; blue-green spot with Ehrlich reagent.

### Conversion of succinaldehyde bis (phenylhydrazone) (V) into 1,4-dihydropyridazine (III)

- A. In 25% acetic acid. A suspension of V<sup>10</sup> (0.133 g., 0.5 mmole, m. p. 114—115°) was stirred at 80° for 2 hours whereupon no apparent dissolution of V took place. The precipitate (0.075 g., m. p. 163—168°) was recrystallized from ethyl acetate; 78% of III identified by m. p., IR and UV spectra was obtained.
- B. Into a solution of V (0.100 g., 0.38 mmole) in dry benzene (15 ml.) anhydrous hydrogen chloride was bubbled for 5 minutes. A crystalline precipitate deposited immediately; after standing for 1 hour at room temperature it was filtered off and extracted with hot ethyl acetate. The evaporation of the solvent left a solid (42 mg., m. p. 165—168°) which was identified as III (71%)

yield). The ethyl acetate-nonsoluble part was dissolved in hot water, some charcoal added and the solution filtered. On cooling 50 mg. (92%) of crystals identified as phenylhydrazine hydrochloride were obtained.

*Attempted preparation of 1-(2,4-dinitrophenyl)-1,4-dihydropyridazine*

2,4-Dinitrophenylhydrazine (0.496 g., 2.5 mmole) was dissolved in 40 ml. of an acetic acid — water — ethanol mixture, 0.3 ml. conc. hydrochloric acid added and treated with 2.5 mmole succinaldehyde bis (diethyl acetal) at 80° for 2 hours. A yellow solid (300 mg.) precipitated; it was filtered off, washed with water, ethanol and ether. After one recrystallization from nitrobenzene, the crystals had m. p. 260° (decomp.) and proved to be identical (superimposable IR spectrum, mixed m. p.) with succinaldehyde bis (2,4-dinitrophenylhydrazone) (m. p. 280°<sup>12</sup>), prepared in the standard way. Yield: 54%. The evaporation of the reaction mixture left 220 mg. of a solid which was recrystallized twice from acetone—petroleum—ether: m. p. 192—194°. It was identified as *N'*-acetyl-*N*-(2,4-dinitrophenyl)-hydrazine; (m. p. 193—194°<sup>13</sup>); yield 31%.

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IZVOD

**Dobivanje dihidropiridazina iz sukcin aldehida bis (dietil acetala) i fenilhidrazina**

*D. Desaty, O. Hadžija i D. Keglević*

Sukcin aldehid bis (dietil acetal) ciklizira sa fenilhidrazinima u 25% octenoj kiselini u dihidropiridazine I—IV. Struktura spojeva I—IV utvrđena je na temelju njihovih spektralnih i kemijskih svojstava. Proučavani su uvjeti pod kojima dolazi do stvaranja 1-*N*-aril-dihidropiridazina.

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