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Original Scientific Paper

Syntheses in the Pyridazine Series. XXXII. Some Investigations on Polynuclear Systems Containing a Pyridazine Ring*

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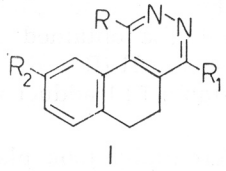
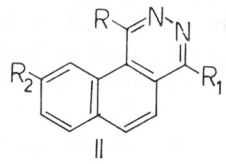
Some 5,6-dihydrobenzo[*f*]phthalazines have been aromatized to II and the structures of a number of nitro derivatives prepared from several polynuclear systems (III, IV, V), have been established.

Polynuclear systems developed from 5,6-dihydrobenzo[*f*]-phthalazine have been the subject of our previous investigations.[1,2] Our main aim in undertaking the present work was to prepare the fully aromatic benzo[*f*]phthalazines and to investigate electrophilic substitutions on their 5,6-dihydro analogs (I) and the helicene (III, IV) and steroid types (V) of related polycycles.



I



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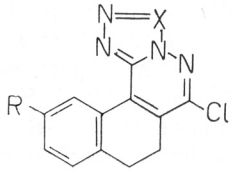
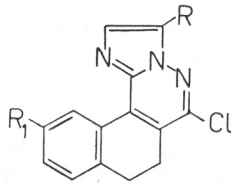
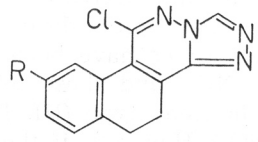


III



IV



V

Aromatization of the dihydroxy compound I ($R = R_1 = OH$, $R_2 = H$)** could be smoothly accomplished with equimolar quantities of bromine in

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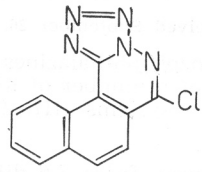
** This and related compounds are for the sake of simplicity written in the enolized »hydroxyl« form, although one of these »hydroxyl« groups is probably in the oxo form by analogy with the related simple pyridazines. (see Ref. 3).

glacial acetic acid to afford II ($R = R_1 = OH$, $R_2 = H$). In a similar experiment with the dichloro analog (I, $R = R_1 = Cl$, $R_2 = H$) besides the generation of the double bond, hydrolytic replacement of the chlorine by a hydroxy group also took place. We have established previously[1] that halogen at position 1 in this tricyclic system is more reactive and that it is preferentially replaced in nucleophilic substitutions. In the present case, however, the lability of the chlorine atom is further increased by acid catalysis and/or by a hydrogen-bonded transition state, involving acetic acid. On the other hand, the hydroxy-chloro compound (I, $R = OH$, $R_1 = Cl$, $R_2 = H$) or the parent heterocycle (I, $R = R_1 = R_2 = H$) as well as the tetracyclic compound (III, $X = N$, $R = H$) were again normally dehydrogenated to II ($R = OH$, $R_1 = Cl$, $R_2 = H$, or $R = R_1 = R_2 = H$) or VI, respectively.



VI

Replacement of a hydroxyl function with a chlorine atom by means of phosphorus oxychloride in the presence of *N,N*-dimethylaniline could be accomplished in the aromatic and dihydro-series (I or II, $R = R_1 = Cl$, $R_2 = H$) without affecting the reduced 5,6-bond in the last case. The parent 14-π electron heterocycle (II, $R = R_1 = R_2 = H$) could be obtained in good yield by catalytic dehalogenation of both chlorine atoms in II ($R = R_1 = Cl$, $R_2 = H$). It forms stable salts with mineral acids and a stable 1 : 1 adduct with bromine, most likely of the n-type[4].

Since with bromine dehydrogenation preferentially took place, as shown above, nitration has been tried in order to establish the susceptibility for and pattern of electrophilic substitutions in the investigated heterocycles. So far, no such reactions have been studied with the related benzo[*f*]-isoquinolines or benzo[*h*]isoquinolines which would allow prediction to be made for benzo[*f*]phthalazines. 5,6-Dihydrobenzo[f]phthalazine was nitrated and only a mononitro derivative, which was shown by analysis and NMR spectroscopy to be the 9-nitro derivative (I, $R = R_1 = H$, $R_2 = NO_2$), was isolated. Similar substitutions have been observed on the 1,4-dichloro analog (I, $R = R_1 = Cl$, $R_2 = NO_2$) and those tetracyclic compounds with a condensed azole ring of the helicene type (III, $R = NO_2$, $X = CH$ or N) or the steroid type (V, $R = = NO_2$). However, if the condensed ring is an imidazole, a second nitro group enters this ring (IV, $R = R_1 = NO_2$) which is not surprising in view of the recently established reactivity of the imidazole part of imidazo(1,2-*b*)pyridazines toward electrophilic substitutions[5,6]. In no case was dehydrogenation of the $—CH_2—CH_2—$ grouping observed. These results are understandable if we consider the dihydrobenzo[*f*]phthalazine system as an ortho substituted benzene. Thus, the pattern of orientation is a consequence of the composite effects of an *o,p*-directing alkyl group and a *m*-directing π-deficient pyridazine ring.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are corrected. NMR measurements were made with a JEOL JNM—C—6OHL spectrometer using tetramethylsilane as internal standard.

Naphthalene-1,2-dicarboxylic acid anhydride was prepared from the corresponding 3,4-dihydro compound by sulfur dehydrogenation according to the procedure of Fieser and Hershberg.[7]

1,4-Dihydroxybenzo[f]*phthalazine* (II, R = R_1 = OH, R_2 = H)

a) A solution of naphthalene-1,2-dicarboxylic acid anhydride (1.98 g.) in glacial acetic acid (10 ml.) was treated with hydrazine hydrate (1 ml. of 80%) and the mixture was heated under reflux for 30 min. Upon cooling the separated crystals were filtered off, washed with water and crystallized from a large amount of glacial acetic acid (yield 88%). M. p. 333—334°.

Anal. $C_{12}H_8N_2O_2$ (212.20) calc'd.: C 67.92; H 3.80; N 13.20%
found: C 68.06; H 4.18; N 13.33%

b) A mixture of I (R = R_1 = OH, R_2 = H; 1.12 g.), glacial acetic acid (10 ml.) and anhydrous sodium acetate (0.82 g.) was heated to boiling and a solution of bromine in glacial acetic acid (2 g. in 5 ml.) was added. The mixture was heated under reflux for 2 hrs. and the separated product was recrystallized for analysis from a large quantity of glacial acetic acid. The yield was almost quantitative, m. p. 331—333°. The compound was found to be identical with the product as prepared under *a*).

4-Chloro-1-hydroxy-5,6-dihydrobenzo[f]*phthalazine* (I, R = OH, R_1 = Cl, R_2 = H)

1,4-Dichloro-5,6-dihydrobenzo*[f]*phthalazine[1,8] (1.25 g.) was heated with glacial acetic acid (8 ml.) under reflux for 2 hrs. To the cooled reaction mixture water (8 ml.) was added and the separated product was recrystallized from glacial acetic acid (84% yield). M. p. 283—284°.

Anal. $C_{12}H_9ClN_2O$ (232.67) calc'd.: C 61.95; H 3.90; N 12.04%
found: C 62.00; H 3.98; N 11.87%

4-Chloro-1-hydroxybenzo[f]*phthalazine* (II, R = OH, R_1 = Cl, R_2 = H)

a) 1,4-Dichloro-5,6-dihydrobenzo*[f]*phthalazine[1] (1.5 g.) was dissolved in warm glacial acetic acid (6 ml.) and the solution was treated with bromine (1 g.) and sodium acetate (1 g.). Thereafter, the reaction mixture was heated under reflux until the product separated (about 30 min.); upon dilution with water (5 ml.) the product which separated was recrystallized from glacial acetic acid (yield 88%). M. p. 273—276°. NMR spectrum in $(CD_3)_2SO$: τ = 1.46 (doublet, H_5), 2.21 (doublet, H_6), 2.05 (multiplet, $H_7H_8H_9$), — 0.12 (multiplet, H_{10}); $J_{5,6}$ = 9.0.

Anal. $C_{12}H_7ClN_2O$ (230.65) calc'd.: C 62.48; H 3.06; N 12.14%
found: C 62.30; H 3.24; N 12.22%

b) A mixture of I (R = OH, R_1 = Cl, R_2 = H) (1.16 g.), glacial acetic acid (10 ml.), anhydrous sodium acetate (0.82 g.) and bromine (2.0 g.) was heated under reflux for 30 min. The separated product, after recrystallization from glacial acetic acid melted at 273—274° and was found to be identical with the product obtained as under *a*).

1,4-Dichloro-5,6-dihydrobenzo[f]*phthalazine* (I, R = R_1 = Cl, R_2 = H)

Compound I (R = OH, R_1 = Cl, R_2 = H) (0.5 g.) was heated with phosphorus oxychloride (5 ml.) and *N,N*-dimethylaniline (0.5 ml.) under reflux until a solution was obtained (approx. 30 min.). Excess phosphorus oxychloride was distilled off *in vacuo* and the residue was poured onto crushed ice (10 g.). The crude product (76% yield) was recrystallized for analysis from ethanol, m. p. 124—125°. The compound is identical with the previously prepared product[1,8].

1,4-Dichlorobenzo[f]*phthalazine* (II, R = R_1 = Cl, R_2 = H)

a) Compound II (R = R_1 = OH, R_2 = H) (2.12 g.), phosphorus oxychloride (21 ml.) and *N,N*-dimethylaniline (2.1 ml.) were heated under reflux for 1 hr., excess phosphorus oxychloride was distilled off, and the residue poured onto crushed ice (40 g.) under stirring. The separated product was filtered off and washed with iced water (yield almost quantitative). The compound was purified by recrystallization from ethanol, m. p. 155—156°. NMR spectrum ($CDCl_3$): τ = 2.10 (multiplet, H_5—H_9), 0.43 (multiplet, H_{10}).

Anal. $C_{12}H_6Cl_2N_2$ (249.10) calc'd: C 57.85; H 2.43; N 11.25%
found: C 58.11; H 2.68; N 11.36%

b) The same procedure as above was applied to compound II (R = OH, R_1 = Cl, R_2 = H) which was transformed in 81% yield. M. p. 155—156° and mixed m. p. undepressed with a specimen obtained as described under *a*).

Benzo[f]*phthalazine* (II, R = R_1 = R_2 = H)

a) To a solution of II (R = R_1 = Cl, R_2 = H) (2.49 g.) in methanol (100 ml.) palladized charcoal (0.8 g. of 5%) and conc. ammonia (3 ml.) were added. The mixture was stirred in an atmosphere of hydrogen at room temperature until absorption of the necessary hydrogen (about 450 ml) was complete. After filtration, the solution was evaporated to dryness *in vacuo* and the residue was treated with water (10 ml.) and filtered. Recrystallization was effected from a mixture of benzene and *n*-hexane (1 : 1) (yield 82%), m. p. 123—124°; NMR spectrum in $CDCl_3$: τ = — 0.5 (singlet, H_1), 0.42 (singlet, H_4), 1.84 (doublet, H_5), 2.27 (doublet, H_6), 2.12 (multiplet, H_7—H_9), 1.22 (multiplet, H_{10}); $J_{5,6}$ = 9.0.

Anal. $C_{12}H_8N_2$ (180.20) calc'd.: C 79.98; H 4.48; N 15.55%
found: C 80.18; H 4.76; N 15.36%

The compound formed a hydrobromide, m. p. 251—253° (from ethanol).

Anal. $C_{12}H_9BrN_2$ (261.12) calc'd.: C 55.19; H 3.47; N 10.73%
found: C 55.28; H 3.63; N 10.59%

The corresponding hydrochloride melted at 224—226° (from ethanol) and the corresponding hydrogen sulfate had m. p. 219—220° (from ethanol).

Anal. $C_{12}H_{10}N_2O_4S$ (278.29) calc'd.: C 51.80; H 3.62; N 10.07; S 11.50%
found: C 52.08; H 3.91; N 10.21; S 11.81%

The heterocycle when dissolved in glacial acetic acid and treated with one equivalent of bromine at room temperature, formed a complex with bromine and this was crystallized from glacial acetic acid. It decomposed upon heating over 180°.

Anal. $C_{12}H_8Br_2N_2$ (340.04) calc'd.: C 42.39; H 2.37; N 8.23%
found: C 42.56; H 2.47; N 8.41%

Heating this complex in ethanol regenerated the starting heterocycle.

b) To a warm solution of the oily 5,6-dihydrobenzo[f]phthalazine[1] (2.0 g.) in glacial acetic acid (4 ml.) bromine (3.5 g.) and sodium acetate (0.9 g.) were added. The reaction mixture was heated under reflux for 45 min., water (3 ml.) was added and the separated product was filtered off. Recrystallization was accomplished from glacial acetic acid (75% yield), m. p. 214—216°. The product was analyzed for a bromine complex of the benzo*[f]*phthalazine hydrobromide.

Anal. $C_{12}H_8N_2 \cdot HBr \cdot 1/2Br_2$ (341.04) calc'd.: C 42.26; H 2.66; N 8.21%
found: C 42.32; H 3.01; N 8.01%

When this product (0.345 g.) was dissolved in ethanol and the solution heated under reflux for 30 min., charcoaled and filtered, a product separated from the filtrate, which had m. p. 251—253° and which was found to be identical in all respects with benzo*[f]*phthalazine hydrobromide.

This hydrobromide (0.28 g.) was dissolved in ethanol, sodium bicarbonate (1 g.) was added and the mixture was boiled for 5 min. The cooled mixture was filtered and the ehanolic solution evaporated *in vacuo* to dryness. The residue was treated with water (20 ml.) and extracted three times with chloroform (30 ml.). The dried extracts were evaporated to dryness and the residue was recrystallized from chloroform and *n*-hexane (1 : 1). The pure compound melted at 122—123° and was found in all respects to be identical with benzo*[f]*phthalazine obtained as described under *a*).

6-Chlorobenzo[h]*tetrazolo*[5,1-a]*phthalazine* (VI)

A hot solution of 6-chloro-7,8-dihydrobenzo*[h]*tetrazolo[5,1-*a*]phthalazine[1] (0.9 g.) in glacial acetic acid (15 ml.) was treated with bromine (0.6 g.) and sodium acetate (0.63 g.) and heated under reflux for 30 min. To the cold reaction mixture water (10 ml.) was added, the precipitate was filtered off and was recrystallized from glacial acetic acid (yield 62%), m. p. 279—280°. NMR spectrum in $(CD_3)_2SO$: $\tau = 1.37$ (multiplet, H_7—H_{11}), — 0.16 (multiplet, H_{12}).

Anal. $C_{12}H_6ClN_5$ (255.67) calc'd.: C 56.37; H 2.36; N 27.39%
found: C 56.35; H 2.51; N 27.85%

9-Nitro-5,6-dihydrobenzo[f]*phthalazine* (I, R = R_1 = H, R_2 = NO_2)

To stirred concentrated sulfuric acid (2 ml.) 5,6-dihydrobenzo*[f]*phthalazine (0.9 g.) was added and after the mixture was cooled to — 10°, concentrated nitric acid (0.5 ml. of 65%) was added dropwise in such a manner that the temperature did not exceed 0°. After addition was complete the mixture was allowed to warm up to room temperature and at this temperature was then stirred for a further 20 min. The mixture was poured onto crushed ice (30 g.) and neutralized with sodium bicarbonate. The crude product was filtered off and crystallized from methanol (yield 0.76 g., 68%), m. p. 210°. NMR spectrum in $CDCl_3$: $\tau = 0.41$ (singlet, H_1), 0.83 (singlet, H_4), 6.92 (multiplet, H_5, H_6), 2.25 (doublet, H_7), 1.60 (doublet of doublets, H_8), 1.20 (doublet, H_{10}); $J_{7,8} = 9.0$, $J_{8,10} = 2.2$ cps.

Anal. $C_{12}H_9N_3O_2$ (227.22) calc'd.: C 63.43; H 3.99; N 18.49%
found: C 63.14; H 4.24; N 18.25%

In essentially the same way the following nitro compounds were prepared:

1,4-Dichloro-9-nitro-5,6-dihidrobenzo[f]*phthalazine* (I, R = R_1 = Cl, R_2 = NO_2)

The compound was prepared from 1,4-dichloro-5,6-dihydrobenzo*[f]*phthalazine (1.25 g.) in almost quantitative yield. M. p. 256° (from *N,N*-dimethylformamide). NMR spectrum in *N,N*-dimethylformamide-d_7: $\tau = 6.86$ (multiplet, H_5, H_6); 2.41 (doublet, H_7), 1.65 (doublet of doublets, H_8), 0.88 (doublet, H_{10}); $J_{7,8} = 8.25$, $J_{8,10} = 2.2$ cps.

Anal. $C_{12}H_7Cl_2N_3O_2$ (296.11) calc'd.: C 48.67; H 2.38; N 14.19%
found: C 48.41; H 2.61; N 14.45%

6-Chloro-3,11-dinitro-7,8-dihydrobenz[h]*imidazo*[*2,1*-a]*phthalazine*
(IV, R = R_1 = NO_2)

As starting compound 6-chloro-7,8-dihydrobenzo*[h]*imidazo-[2,1-*a*]phthalazine[1] (0.8 g.) was used. The product had m. p. 247° (from *N,N*-dimethylformamide).

Anal. $C_{14}H_8ClN_5O_4$ (345.70) calc'd.: C 48.64; H 2.33; N 20.26%
found: C 48.96; H 2.61; N 20.21%

6-Chloro-11-nitro-7,8-dihydrobenzo[h]-s-*triazolo*[*3,4*-a]*phthalazine*
(III, X = CH, R = NO_2)

The compound was obtained from 6-chloro-7,8-dihydrobenzo[*h*]-*s*-triazolo-[3,4--*a*]phthalazine[1] (0.2 g.) and had m. p. 247—249° (from ethanol). NMR spectrum in D_2SO_4: τ = — 0.50 (singlet, H_3), 6.22 (multiplet, H_7, H_8), 1.83 (doublet, H_9), 1.0 (doublet of doublets, H_{10}), 0.02 (doublet, H_{12}); $J_{9,10} = 8.9$, $J_{10,12} = 2.2$ cps.

Anal. $C_{13}H_8ClN_5O_2$ (301.69) calc'd.: C 51.76; H 2.67; N 23.21%
found: C 51.95; H 2.88; N 22.90%

6-Chloro-11-nitro-7,8-dihydrobenzo[h]*tetrazolo*[*5,1*-a]*phthalazine* (III, X = N, R = NO_2)

The compound was prepared from 6-chloro-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine[1] (1.3 g.), m. p. 267—268° (from *N,N*-dimethylformamide).

Anal. $C_{12}H_7ClN_6O_2$ (302.68) calc'd.: C 47.61; H 2.33; N 27.77%
found: C 48.09; H 2.58; N 28.04%

10-Chloro-8-nitro-4,5-dihydrobenzo[f]-s-*triazolo*[*3,4*-a]*phthalazine* (V, R = NO_2)

The starting compound was 10-chloro-4,5-dihydrobenzo*[f]*-s-triazolo[3,4-*a*]phthalazine (0.64 g.)[1]. The product melted at 265—267° (from *N,N*-dimethylformamide and ethanol).

Anal. $C_{13}H_8ClN_5O_2$ (301.69) calc'd.: C 51.76; H 2.67; N 23.21%
found: C 52.01; H 2.94; N 23.39%

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REFERENCES

1. B. Stanovnik, M. Tišler and P. Škufca, *J. Org. Chem.* **33** (1968) 2910.
2. B. Stanovnik and M. Tišler, *Chimia* **22** (1968) 141.
3. M. Tišler and B. Stanovnik in A. R. Katritzky and A. J. Boulton, Editors, *Advances in Heterocyclic Chemistry*, Vol. **9**, Academic Press, New York, London, 1968, p. 211.
4. J. J. Eisch in A. R. Katritzky and A. J. Boulton, Editors, *Advances in Heterocyclic Chemistry, Vol.* **7**, Academic Press, New York, London, 1966, p. 1.
5. J. Kobe, B. Stanovnik and M. Tišler, *Tetrahedron* **24** (1968) 239.
6. B. Stanovnik and M. Tišler, *Croat. Chem. Acta* **40** (1968) 1.
7. L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.* **57** (1935) 1851.
8. J. Dreiseitel and A. Kocwa, *Dissertationes Pharm.* **11** (1959) 157; *Chem. Abstr.* **54** (1960) 4593.

IZVLEČEK

Sinteze piridazinovih derivatov. XXXII. Raziskave nekaterih policikličnih sistemov s piridazinovim obročem

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Opisane so aromatizacije nekaterih 5,6-dihidrobenzo*[f]*ftalazinov in ugotovljena je bila struktura nitro derivatov nekaterih policikličnih sistemov (III, IV, V).

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