Synthesis of Pyridazine Derivatives. XX. Orientational Effects in Some New Polynuclear Systems Containing a Pyridazine Ring[1]

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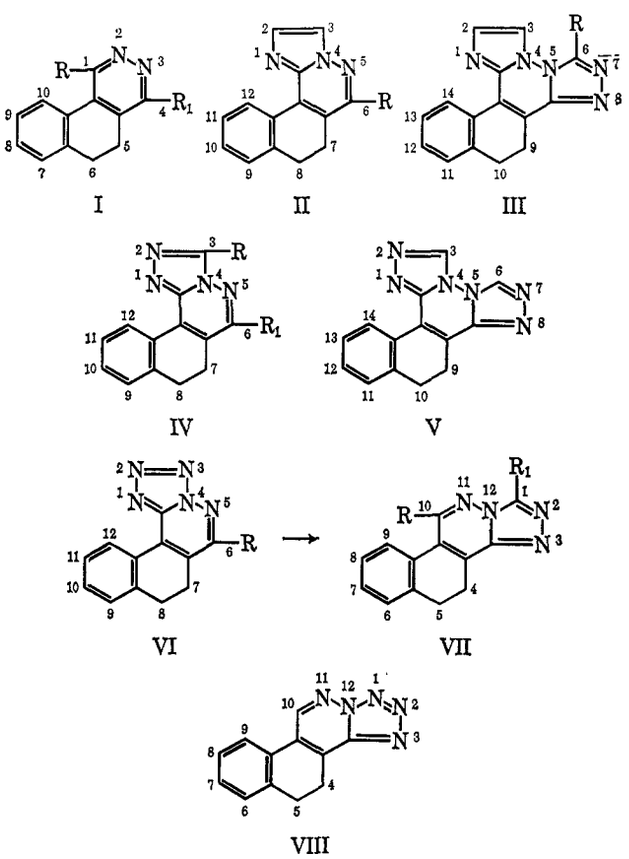
Starting from 5,6-dihydrobenzo[*f*]phthalazines (I) several new polyazaheterocyclic systems (II–VIII) were prepared and their structures were determined. Azidoazomethine–tetrazole equilibrium has been used for selective orientation of some fused rings. Thus, in VI (R = N_3) only one tetrazole ring is present, the other being transformed in an azido group. However, if a new condensed hetero ring has been formed by transforming VI in VII, the originally present tetrazole ring spontaneously assumes the azido form. We could now present evidence that also a fused triazolo ring can efficiently destabilize the adjacent tetrazole ring and compel it to assume the azido form.

As an extension of our recent report on condensed polyazaheterocycles containing a pyridazine ring, fused with another heterocyclic ring,[2-7] it seemed of interest to synthesize and study the aromaticity and orientational effects on polynuclear systems, based on 5,6-dihydrobenzo[*f*]phthalazine.

In order to obtain on the starting ring system different functional groups necessary for further cyclizations, the 1,4-dichloro compound (I, R = R_1 = Cl) was submitted to nucleophilic displacement with ammonia, hydrazine, thiolate, and alkoxide ion. From available data about nucleophilic substitutions on 4-alkyl-3,6-dichloropyridazines it is known that a selective or competitive exchange of halogen atoms is possible and usually the 6-substituted 3-chloro-4-alkylpyridazine isomer prevails.[8-11] Exceptions are reactions with alkoxides and thiolate ion.[8,9,12,13] Since 1,4-dichloro-5,6-dihydrobenzo[*f*]phthalazine can be regarded as a 4-alkyl-5-aryl-3,6-dichloropyridazine and since alkyl substituents are expected to exert a moderately deactivating effect, while the aryl group a slightly activating effect, the replacement of the 1-chlorine atom would be expected to proceed preferentially. This direction of nucleophilic displacement has been indeed observed and in all cases only one isomer (I, R = NH_2, $NHNH_2$, SH or OR′, R_1 = Cl) could be isolated. The presence of a small amount of the second hydrazino isomer (I, R = Cl, R_1 = $NHNH_2$) could be established from the formation of a mixture of triazolo derivatives as discussed later. The above structure assignments have been made on the basis of nmr correlations and chemical evidence.

From the corresponding amino or hydrazino derivatives (I, R = NH_2 or $NHNH_2$, R_1 = Cl) a new fused imidazole (II), triazole (IV) or tetrazole ring (VI) could be formed in the manner, described already in earlier communications on related systems.[2-5] However, if the crude product, obtained from hydrazinolysis of I (R = R_1 = Cl), was treated in the usual way with triethyl orthoformate, two isomerict riazolo derivatives could be isolated in about 6:1 ratio, the isomer IV (R = H, R_1 = Cl) prevailing. The structure of the other isomeric triazolo compound (VII, R = Cl, R_1 = H) has been established by converting it into the corresponding hydrazino compound (VII, R = $NHNH_2$, R_1 = H) and subsequent nitrosation afforded the azide (VII, R = N_3, R_1 = H), which was identical with the product obtained from VI (R = $NHNH_2$) by reaction with diethoxymethyl acetate. The residual 6-chlorine atom in the above systems was submitted to nucleophilic displacement with different nucleophiles, thus producing compounds capable of ring closure to another five-membered azaheterocycle. In this way systems III and V were built up. However, in the case of fused tetrazole rings, azidoazomethine–tetrazole equilibrium could be expected, and therefore such systems were investigated in some detail.



(1) Paper LVII on Heterocycles.
(2) B. Stanovnik, A. Krbavčič, and M. Tišler, *J. Org. Chem.*, **32**, 1139 (1967).
(3) J. Kobe, B. Stanovnik, and M. Tišler, *Tetrahedron*, **24**, 239 (1968).
(4) B. Stanovnik and M. Tišler, *ibid.*, **23**, 2739 (1967).
(5) B. Stanovnik and M. Tišler, *ibid.*, **23**, 387 (1967).
(6) A. Pollak and M. Tišler, *ibid.*, **22**, 2073 (1966).
(7) B. Stanovnik and M. Tišler, *Tetrahedron Lett.*, 33 (1968).
(8) S. Linholter, A. B. Kristensen, R. Rosenoern, S. E. Nelsen, and H. Kaaber, *Acta Chem. Scand.*, **15**, 1660 (1961).
(9) N. Takahayashi, *Chem. Pharm. Bull.* (Tokyo), **5**, 229 (1957).
(10) S. Linholter, R. Rosenoern, and L. Vincents, *Acta Chem. Scand.*, **17**, 960 (1963).
(11) S. Linholter and R. Rosenoern, *ibid.*, **16**, 2389 (1962).
(12) K. Mori, *Yakugaku Zasshi*, **82**, 304 (1962); *Chem. Abstr.*, **58**, 3427 (1963).
(13) T. Nakagome, *ibid.*, **82**, 1005 (1962).

Azidoazomethine–tetrazole equilibrium has been investigated in several heterocyclic systems[5,14–17] and besides structural features, the equilibrium was found to be solvent and temperature dependent and influenced by the presence of other groups present in the heterocyclic ring.[15,18] In the case of present polyazaheterocycles when only one tetrazole ring was fused to the pyridazine ring, no azido form could be detected as judged from infrared spectra of compounds of type VI. However, the formation of a new fused triazolo ring from the corresponding hydrazino derivative (VI, R = $NHNH_2$) with the action of diethoxymethyl acetate or cyanogen bromide resulted in a destabilization and ring opening of the adjacent tetrazole ring, and the azido form (VII, R = N_3, R_1 = H or NH_2) is the predominant form present as judged from the intense azide band in the infrared spectrum. Nevertheless, this does not preclude the possibility that in solution the tetrazole form of this compound could also be present, as already shown in other cases.[18]

Similar observations were made also with compounds of the type VI where a ditetrazole, two isomeric azidotetrazole forms and a diazido form are theoretically possible. The same compound (VI, R = N_3) was obtained, however, by treatment of the 1,4-dichloro compound (I, R = R_1 = Cl) or chlorotetrazole VI (R = Cl) with sodium azide, or by conversion of the latter into the hydrazinotetrazole VI (R = $NHNH_2$) and subsequent nitrosation. Compound VI (R = N_3) exhibited a strong azide band in the infrared spectrum and its structure, as proposed, is assigned also on the basis of nmr correlations.

This facile tetrazole ring opening thus provided a simple way to synthesize compounds structurally related to aza steroids (VII), since the azido group is easily transformed with hydrogen sulfide to the corresponding amino derivative. An alternative possible way to obtain compounds VII (R = R_1 = H) or VIII was to remove the 1-hydrazino group in I (R = $NHNH_2$, R_1 = Cl), to replace the residual 4-chlorine atom with hydrazino group and cyclize this compound with diethoxymethyl acetate or by nitrosation, or treat the 4-chloro derivative (I, R = H, R_1 = Cl) directly with sodium azide to obtain VIII. Compounds of the type VII and VIII are representatives of polyaza steroids[19] of which those containing a pyridazine ring have been reported only recently.[20–24] They are very stable under conditions of electrophilic substitution and they are easily fully aromatized.

An examination of nmr spectra of some representatives of the above mentioned types of compound confirmed the structural assignments. Significant deshielding effect of hindered protons facing a cyclic nitrogen atom or another hindered proton in polycondensed angular aza- or thiaaromatics have been observed in several cases.[25–27] A comparison of nmr spectra of some compounds where sterical effects of substituents or fused rings with regard to the proton of the benzenoid part of the molecule can be anticipated with those of the sterically unhindered derivatives reveals a significant downfield shift of the hindered aromatic proton. The deshielding is evident from data collected in Table I. The methylene protons of the bridging $-CH_2CH_2-$ group appear as singlets (τ 6.88–7.10) except for I (R = SH, R_1 = Cl) and VII (R = R_1 = H or R = Cl, R_1 = H) where they appear as multiplets (centered at τ 7.08 and 6.73 or 6.88, respectively), typical for an AA'BB' pattern.

TABLE I

Compd	R	R_1	Proton	τ
I	H	Cl	H_{10}	2.25
I	Cl	Cl	H_{10}	1.70
I	NH_2	Cl	H_{10}	2.07
I	$NHNH_2$	Cl	H_{10}	1.53
I	OCH_3	Cl	H_{10}	1.72
II	Cl		H_{12}	0.72
IV	H	Cl	H_{12}	0.75
VII	H	H	H_9	2.22
VII	Cl	H	H_9	1.73

Experimental Section[28]

1,4-Dichloro-5,6-dihydrobenzo[*f*]phthalazine (I, R = R_1 = Cl) was prepared from 3,4-dihydro-1,2-naphthalic anhydride[29] according to the procedure of Dreiseitel and Kocwa.[30] Crystallization was conveniently performed from ligroin and benzene (1:1): mp 124–126° (lit.[30] mp 125–127°); nmr ($CDCl_3$), τ 1.70 (multiplet, H_{10}), 2.63 (multiplet, H_7, H_8, H_9), 7.10 (singlet 4 H, $-CH_2CH_2-$). The nmr spectrum was recorded at lower temperatures also and the signal for the last mentioned group becomes somewhat broadened at −92° (in CD_3COCD_3) and at −100° (in CS_2).

1-Amino-4-chloro-5,6-dihydrobenzo[*f*]phthalazine (I, R = NH_2, R_1 = Cl).—Compound I (5 g, R = R_1 = Cl) and liquid ammonia (150 ml) were placed in an autoclave and the mixture was heated at 126–130° for 5 hr. After cooling the autoclave was vented and the residue was treated with water (50 ml). The suspension was filtered and washed with water and alcohol. The crude product is pure enough for further synthetic work, but for analytical purposes it was crystallized from N,N-dimethylformamide (yield 90%): mp 245–246°; nmr (CF_3COOH), τ 2.07 (multiplet, H_{10}), 2.50 (multiplet, H_7, H_8, and H_9), 6.88 (singlet 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_{10}ClN_3$: C, 62.20; H, 4.35; N, 18.13. Found: C, 62.13; H, 4.40; N, 18.64.

4-Chloro-1-hydrazino-5,6-dihydrobenzo[*f*]phthalazine (I, R = $NHNH_2$, R_1 = Cl).—Compound I (1 g, R = R_1 = Cl), hydrazine hydrate (7 ml of 80%), and ethanol (3 ml) were heated under reflux for 1 hr, cooled, and filtered. The crude product (yield 71%) was crystallized from ethanol with the addition of char-

(14) J. H. Boyer and F. C. Canter, *Chem. Rev.*, **54**, 1 (1954).
(15) C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **31**, 2210 (1966), and references to previous papers therein.
(16) G. A. Reynolds, J. A. Van Allan, and J. F. Tinker, *ibid.*, **24**, 1205 (1959).
(17) S. Carboni, A. Da Settimo, and P. L. Ferrarini, *Gazz. Chim. Ital.*, **97**, 1061 (1967), and references to previous papers therein.
(18) C. Temple, M. C. Thorpe, W. C. Coburn, and J. A. Montgomery, *J. Org. Chem.*, **31**, 935 (1966).
(19) A review on steroid derivatives with condensed heterocycles appeared recently: A. A. Akhrem and Yu. A. Titov, *Usp. Khim.*, **36**, 745 (1967).
(20) M. Tomoeda, R. Kikuchi, and M. Urata, *Chem. Pharm. Bull.* (Tokyo), **13**, 517 (1965).
(21) M. Tomoeda and J. Yoshizawa, *Tetrahedron Lett.*, 975 (1967).
(22) K. Schubert and K. Böhme, *Chem. Ber.*, **93**, 1884 (1960).
(23) A. van der Gen, W. A. Zunnebeld, U. K. Pandit, and H. O. Huisman, *Tetrahedron*, **21**, 3651 (1965).
(24) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Amer. Chem. Soc.*, **76**, 552 (1954).
(25) R. H. Martin, N. Defay, F. Geerts-Evrard, and D. Bogaert-Verhoogen, *Tetrahedron Suppl.*, **8**, 181 (1966).
(26) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **32**, 2616 (1967).
(27) T. E. Young and C. J. Ohnmacht, *ibid.*, **32**, 1558 (1967).
(28) Melting points were taken on a Kofler micro hot stage and are corrected. Infrared spectra were determined as mulls in Nujol or hexachlorobutadiene on a Perkin-Elmer Model 21 spectrophotometer. Nmr measurements were made with a 60 Mc instrument using tetramethylsilane standard. The chemical shift values are expressed in τ values.
(29) E. B. Hershberg and L. F. Fieser, "Organic Syntheses," Coll Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., 1948, p 194.
(30) J. Dreiseitel and A. Kocwa, *Dissertationes Pharm.*, **11**, 157 (1959); *Chem. Abstr.*, **54**, 4593 (1960).

coal three times: mp 175–178°; nmr (CF_3COOH), τ 1.53 (multiplet, H_{10}), 2.50 (multiplet, H_7, H_8, and H_9), 6.88 (singlet 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_{11}ClN_4$: C, 58.42; H, 4.49; N, 22.72. Found: C, 58.71; H, 4.58; N, 22.60.

The benzylidene derivative (I, R = $NHN{=}CH_6H_5$, R_1 = Cl) had mp 231–233° (from ethanol).

Anal. Calcd for $C_{19}H_{15}ClN_4$: N, 16.76. Found: N, 17.04.

The thiosemicarbazide derivative (I, R = $C_6H_5NHCSNHNH$, R_1 = Cl) was obtained in the reaction with phenyl isothiocyanate, mp 198–200° (from ethanol).

Anal. Calcd for $C_{19}H_{16}ClN_5S$: C, 59.75; H, 5.31; N, 18.34; S, 8.40. Found: C, 60.04; H, 5.32; N, 18.68; S, 8.18.

4-Chloro-1-methoxy-5,6-dihydrobenzo[*f*]phthalazine (I, R = OCH_3, R_1 = Cl).—To a suspension of 2.51 g of I (R = R_1 = Cl) in 20 ml of absolute methanol a solution of sodium methylate, prepared from 0.23 g of sodium and 5 ml of methanol, was added. Upon heating under reflux for 15 min the reaction mixture was filtered hot, the filtrate was evaporated to one-third of its original volume and poured into 30 ml of iced water. The crude product was crystallized from ethanol to yield 1.9 g (76%): mp 145–147°; nmr ($CDCl_3$), τ 1.72 (multiplet, H_{10}), 2.70 (multiplet, H_7, H_8, and H_9), 7.17 (singlet 4 H, $-CH_2CH_2-$), 5.82 (singlet 3 H, CH_3O).

Anal. Calcd for $C_{13}H_{11}ClN_2O$: C, 63.28; H, 4.49; N, 11.36. Found: C, 63.02; H, 4.65; N, 11.39.

4-Chloro-1-ethoxy-5,6-dihydrobenzo[*f*]phthalazine (I, R = OC_2H_5, R_1 = Cl) was prepared in an analogous manner, mp 110° (from ethanol).

Anal. Calcd for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.03; N, 10.75. Found: C, 64.26; H, 5.17; N, 10.73.

1-Methoxy-5,6-dihydrobenzo[*f*]phthalazine (I, R = OCH_3, R_1 = H).—To a solution of 0.68 g of I (R = OCH_3, R_1 = Cl) in 50 ml of methanol, 3 ml of concentrated ammonia and 0.5 g of 5% palladized charcoal were added and the mixture was stirred in an atmosphere of hydrogen at room temperature until absorption of hydrogen stopped. Upon filtration, the solution was evaporated to dryness *in vacuo* and the residue was crystallized from *n*-hexane (yield 86%), mp 114–115°.

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.77; H, 5.85; N, 13.00.

Similarly, the 1-ethoxy compound (I, R = OC_2H_5, R_1 = H) was prepared in 67% yield, mp 93–94° (from *n*-hexane).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.12; H, 6.15; N, 12.45.

5,6-Dihydrobenzo[*f*]phthalazine sulfate (I, R = R_1 = H; H_2SO_4) was prepared in essentially the same way. After evaporation of the filtrate to dryness the residual oil was treated with *n*-hexane (5 ml for 1.5 g of the oil) and concentrated sulfuric acid (0.8 ml) was then added. Upon cooling on ice the sulfate was separated and was crystallized from ethanol (yield 72%), mp 200–201°.

Anal. Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.43; H, 4.32; N, 9.99; S, 11.42. Found: C, 51.33; H, 4.24; N, 9.82; S, 11.31.

4-Chloro-1-mercapto-5,6-dihydrobenzo[*f*]phthalazine (I, R = SH, R_1 = Cl).—To 0.25 g of I (R = R_1 = Cl) a freshly prepared cold ethanolic solution of KSH (0.3 g of KOH were dissolved in 15 ml of ethanol and hydrogen sulfide was introduced for 1 hr) was added. The mixture was gently heated on water bath for a short time to dissolve the starting compound. The filtered solution was treated with 15 ml of cold water and neutralized with acetic acid to pH 7. The crude product (yield 80%) was dissolved in hot aqueous solution of $NaHCO_3$ and filtered, and the filtrate was acidified upon cooling with acetic acid. The product was filtered, washed with water, and dried (yield 41%): mp 108–111°; nmr ($CDCl_3$), τ 1.75 (multiplet, H_{10}), 2.70 (multiplet, H_7, H_8, and H_9), 7.08 (multiplet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_9ClN_2S$: C, 57.94; H, 3.65; N, 11.27. Found: C, 58.23; H, 3.64; N, 11.08.

The corresponding S-methyl derivative (I, R = SCH_3, R_1 = Cl) was prepared in the usual way, using methyl iodide as alkylating agent, mp 83–85° (from methanol).

Anal. Calcd for $C_{13}H_{11}ClN_2S$: C, 59.41; H, 4.22. Found: C, 59.70; H, 4.51.

6-Chloro-7,8-dihydrobenz[*h*]imidazo[2,1-*a*]phthalazine (II, R = Cl).—To an ethanolic solution (50 ml) of bromoacetaldehyde, prepared from its dimethyl acetal (5 g) according to the procedure described in an earlier paper,[4] 5 g of I (R = NH_2, R_1 = Cl) was added and the mixture was heated under reflux for 4 hr. The cooled solution was poured into 50 ml of water and the resulting suspension was neutralized with solid $NaHCO_3$ until pH 7. After standing on ice overnight, the crude product was collected and crystallized from ethanol (yield 52%): mp 154–155°; nmr ($CDCl_3$), τ 2.28 (doublet, H_2), 2.17 (doublet, H_3), 2.66 (multiplet, H_9, H_{10}, and H_{11}), 0.72 (multiplet, H_{12}), 7.05 (singlet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{14}H_{10}ClN_3$: C, 65.75; H, 4.34; N, 16.44. Found: C, 65.98; H, 4.33; N, 16.63.

7,8-Dihydrobenz[*h*]imidazo[2,1-*a*]phthalazine (II, R = H).—A mixture of 0.25 g of II (R = Cl), 50 ml of methanol, 0.1 g of powdered KOH, and 0.5 g of 5% palladized charcoal was stirred in an atmosphere of hydrogen at room temperature until the uptake subsided. The filtered solution was evaporated to dryness at 35° (17 mm). The residue was suspended in 30 ml of water, filtered and crystallized from aqueous ethanol (1:1) (yield 48%), mp 106–108°.

Anal. Calcd for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.85; H, 5.21; N, 19.08.

6-Hydrazino-7,8-dihydrobenz[*h*]imidazo[2,1-*a*]phthalazine (II, R = $NHNH_2$).—A mixture of II (6.6 g, R = Cl), 50 ml of 80% hydrazine hydrate, and 10 ml of ethanol was heated under reflux for 5 hr. The product was purified by crystallization from ethanol (yield 40%), mp 200–202°.

Anal. Calcd for $C_{14}H_{13}N_5$: C, 66.93; H, 5.21; N, 27.87. Found: C, 66.98; H, 5.34; N, 27.72.

It forms a benzylidene derivative, mp 125–127°.

Anal. Calcd for $C_{21}H_{17}N_5$: N, 20.64. Found: N, 20.89.

The *p*-dimethylaminobenzylidene derivative had mp 117–119°

Anal. Calcd for $C_{23}H_{22}N_6$: N, 21.98. Found: N, 21.93.

6-(4′-Phenylthiosemicarbazido)-7,8-dihydrobenz[*h*]imidazo-[2,1-*a*]phthalazine (II, R = $C_6H_5NHCSNHNH$).—Compound II (0.25 g, R = $NHNH_2$) was dissolved in 15 ml of hot ethanol, 0.14 g of phenyl isothiocyanate were added, and the mixture was left aside to cool slowly to room temperature. The separated product was filtered and washed with 5 ml of hot ethanol (yield 52%), mp 196–198°.

Anal. Calcd for $C_{21}H_{18}N_6S$: C, 65.26; H, 4.70; N, 21.75. Found: C, 65.12; H, 4.70; N, 21.85.

6-Mercapto-9,10-dihydrobenz[*f*]imidazo[1,2-*c*]-*s*-triazolo[3,4-*a*]phthalazine (III, R = SH).—The above compound II (0.1 g, R = $C_6H_5NHCSNHNH$) was heated under reflux in 10 ml of 1,2-propylene glycol for 20 min. Upon cooling, 30 ml of cold water was added and, after standing on ice for some time, the product was filtered off and crystallized from ethanol (yield 80%), mp 327° dec.

Anal. Calcd for $C_{15}H_{11}N_5S$: C, 61.43; H, 3.78; N, 23.88; S, 10.91. Found: C, 61.33; H, 3.83; N, 23.76; S, 10.74.

9,10-Dihydrobenz[*f*]imidazo[1,2-*c*]-*s*-triazolo[3,4-*a*]phthalazine (III, R = H).—A mixture of 0.3 g of II (R = $NHNH_2$) and 0.5 ml of diethoxymethyl acetate was refluxed on an oil bath for 10 min, cooled, and treated with 0.5 ml of ethanol. After standing on ice for 15 min the separated product was filtered and washed with 1 ml of ethanol (yield 17%), mp 311–313°.

Anal. Calcd for $C_{15}H_{11}N_5$: C, 68.95; H, 4.24; N, 26.81. Found: C, 69.13; H, 4.56; N, 26.61.

6-Chloro-3-mercapto-7,8-dihydrobenzo[*h*]-*s*-triazolo[3,4-*a*]-phthalazine (IV, R = SH, R_1 = Cl).—Compound I (0.2 g) (R = $C_6H_5NHCSNHNH$, R_1 = Cl) and 20 ml of 1,2-propylene glycol were heated under reflux for 20 min and the reaction mixture was thereafter diluted with 50 ml of water. The crude product was collected and purified by dissolution in hot saturated aqueous $NaHCO_3$, addition of charcoal, and filtration, and the cooled filtrate was acidified with glacial acetic acid to neutral reaction to yield 42% of product, mp 129–131°. The compound is present in the thioamide form since in the ir spectrum (Nujol) no SH bands are discernible.

Anal. Calcd for $C_{13}H_9ClN_4S$: C, 53.87; H, 3.13; N, 19.33. Found: C, 53.55; H, 3.08; N, 19.02.

The S-methyl derivative was prepared in the usual way, mp 142–143° (aqueous ethanol).

Anal. Calcd for $C_{14}H_{11}ClN_4S$: N, 18.45; S, 10.55. Found: N, 18.13; S, 10.55.

6-Chloro-7,8-dihydrobenzo[*h*]-*s*-triazolo[3,4-*a*]phthalazine (IV, R = H, R_1 = Cl).—Diethoxymethyl acetate (0.5 ml) was added to 0.4 g of I (R = $NHNH_2$, R_1 = Cl) and the mixture was heated under reflux for 5 min. Upon cooling, the reaction mixture was diluted with 1.5 ml of ethanol and, after standing on ice for 15 min, the separated product was crystallized from ethanol to give the pure compound in 57% yield, mp 240–242°.

Anal. Calcd for $C_{13}H_9ClN_4$: C, 60.81; H, 3.53; N, 21.83. Found: C, 60.41; H, 3.90; N, 21.70.

7,8-Dihydrobenzo[*h*]-*s*-triazolo[3,4-*a*]phthalazine (IV, R = R$_1$ = H).—To a solution of 0.25 g of the above compound IV (R = H, R$_1$ = Cl) in 50 ml of absolute methanol 0.1 g of KOH and 0.5 g of 5% palladized charcoal were added and the mixture was stirred in an atmosphere of hydrogen at room temperature until the uptake of hydrogen ceased. The filtered solution was evaporated to dryness, the residue was suspended in water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and filtered, the solvent was evaporated, and the residue was crystallized from ethanol to give the pure compound in 56% yield, mp 215–216°.

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.08; H, 4.38; N, 25.34.

6-Hydrazino-7,8-dihydrobenzo[*h*]-*s*-triazolo[3,4-*a*]phthalazine (IV, R = H, R$_1$ = NHNH$_2$).—A reaction mixture consisting of 0.4 g of IV (R = H, R$_1$ = Cl), 3 ml of 80% hydrazine hydrate, and 0.5 ml of ethanol was heated under reflux for 20 min. The product which separated was filtered, washed with ethanol, and recrystallized from ethanol with the addition of charcoal (yield 91%), mp 246–248°.

Anal. Calcd for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.32. Found: C, 61.81; H, 4.92; N, 33.45.

9,10-Dihydrobenzo[*f*]bis-*s*-triazolo[3,4-*a*,4,3-*c*]phthalazine (V).—A mixture of 0.5 g of compound IV (R = H, R$_1$ = NHNH$_2$) and 2 ml of diethoxymethyl acetate was heated under reflux for 10 min. Upon cooling, 5 ml of ethanol were added, the precipitate was filtered and washed with ethanol. Crystallization was performed from N,N-dimethylformamide to yield 0.45 g (83%), mp 333–334°.

Anal. Calcd for $C_{14}H_{10}N_6$: C, 64.11; H, 3.84; N, 32.05. Found: C, 64.23; H, 4.11; N, 31.85.

6-Chloro-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = Cl).—Compound I (0.6 g) (R = NHNH$_2$, R$_1$ = Cl) was dissolved in 6 ml of 2 *N* hydrochloric acid, the solution was cooled on ice, and a saturated aqueous solution of $NaNO_2$ was added dropwise until a positive reaction on starch–KI paper. During this reaction, temperature was kept below 5°. The resulting precipitate was filtered, washed with ice water, air dried, and crystallized from ethanol with the addition of charcoal (yield 58%), mp 163–165°. The compound exhibited no azide band in the ir spectrum.

Anal. Calcd for $C_{12}H_8ClN_5$: C, 55.93; H, 3.13; N, 27.17. Found: C, 55.73; H, 3.44; N, 27.35.

6-Amino-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = NH$_2$). **A.**—The above chloro compound VI (1 g, R = Cl) and 150 ml of liquid ammonia were placed in an autoclave and the mixture was heated at 120° for 4 hr. Ammonia was then left to evaporate and the brown residue was purified by crystallization from ethanol to yield 68%, mp 236–238°.

Anal. Calcd for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.69; H, 4.52; N, 35.36.

B.—Into a hot ethanolic solution (20 ml) of 0.5 g of VI (R = N$_3$) hydrogen sulfide was bubbled for about 15 min until no more precipitate was formed. After crystallization from ethanol the pure compound melted at 236–238° to yield 0.4 g. Mixture melting point with the compound prepared as under A was undepressed. Ir (Nujol) bands were at 3279 and 3175 cm^{-1} (NH); no azide band appeared.

6-Hydrazino-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = NHNH$_2$).—A mixture of 2.57 g of VI (R = Cl), 10 ml of 80% hydrazine hydrate, and 1 ml of ethanol was heated under reflux for 30 min. The separated crude product was crystallized from N,N-dimethylformamide with the addition of charcoal to yield 2.0 g (79%), mp 265–267° dec.

Anal. Calcd for $C_{12}H_{11}N_7$: C, 56.91; H, 4.38; N, 38.72. Found: C, 56.92; H, 4.70; N, 38.92.

6-Azido-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = N$_3$). **A.**—A mixture of 2.5 g of I (R = R$_1$ = Cl), 2.6 g of sodium azide, and 30 ml of ethanol was heated on a water bath for 5 hr under reflux. The cooled reaction mixture was diluted with 50 ml of water and the obtained product was crystallized from ethanol to yield 54%: mp 192–195°; ir (Nujol), strong band at 2128 cm^{-1} (N$_3$); nmr ($CDCl_3$), τ 2.57 (multiplet, H$_9$, H$_{10}$, H$_{11}$, and H$_{12}$), 7.02 (singlet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{12}H_8N_8$: C, 54.54; H, 3.05; N, 42.41. Found: C, 54.22; H, 3.24; N, 42.54.

B.—A solution of 0.3 g of VI (R = Cl) in 20 ml of ethanol was treated with an aqueous solution of sodium azide (0.2 g in 1 ml of water) and then heated under reflux for 3 hr. The resulting product was collected, washed with ethanol, and water to give 0.2 g of the compound, identical with that prepared as under A.

C.—A solution of 0.3 g of VI (R = NHNH$_2$) in 6 ml of 2 *N* hydrochloric acid was treated dropwise with a saturated solution of sodium nitrite in that manner that the temperature did not exceed 5°. The end point of the reaction was detected by means of KI–starch paper. The separated product was purified from ethanol and charcoaled. The compound was identical with compounds as prepared under A or B. Mixture melting points were undepressed and ir spectra were identical.

7,8-Dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (VI, R = H).—The 6-chloro derivative (VI, R = Cl, 1.27 g) was suspended in 100 ml of methanol, 3 ml of concentrated ammonia and 0.5 g of 5% palladized charcoal were added and the mixture stirred in an atmosphere of hydrogen at room temperature until uptake was no more discernible. The filtered solution was evaporated *in vacuo* to dryness, and the residue was crystallized from ethanol to give 0.4 g (36%) of the pure compound, mp 193–195°.

Anal. Calcd for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.38. Found: C, 64.40; H, 4.31; N, 31.54.

10-Chloro-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = Cl, R$_1$ = H).—The crude reaction product (1 g) obtained in hydrazinolysis of I (R = R$_1$ = Cl) as described for the preparation of I (R = NHNH$_2$, R$_1$ = Cl) was heated with triethyl orthoformiate (5 ml) under reflux for 3 hr. From the hot reaction mixture a product was filtered off, crystallized from ethanol, and identified as compound IV (R = H, R$_1$ = Cl) to yield 72%, mp 240–242°, a mixture melting point with an authentic specimen was undepressed.

From the filtrate another product separated upon cooling, this was crystallized from ethanol and identified as compound VII (R = Cl, R$_1$ = H) to yield 15%: mp 176–177°; nmr ($CDCl_3$), τ 0.79 (singlet, H$_1$), 1.73 (multiplet, H$_9$), 2.54 (multiplet, H$_6$, H$_7$, and H$_8$), 6.88 (multiplet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{13}H_9N_4Cl$: C, 60.81; H, 3.53; N, 21.83. Found: C, 60.71; H, 3.82; N, 21.86.

1-Amino-10-azido-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = N$_3$, R$_1$ = NH$_2$).—To a boiling solution of 1.25 g of VI (R = NHNH$_2$) in 25 ml of ethanol 0.53 g of cyanogen bromide were added and heating was continued for further 5 min. Upon cooling, the crude hydrobromide salt separated and was filtered off and suspended in 3 ml of water. The suspension was treated with a saturated aqueous solution of Na_2CO_3 (5 ml) and stirred at room temperature for 15 min. The free base was collected (0.65 g, 47%) and crystallized from N,N-dimethylformamide: mp 255–256° dec; ir (Nujol), strong azide band at 2128 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}N_8$: C, 56.11; H, 3.62; N, 40.27. Found: C, 56.40; H, 3.85; N, 40.53.

1,10-Diamino-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = R$_1$ = NH$_2$).—The above compound VII (278 mg, R = N$_3$, R$_1$ = NH$_2$) was dissolved in 10 ml of boiling ethanol and hydrogen sulfide was bubbled in this solution for 15 min. The crude product, which separated, was collected and crystallized from N,N-dimethylformamide to yield 138 mg (55%), mp >325°.

Anal. Calcd for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.32. Found: C, 61.63; H, 4.92; N, 33.08.

10-Hydrazino-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = NHNH$_2$, R$_1$ = H).—The corresponding chloro compound (VII, R = Cl, R$_1$ = H, 1 g) was heated with hydrazine hydrate (10 ml of 80%) under reflux for 1 hr. Upon cooling the separated product was filtered off and crystallized from N,N-dimethylformamide to yield 0.87 g, mp 285–290° dec.

Anal. Calcd for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.32. Found: C, 61.63; H, 5.14; N, 33.69.

10-Azido-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = N$_3$, R$_1$ = H). **A.**—A mixture of VI (R = NHNH$_2$, 0.5 g) and diethoxymethyl acetate (2 ml) was heated under reflux for 5 min. Some product separated already during heating and the rest separated after addition of 2 ml of ethanol. The filtered product was washed several times with ethanol. For analytical purposes it was crystallized from 0.5 ml of diethoxymethyl acetate to yield 0.35 g (67%): mp 220–222°; ir (Nujol), strong azide band at 2128 cm^{-1}.

Anal. Calcd for $C_{13}H_9N_7$: C, 59.31; H, 3.45; N, 37.25. Found: C, 59.66; H, 3.48; N, 37.35.

B.—Compound VII (R = NHNH$_2$, R$_1$ = H, 0.5 g), dissolved in an ice cold solution of 5 ml of 10% hydrochloric acid, was

treated dropwise with an aqueous solution of sodium nitrite (0.15 g of $NaNO_2$ in 1 ml of water). The reaction mixture was cooled and stirred for 30 min, the product was separated and washed with 5 ml of ice-cold water. Upon crystallization from ethanol the compound (0.25 g) had mp 220–222°. Its ir spectrum was identical with that of the compound obtained under A.

4-Chloro-5,6-dihydrobenzo[*f*]phthalazine (I, R = H, R_1 = Cl).—To a boiling solution of 1.23 g of I (R = $NHNH_2$, R_1 = Cl) in a mixture of water and ethanol (4:1) a solution of hydrated cupric sulfate (2.5 g in 10 ml water) was added and the mixture was heated under reflux until it became clear. It was then made alkaline by adding a 10% aqueous solution of NaOH and filtered hot, and the residue was washed with 50 ml of hot water. The combined filtrates were evaporated to about 30 ml and then left on ice overnight. The collected crystals (250 mg, 24%) were crystallized for analytical purposes from ethanol: mp 118–119°; nmr ($CDCl_3$), τ 2.78 (multiplet, H_7, H_8, and H_9), 2.25 (multiplet, H_{10}), 7.03 (singlet, 4 H, $-CH_2CH_2-$), H_1 was covered with the multiplet of H_7, H_8, and H_9.

4-Hydrazino-5,6-dihydrobenzo[*f*]phthalazine (I, R = H, R_1 = $NHNH_2$).—The above compound (I, R = H, R_1 = Cl) (1.08 g), 8 ml of 80% hydrazine hydrate, and 1 ml of ethanol were heated under reflux for 3 hr. After addition of 10 ml of ethanol, the mixture was left aside overnight. Water (20 ml) was added and the mixture was extracted five times with an equal volume of benzene. The collected benzene extracts were dried and evaporated to an oily residue. Ethanol (15 ml) was added and hydrogen chloride introduced for few minutes. The solution was again evaporated and to the oily residue 10 ml of *n*-hexane was added. Upon standing on ice the dihydrochloride salt crystallized to yield 0.8 g (77%), mp 253–254°.

Anal. Calcd for $C_{12}H_{14}Cl_2N_4$: C, 50.51; H, 4.95; N, 19.64. Found: C, 50.28; H, 4.78; N, 19.52.

The free base, which can be obtained from the salt, appears to be sensitive to oxidation and upon attempted crystallization or after standing on air decomposes slowly.

4,5-Dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII, R = R_1 = H).—A mixture of the above free base (I, R = H, R_1 = $NHNH_2$, 0.53 g) and 2 ml of diethoxymethyl acetate was heated under reflux for 5 min and cooled, and the reaction mixture was treated with 2 ml of ethanol. The crude product was separated, washed with ethanol, and crystallized from 0.5 ml of diethoxymethyl acetate to give 0.41 g (74%) of the pure product: mp 220–222°; nmr ($CDCl_3$), τ 2.22 (multiplet, H_9), 2.58 (multiplet, H_1, H_6, H_7, H_8, and H_{10}), 6.73 (multiplet, 4 H, $-CH_2CH_2-$).

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found: C, 70.46; H, 4.77; N, 25.05.

10-Amino-4,5-dihydrobenzo[*f*]-*s*-triazolo[3,4-*a*]phthalazine (VII R = NH_2, R_1 = H).—A hot solution of 100 mg of VII (R = N_3, R_1 = H) in 10 ml of ethanol was treated with hydrogen sulfide for 15 min. Purification of the separated product was performed from N,N-dimethylformamide and afforded 63 mg of the pure product, mp >320°.

Anal. Calcd for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.72; H, 4.51; N, 29.28.

4,5-Dihydrobenzo[*f*]tetrazolo[5,1-*a*]phthalazine (VIII). A.—Compound I (0.54 g, R = H, R_1 = Cl), 0.35 g of sodium azide, and 4 ml of 1,3-propylene glycol were heated under reflux for 2 hr. Upon cooling, 10 ml of water was added and the mixture was left on ice overnight. The separated product was crystallized from N,N-dimethylformamide to give 0.4 g (71%) of the product with mp 236–238°. The ir spectrum exhibited no bands characteristic for the presence of azide group. Nmr ($CDCl_3$) peaks were at τ 2.55 (multiplet, H_6, H_7, H_8, H_9), 2.75 (singlet, H_{10}), 6.90 (singlet, 4 H, $-CH_2CH_2-$).

B.—A solution of 0.3 g of I (R = H, R_1 = $NHNH_2$) in 3 ml of 50% acetic acid was cooled on ice and treated dropwise with a solution of 0.12 g of sodium nitrite in 1 ml of water. The separated product (0.21 g) was crystallized from N,N-dimethylformamide. Melting point and mixture melting point with the compound prepared as under A were undepressed.

Registry No.—I (R = R_1 = Cl), 16719-59-8; I (R = NH_2; R_1 = Cl), 16749-03-4; I (R = $NHNH_2$; R_1 = Cl), 16719-60-1; I (R = NHN = CHC_6H_5; R_1 = Cl), 16719-61-2; I (R = $C_6H_5NHCSNHNH$; R_1 = Cl), 16719-62-3; I (R = OCH_3; R_1 = Cl), 16719-63-4; I (R = OC_2H_5; R_1 = Cl), 16753-63-2; I (R = OCH_3; R_1 = H), 16719-64-5; I (R = OC_2H_5; R_1 = H), 16719-65-6; I (R = R_1 = $H\cdot H_2SO_4$), 16753-64-3; I (R = SH; R_1 = Cl), 16719-66-7; I (R = SCH_3; R_1 = Cl), 16719-67-8; I (R = H; R_1 = Cl), 16719-68-9; I (R = H; R_1 = $NHNH_2$), 16719-69-0; II (R = Cl), 16719-70-3; II (R = H), 16719-71-4; II (R = $NHNH_2$), 16719-72-5; II (R = *p*-$Me_2NC_6H_5CH$=NNH), 16719-73-6; II (R = C_6H_5-NHCSNHNH), 16719-74-7; III (R = SH), 16719-75-8; III (R = H), 16719-76-9; IV (R = H; R_1 = Cl), 16719-94-1; IV (R = R_1 = H), 16719-77-0; IV (R = H; R_1 = $NHNH_2$), 16719-78-1; V, 16719-79-2; VI (R = Cl), 16719-80-5; VI (R = NH_2), 16719-81-6; VI (R = $NHNH_2$), 16719-82-7; VI (R = N_3), 16719-83-8; VI (R = H), 16719-84-9; VII (R = Cl; R_1 = H), 16719-85-0; VII (R = N_3; R_1 = NH_2), 16719-86-1; VII (R = R_1 = NH_2), 16719-87-2; VII (R = $NHNH_2$; R_1 = H), 16719-88-3; VII (E = N_3; R_1 = H), 16719-89-4; VII (R = R_1 = H), 16719-90-7; VII (R = NH_2; R_1 = H), 16719-91-8; VIII, 16719-92-9; IV (R = SH; R_1 = Cl), 16719-93-0; IV (R = SMe; R_1 = Cl), 16753-65-4.

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