

## A Reinvestigation of the Structures of the Condensation Products of Phenylhydrazine and Succinaldehyde

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The acid-catalyzed condensation of *p*-bromophenylhydrazine and 2,5-dimethoxytetrahydrofuran, used as a source of succinaldehyde, has been shown to give a reaction product, which by column chromatography was separated in two crystalline compounds. Their structures have been analyzed by single crystal X-ray diffraction methods and have shown them to be the diastereomeric racemates (4*aRS*,4*bSR*,13*bRS*)-12-bromo-1-(4'-bromophenyl)-1,4*a*,4*b*,5,6,13*b*-hexahydro-4*H*-dipyridazino[1,6-*a*:4,3-*c*]quinoline and (4*aRS*,4*bRS*,13*bRS*)-12-bromo-1-(4'-bromophenyl)-1,4*a*,4*b*,5,6,13*b*-hexahydro-4*H*-dipyridazino[1,6-*a*:4,3-*c*]quinoline.

Phenylhydrazine and 2,5-dimethoxytetrahydrofuran have been shown to produce an analogous mixture of racemates.

The compounds are derivatives of the new ring system 4*H*-dipyridazino[1,6-*a*:4,3-*c*]quinoline.

The acid-catalyzed condensations of 1,4-dicarbonyl compounds and hydrazines are reported to produce mono- and bishydrazones as well as dihydropyridazines.<sup>1</sup> Succinaldehyde bis(diethylacetal) and 2,5-diethoxytetrahydrofuran, used as sources of succinaldehyde, have each been condensed with phenylhydrazine, both reactions giving a product with m.p. 184–185°C. Several authors<sup>2-4</sup> postulate that this is 1-phenyl-1,4-dihydropyridazine, C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>. A reaction product with the same melting point has been prepared by Ciamician and Zanetti<sup>5</sup> by elimination of one phenylhydrazine moiety during acid treatment of succinaldehyde bis(phenylhydrazone). These authors, however, proposed that it was a "double molecule of a pyridazine derivative" with the formula C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>. This proposal was based on chemical investigations, as well as on a cryoscopic determination of the molecular weight.

These discrepancies, and the additional fact that, for example, 1-phenyl-3-methyl-pyridazone-(6) is transformed upon reduction into a material with the formula C<sub>22</sub>H<sub>24</sub>H<sub>4</sub>, m.p. 200°C,<sup>6</sup> which is proposed by Ciamician and Zanetti to be a higher homologue of the above mentioned double molecule, led us to reinvestigate the molecular structure of the substance with m.p. 184–185°C, using both spectroscopic methods and X-ray diffraction methods.

The material to be studied was synthesized by an improved method, using phenylhydrazine, 2,5-dimethoxytetrahydrofuran and boron trifluoride etherate. TLC of the condensation product showed two spots. The corresponding compounds were separated by column chromatography to give I: m.p. 184–185.5°C, and II: m.p. 179–181°C. The microanalyses of I and II were consistent with the formula  $(C_5H_5N)_n$ , and the mass spectra of I and II both suggested an ion of  $m/e=316$ , leading, therefore, to the formula  $C_{20}H_{20}N_4$ , as proposed by Ciamician and Zanetti.<sup>5</sup>

TLC of the reaction product prepared as described by Ciamician and Zanetti also shows two spots, with  $R_F$ -values identical to those of I and II. Furthermore, the IR-spectrum of this substance is identical with that of a mixture of I and II. This clearly indicates that the reaction product prepared from 2,5-dimethoxytetrahydrofuran and that described by Ciamician and Zanetti each consists of a mixture of I and II.

Since no conclusive evidence regarding the identity of the structures was drawn from the combined IR-,  $^1H$  NMR-, and mass spectra of I and II, X-ray methods were invoked.

The X-ray determinations were carried out on the corresponding *p*-bromo-derivatives, which were synthesized from 2,5-dimethoxytetrahydrofuran and *p*-bromophenylhydrazine. TLC of the reaction product showed two spots, and the corresponding compounds were separated by column chromatography to give III: m.p. 264–266°C (decomp.), and IV: m.p. 248–251°C (decomp.). The microanalyses in both cases were consistent with  $(C_{10}H_9BrN_2)_n$ , and the mass spectra of both III and IV suggested an ion of  $m/e=474$ , concordant with the formula  $C_{20}H_{18}Br_2N_4$ .

#### DETERMINATION OF THE STRUCTURES

The structures of the bromo-derivatives III and IV were determined from three-dimensional single crystal X-ray diffraction data. Figs. 1 and 2 show

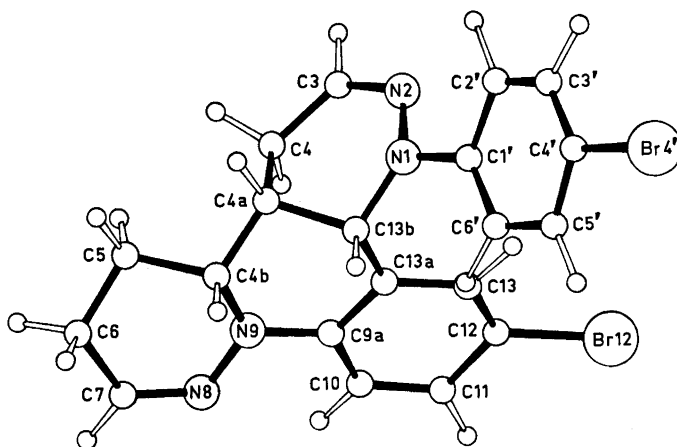


Fig. 1. The molecular structure of one of the enantiomers of the racemic compound III.

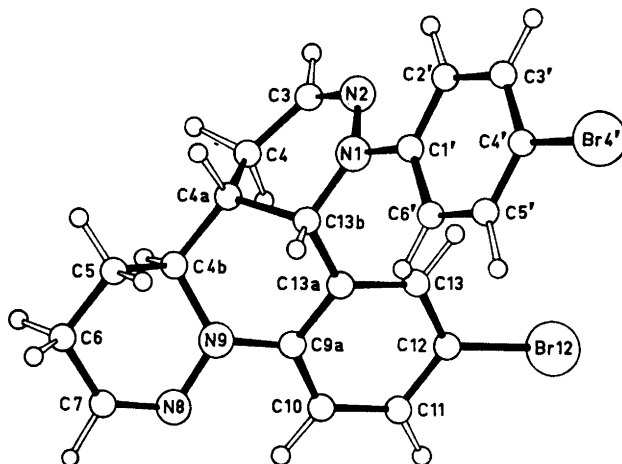


Fig. 2. The molecular structure of one of the enantiomers of the racemic compound IV.

the molecular structures of III and IV, deduced from the final positional parameters of the analyses.

Both compounds are derivatives of a new heterocyclic ring system, 4*H*-dipyridazino[1,6-*a*:4,3-*c*]quinoline.

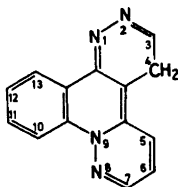


Fig. 3. 4*H*-Dipyridazino[1,6-*a*:4,3-*c*]quinoline.

They have three centers of chirality, at C(4*b*), C(4*a*) and C(13*b*), respectively, and differ only in the chirality at C(4*b*). Hence the compounds are diastereomers, the crystals of each having been produced as racemates. In some cases (freshly prepared charges), each of the enantiomers was found to crystallize separately. A crystal structure determination of one of the enantiomers of III has been carried out; its molecular structure agrees with that found in the corresponding racemic compound. A detailed account of the crystallographic work will be published elsewhere.<sup>7</sup>

After the structures had been elucidated from the X-ray analyses, it was possible to make the following structural assignments of the signals in the <sup>1</sup>H NMR-spectra of compounds I–IV (Table 1).

The mass spectra of I and II show degradation patterns, the only differences between the two being in the relative peak intensities. The spectra of III and IV show corresponding similarities.

The pattern of I with bromine superimposed is found in the spectrum of III, and a similar relationship is found between the spectra of II and IV (Table 2).

Table 1.  $^1\text{H}$  NMR-spectral data of compounds I–IV as 10 % solutions ( $\tau$ -values).

Compound Solvent	I $\text{CDCl}_3$	II $\text{CDCl}_3$	III $(\text{CD}_3)_2\text{SO}$	IV $(\text{CD}_3)_2\text{SO}$
a	2.2–3.6	2.3–3.6	2.5–3.5	2.3–3.4
b	4.7	5.1	4.5	5.0
c	5.8–6.5	6.8–7.4	5.9–6.5	6.3–6.9
d			6.5–7.2	6.9–7.3
e	6.3–8.6	7.4–8.7	7.2–8.6	7.3–8.7

a: A region of ill defined signals, attributed to the aromatic protons (I and II=9H, III and IV=7H) and two  $\begin{array}{c} \text{H} \\ \diagdown \\ \text{C}=\text{N} \end{array}$  protons.

b: A poorly resolved doublet, centered at the tabulated values assigned as due to the 13b proton.

c: A multiplet attributed to the 4b proton.

d: A multiplet attributed to the 4a proton.

e: A region of ill defined signals assigned as due to six methylene protons at C(4), C(5), and C(6) of III and IV, and to six methylene protons at C(4), C(5), and C(6), and the methine proton at C(4a) of I and II, respectively.

*Correlation of the structural evidence of the compounds I–IV.* The X-ray analyses showed the compounds III and IV to be diastereomers, which in turn were found as racemates. The interrelationship between the  $^1\text{H}$  NMR

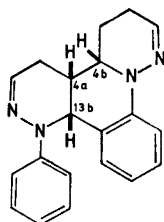


Fig. 4. The structure of one of the enantiomers of the racemic compound I.

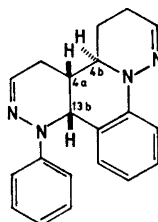


Fig. 5. The structure of one of the enantiomers of the racemic compound II.

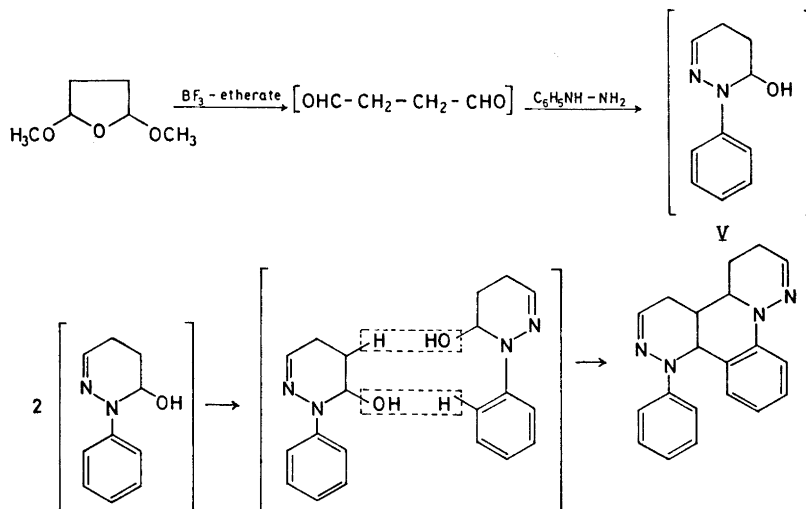
and the mass spectra, respectively, of I > < II and III > < IV clearly indicate a similar relationship between the compounds I and II. Consequently, the formulas of I and II are as follows, the only difference being the opposite chirality at C(4b).

Table 2. Mass spectral data for compounds I–IV. *m/e*-Values and intensities of peaks higher than 15 % of base peak, and a few less intense, but pertinent peaks, are stated.

I	III	II	IV
	477(13)		477(3)
	476(47)		476(13)
317(21)	475(22)	317(8)	475(7)
316(M <sup>+</sup> ,94)	474(M <sup>+</sup> ,100)	316(M <sup>+</sup> ,32)	474(26,M <sup>+</sup> )
	473(14)		473(3)
	472(50)		472(13)
	304(39)		304(16)
224(31)	302(50)	224(11)	302(18)
	289(9)		289(4)
209(8)	287(16)	209(4)	287(6)
207(8)	285(10)	207(5)	285(4)
	277(14)		277(7)
	276(72)		276(32)
197(15)	275(33)	197(8)	275(16)
196(76)	274(78)	196(32)	274(34)
195(25)	273(17)	195(13)	273(11)
	264(56)		264(24)
	263(89)		263(94)
184(38)	262(61)	184(22)	262(28)
183(100)	261(94)	183(100)	261(100)
182(14)	260(17)	182(6)	260(7)
181(13)	259(16)	181(7)	259(6)
	249(10)		249(4)
	248(15)		248(6)
169(12)	247(11)	169(5)	247(4)
168(18)	246(12)	168(10)	246(6)
	237(15)		237(5)
158(10)	236(20)	158(4)	236(8)
156(15)	234(15)	156(8)	234(7)
	209(22)		209(13)
129(38)	207(24)	129(17)	207(12)
	157(17)		157(8)
77(27)	155(14)	77(16)	155(8)
	128(20)		128(11)
	82(15)		82(3)
	80(15)		80(3)
	44(61)		44(9)
43(11)	43(22)	43(4)	43(44)
41(3)	41(26)	41(7)	41(3)

It is proposed that the ring closure takes place as shown on p. 2399.

The compounds may be formed by *intermolecular* dehydration between pairs of molecules of the intermediate V and involving a hydrogen atom from one of the phenyl groups. The intermediate V was also postulated by Desaty *et al.*<sup>4</sup>



## EXPERIMENTAL

## X-Ray crystallography

The compounds III and IV crystallize from a mixture of benzene-ethanol, 3:1, as monoclinic needles, space group  $P2_1/c$ . The unit cell dimensions, determined from series of  $\theta$ -values, are  $a = 12.20 \pm 0.03$  Å,  $b = 10.12 \pm 0.11$  Å,  $c = 16.37 \pm 0.02$  Å,  $\beta = 110.40 \pm 0.15^\circ$  for III, and  $a = 7.430 \pm 0.004$  Å,  $b = 15.444 \pm 0.008$  Å,  $c = 15.991 \pm 0.009$  Å,  $\beta = 93.47 \pm 0.06^\circ$  for IV; in each case, there are 4 molecules in the unit cell. The three-dimensional X-ray diffraction intensity data were collected on an automatic three-circle diffractometer (ENRAF-NONIUS), using  $\text{MoK}\alpha$  radiation.

Both structures were solved by the heavy-atom method, after the bromine atomic coordinates had been deduced from the respective three-dimensional Patterson syntheses. The positions of the hydrogen atoms were found from the difference Fourier maps, calculated towards the end of the refinement process, and subsequently the contributions of these atoms were included in the calculations. The parameters of the heavier atoms were refined by the full matrix least squares method. The final conventional  $R$ -values were 0.101 and 0.086 for III and IV, respectively. The corresponding positional parameters are given in Tables 3 and 4.

## Syntheses

*1-Phenyl-1,4a,4b,5,6,13b-hexahydro-4H-dipyridazino[1,6-a:4,3-c]quinoline.* To a mixture of 6.60 g (0.050 mol) of 2,5-dimethoxytetrahydrofuran, 5.40 g (0.050 mol) of phenylhydrazine and 25 ml of ethanol were added 7.10 g (0.050 mol) of boron trifluoride etherate. The mixture was refluxed for 10 min, cooled to room temperature, and poured into 150 ml of water. The crystals which resulted were filtered, washed twice with water, and once with ethanol. The yield of crude material was 7.27 g (92%). 500 mg of crude product were recrystallized from ethyl acetate to give 300 mg of almost colourless product, m.p.  $183 - 185^\circ\text{C}$  (Ref. 5,  $184 - 185^\circ\text{C}$ ). TLC on silica gel-GF<sub>254</sub> (Merck), using benzene as the developing solvent, in an unsaturated chamber showed two spots when made visible under short wave UV-light or with iodine vapour. (Found after drying at room temperature/2mm: C 75.6; H 6.7; N 17.7. Calc. for  $\text{C}_{20}\text{H}_{20}\text{N}_4$ : C 75.9; H 6.4; N 17.9.)

1500 mg of crude product were chromatographed on a column of 150 g of silica gel (0.05–0.20 mm (Merck)) activated at 120°C, and impregnated with 10 % of water. Benzene, to which gradually increasing amounts of chloroform were added until pure chloroform was reached, was used as eluent. The following fractions were obtained:

a. 300 mg of crude I, which were recrystallized from ethyl acetate, to give 200 mg of colourless crystals, m.p. 184–185.5°C. (Found after drying at room temperature/2 mm: C 76.10; H 6.40; N 17.80. Calc. for  $C_{20}H_{20}N_4$ : C 75.92; H 6.37; N 17.71.)

b. 300 mg of crude II, which were recrystallized from ethyl acetate to give 200 mg of colourless crystals, m.p. 179–181°C. (Found after drying at room temperature/2 mm: C 75.90; H 6.44; N 17.65. Calc. for  $C_{20}H_{20}N_4$ : see above.)

Table 3. Final positional parameters of atoms of III, expressed as fractions of the unit cell edges. Standard deviations times  $10^4$  in parentheses.

Atom	<i>x</i>	<i>y</i>	<i>z</i>
Br(12)	1.3936 (2)	0.1058 (2)	0.4354 (2)
Br(4')	1.5664 (2)	0.8316 (2)	0.2808 (2)
N(1)	1.1272 (14)	0.5060 (15)	0.2417 (11)
N(2)	1.0840 (16)	0.4306 (15)	0.1675 (12)
N(8)	0.8863 (14)	0.3507 (16)	0.4576 (9)
N(9)	0.9393 (11)	0.3891 (15)	0.4006 (8)
C(3)	0.9750 (17)	0.3786 (18)	0.1501 (12)
C(4)	0.9063 (17)	0.3931 (20)	0.2076 (13)
C(4a)	0.9459 (16)	0.5047 (19)	0.2718 (13)
C(4b)	0.9026 (16)	0.5067 (19)	0.3454 (13)
C(5)	0.7673 (18)	0.5183 (21)	0.3130 (14)
C(6)	0.7279 (16)	0.5119 (20)	0.3891 (13)
C(7)	0.7906 (19)	0.4136 (21)	0.4547 (15)
C(9a)	1.0448 (16)	0.3255 (21)	0.4092 (12)
C(10)	1.0763 (16)	0.2112 (19)	0.4595 (13)
C(11)	1.1815 (18)	0.1514 (21)	0.4721 (14)
C(12)	1.2507 (16)	0.1970 (19)	0.4207 (12)
C(13)	1.2199 (15)	0.3073 (18)	0.3739 (12)
C(13a)	1.1151 (15)	0.3747 (17)	0.3636 (11)
C(13b)	1.0856 (15)	0.5009 (18)	0.3125 (12)
C(1')	1.2404 (15)	0.5741 (17)	0.2553 (13)
C(2')	1.2574 (16)	0.6046 (19)	0.1786 (12)
C(3')	1.3518 (16)	0.6786 (19)	0.1905 (12)
C(4')	1.4235 (17)	0.7217 (19)	0.2658 (14)
C(5')	1.4163 (18)	0.6903 (20)	0.3427 (14)
C(6')	1.3146 (17)	0.6166 (20)	0.3324 (13)

12-Bromo-1-(4'-bromophenyl)-1,4a,4b,5,6,13b-hexahydro-4H-dipyridazino[1,6-a:4,3-c]quinoline. 1.32 g (0.01 mol) of 2,5-dimethoxytetrahydrofuran were added to a solution of 2.24 g (0.01 mol) of *p*-bromophenylhydrazine hydrochloride in 50 ml of ethanol. The mixture was refluxed for 1 min and cooled to  $-25^\circ\text{C}$ .

The resulting crystals were filtered, washed once with ethanol, and dried to give 1.40 g (60 %) of crude material.

1.20 g of crude product were recrystallized from ethyl acetate, to give 0.70 g of colourless crystals, m.p. 241–242°C (decomp.). (Found after drying at room temperature/2mm: C 50.63; H 3.89; Br 33.38; N 11.60. Calc. for  $C_{20}H_{18}Br_2N_4$ : C 50.65; H 3.83; Br 33.70; N 11.82.)

Thin-layer chromatography under the same conditions as above showed two spots.

500 mg of product were column chromatographed on 50 g of silica gel (0.05–0.20 mm (Merck)), treated as described above. Benzene eluent yielded the following fractions:

a. 200 mg of crude III, which were recrystallized from acetone-methylene chloride, to give crystals with m.p. 264–266°C (decomp.). (Found after drying at room temperature/2mm: C 50.72; H 3.86; Br 33.88; N 11.81. Calc. for  $C_{20}H_{18}Br_2N_4$ : C 50.65; H 3.83; Br 33.70; N 11.82.)

b. 200 mg of crude IV, which were recrystallized from acetone-chloroform, to give crystals with m.p. 248–251°C (decomp.). (Found after drying at room temperature/2mm: C 50.42; H 3.87; Br 33.51; N 11.65. Calc. for  $C_{20}H_{18}Br_2N_4$ : see above.)

The melting points are corrected ( $\pm 0.5^\circ\text{C}$ ) and were determined with a hot stage microscope (Mikroskop-Heiztisch Ernst Leitz G.m.b.H., Wetzlar).

The IR-spectra were recorded in potassium bromide discs on a Perkin-Elmer spectrophotometer, Model 125.

The  $^1\text{H}$  NMR-spectra were recorded on a JEOL JNM-C 60HL instrument, operating at a fixed frequency of 60 MHz and using tetramethylsilane as internal standard.

The mass spectra were measured on an AEJ MS 902 mass spectrometer (direct inlet) at 70 eV; ion source temperature 200°C; ionization current 100  $\mu\text{A}$ .

Microanalyses were performed by Preben Hansen, Microanalytical Laboratory, University of Copenhagen.

Table 4. Final positional parameters of atoms of IV, expressed as fractions of the unit cell edges. Standard deviations times  $10^4$  in parentheses.

Atom	x	y	z
Br(12)	0.2787 (2)	1.2651 (1)	0.3383 (1)
Br(4')	–0.6357 (2)	1.1472 (1)	0.0869 (1)
N(1)	0.0297 (15)	0.9527 (8)	0.2216 (8)
N(2)	0.1626 (18)	0.9432 (8)	0.1647 (7)
N(8)	0.2118 (16)	0.8878 (9)	0.5513 (9)
N(9)	0.1869 (14)	0.9016 (8)	0.4662 (9)
C(3)	0.3139 (23)	0.9054 (11)	0.1931 (10)
C(4)	0.3547 (20)	0.8685 (9)	0.2743 (9)
C(4a)	0.1788 (18)	0.8519 (9)	0.3192 (9)
C(4b)	0.2134 (19)	0.8273 (9)	0.4093 (10)
C(5)	0.0833 (22)	0.7549 (12)	0.4369 (11)
C(6)	0.1280 (23)	0.7330 (12)	0.5252 (11)
C(7)	0.1835 (25)	0.8086 (14)	0.5756 (12)
C(9a)	0.2138 (17)	0.9856 (9)	0.4405 (8)
C(10)	0.2893 (20)	1.0486 (10)	0.4923 (9)
C(11)	0.3105 (19)	1.1314 (10)	0.4633 (10)
C(12)	0.2521 (19)	1.1512 (10)	0.3787 (9)
C(13)	0.1769 (19)	1.0870 (9)	0.3276 (9)
C(13a)	0.1588 (17)	1.0055 (8)	0.3599 (8)
C(13b)	0.0665 (19)	0.9350 (9)	0.3080 (9)
C(1')	–0.1252 (20)	0.9965 (9)	0.1890 (9)
C(2')	–0.1644 (21)	1.0000 (10)	0.1031 (10)
C(3')	–0.3191 (20)	1.0454 (10)	0.0723 (9)
C(4')	–0.4234 (20)	1.0863 (9)	0.1286 (10)
C(5')	–0.3911 (20)	1.0804 (10)	0.2133 (10)
C(6')	–0.2370 (20)	1.0375 (10)	0.2434 (9)

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