Polyazasteroids. III (1). 1,2,4-Triazolo[3,4-*a*]benzo[*f*]isoquinoline. Synthesis of the Diazaphenanthrene Alkaloid Perlolidine and its 1,8-Phenanthroline Isomer

I. Lalezari and S. Nabahi (2)

Division of Immunohematology, Department of Medicine, Montefiore Hospital and Medical Center and Albert Einstein College of Medicine, 111 E. 210 St., Bronx, New York, 10467, USA

Received June 26, 1980

A series of 1,2,4-triazolo[3,4-*a*]benzo[*f*]isoquinolines, which constitutes a new class of polyazasteroidal compounds, were synthesized. A simple synthesis of the diazaphenanthrene alkaloid perlolidine as well as 1,8-phenanthrolin-7-(8*H*)one is reported.

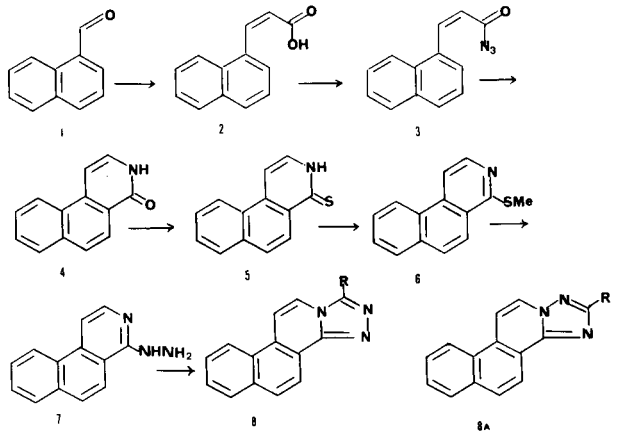
J. Heterocyclic Chem., **17**, 1761 (1980).

In connection with a research program concerning the synthesis of polyazasteroidal compounds (1,3), we wish to report the synthesis and structure elucidation of 1,2,4-triazolo[3,4-*a*]benzo[*f*]isoquinolines (**8a-c**) which constitute a new class of polyazasteroidal compounds. The starting material 3,4-dihydrobenzo[*f*]isoquinolin-4-one (**4**) was prepared by the method of Eloy and Deryckere (4), except that the naphthalene-1-acrylic acid (**2**) was prepared from 1-naphthaldehyde (**1**) (5).

The 3,4-dihydrobenzo[*f*]isoquinolin-4-one (**4**) was treated with phosphorous pentasulfide in pyridine to give the desired 4-thione **5**, which was subsequently methylated. The methythio derivative **6** obtained was reacted with hydrazine hydrate to give 4-hydrazinobenzo[*f*]isoquinoline (**7**). The reaction of the latter hydrazino compound with *ortho*-esters did not give the desired steroidal compounds **8**. However, the hydrazine **7** in aliphatic acids followed by cyclization with polyphosphoric acid led to the formation of the 1,2,4-triazolo[3,4-*a*]benzo[*f*]isoquinolines (**8a-c**) (see Scheme I).

A similar ring formation reaction was reported in the synthesis of 1,2,4-triazolo[3',4':2,3]pyrimido[4,5-*c*]quinolin-11-(12*H*)ones (3).

Recently, Schneller and Bartholomew (6) have prepared a series of 1,2,4-triazolo[4,3-*a*]pyridines through the acylation of the appropriate hydrazino compounds followed by cyclization with phosphorous oxychloride. Similarly, Hajos and Messmer (7) have synthesized a series of 1,2,4-triazolo-[4,3-*b*]isoquinolines using plyphosphoric acid as a condensing agent. On the basis of this observations and the fact that the physical and spectroscopical properties of the compound **8** were not affected by acid, base or heat, the compounds obtained were assigned as 1,2,4-triazolo[3,4-*a*]-benzo[*f*]isoquinolines (**8**) rather than the isomeric 1,2,4-triazolo[5,1-*a*]benzo[*f*]isoquinolines (**8A**). This was strongly supported by the nmr signal for C_1H of the compound **8a**, which appears at 9.51 ppm. The compounds **8A** are the possible isomers which could be formed through a Dimroth type rearrangement reported in several ring-fused 1,2,4-triazole systems. The rearrangement of several 1,2,4-triazolo[4,3-*a*]pyridines has been studied by Potts and Surapaneni (8).



Scheme I

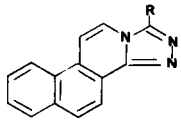
Attempts were made to synthesize the 5-azaanalogues of **8**. The diazaphenanthrene alkaloid perlolidine (**12**) required for the synthesis of polyazasteroidal compounds **16** was prepared by a simple novel method based on Eloy and Deryckere reaction (4) using 4-methylquinoline (**9**) as starting material. The reaction of the latter compound with trichloroacetaldehyde afforded β-4-quinolylacrylic acid (**10**) (9). The azide **11** of this acid underwent a Curtius type rearrangement giving high yield of perlolidine (**12**) a naturally occuring alkaloid prepared also by an independant method (10).

Perlolidine (**12**) was reacted with phosphorous pentasulfide in pyridine to give benzo[*c*][2,7]naphthyridine-5-(6*H*)thione (**13**). The methylation of **13** gave the 4-methylthio **14**. The latter compound failed to give the desired 4-hydrazino compound **15** through hydrazinolysis (see Scheme II).

Attempts was also made to synthesize the 9-azaanalogue **24** of polyazasteroidal compounds **8**. 8-Quinolincarboxaldehyde (**17**) (11) was used as starting material. The β-8-quinolylacrylic acid (**18**) was prepared according to the literature (12). The azide **19** was prepared from the acid **18**

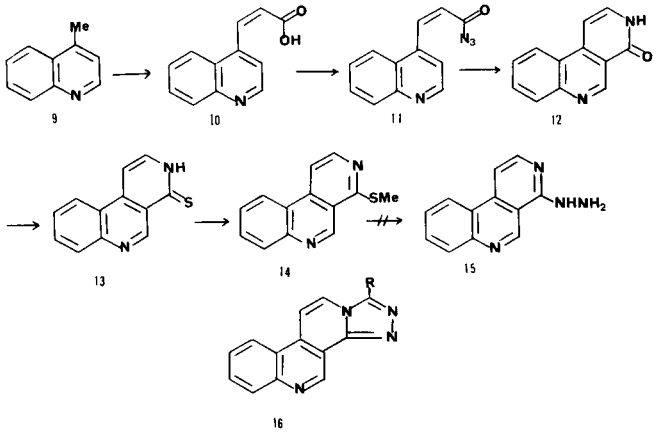
0022-152X/80/081761-03$02.25

Table I



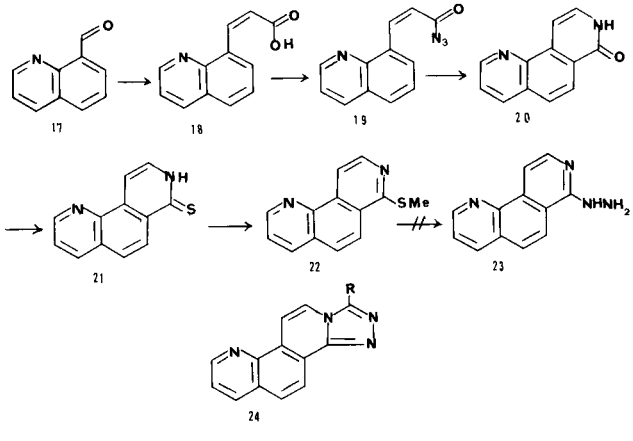
Compound No.	R	M.p. °C.	Yield %	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
8a	H	>300	80	$C_{14}H_9N_3$	76.71	76.80	4.10	4.33	19.17	19.44
8b	CH_3 (a)	270	81	$C_{15}H_{11}N_3$	77.25	77.31	4.72	4.69	18.02	17.93
8c	C_2H_5 (b)	240	78	$C_{16}H_{13}N_3$	77.73	77.69	5.26	5.28	17.00	17.12

(a) Ms: m/e (relative intensity), M^+ 233 (100), M-CH_3CN 192 (62), M-$C_2H_2N_3$ 165 (26). (b) Ms: m/e (relative intensity) M^+ 247 (80), M-CH_3 232 (65), M-C_2H_4 219 (100), M-C_2H_5CN 192 (52), M-$C_2H_5CN_2$ 178 (26), M-$C_2H_5CN_3$ 164 (56).



Scheme II

and subjected to Curtius type rearrangement giving a high yeild of 1,8-phenanthroline-7-(8*H*)thione (**21**), which was methylated to give 7-methylthio-1,8-phenanthroline (**22**). The reaction of hydrazine hydrate in different conditions failed to convert the methylthio compound **22** to the desired hydrazino derivative **23** (see Scheme III).



Scheme III

The structure elucidation of all compounds prepared was done by spectroscopical and analytical methods.

The physical properties of polyazasteroidal compounds **8** are summarized in Table I.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Ir spectra were recorded on a Beckman Model 9 spectrograph. Nmr spectra were run on a Varian T-60 instrument and mass spectra were obtained in a Varian-Mat Ms-311 spectrograph.

3,4-Dihydrobenzo[*f*]isoquinoline-4-thione (**5**).

To a solution of 3.90 g. (0.02 mole) of 3,4-dihydrobenzo[*f*]isoquinolin-4-one (**4**) (4) in 40 ml. of dry pyridin, 4.44 g. (0.02 mole) of powdered phosphorous pentasulfide was added. After 4 hours refluxing, the solvent was evaporated under reduced pressure and the residue was washed with water and recrystallized from acetic acid to give 2.80 g. (67%) of the thione **5**, m.p. 230-235°; ir: 3030 and 1610, aromatics, 1570 cm^{-1}, thioamide; molecular weight by mass spectroscopy m/e 211.

Anal. Calcd. for $C_{13}H_9NS$: C, 73.93; H, 4.26; 6.63. Found: 74.06; H, 4.10; N, 6.43.

4-Methylthiobenzo[*f*]isoquinoline (**6**).

To a solution of 2.11 g. (0.01 mole) of 3,4-dihydrobenzo[*f*]isoquinoline-4-thione (**5**) in 30 ml. of 96% alcohol containing 2.80 g. (0.05 mole) of potassium hydroxide, 1.42 g. (0.01 mole) of methyl iodide was added and the solution was refluxed for 15 minutes. After cooling, the reaction mixture was diluted with water and the precipitate was recrystallized from alcohol to give 1.93 g. (86%), m.p. 120-121°; nmr (deuteriochloroform): 7.36-8.80 (m, 8H, aromatics), 2.80 (s, 3H, CH_3); molecular weight by mass spectroscopy m/e 225.

Anal. Calcd. for $C_{14}H_{11}NS$: C, 74.66; H, 4.88; N, 6.22. Found: C, 74.50; H, 5.01, N, 6.42.

4-Hydrazinobenzo[*f*]isoquinoline (**7**).

A mixture of 2.25 g. (0.01 mole) of methylthio **6** and 1 g. (excess) of 98% hydrazine hydrate in 20 ml. ethylene glycol monoethyl ether was refluxed for 70 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in chloroform and the almost pure hydrazine derivative was precipitated by the addition of light petroleum ether to give 2.02 g. (96%). An analytical sample was prepared through recrystallization from ethylene glycol monoethyl ether, m.p. > 300°; ms: m/e (relative intensity) M^+ 209 (100), M-N_2H_3 178 (21), M-CH_3N_3 152 (23).

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.64; H, 5.26; N, 20.09. Found: C, 74.60; H, 5.29, N, 19.89.

1,2,4-Triazolo[3,4-*a*]benzo[*f*]isoquinoline (**8a**).

A solution of 209 mg. (1 mmole) of hydrazine **7** in 10 ml. of 99% formic acid was refluxed for 4 hours. After evaporation of the excess acid under

reduced pressure, 5 g. of polyphosphoric acid was added to the residue and the mixture was heated at 170° for 30 minutes. After cooling, the mixture was diluted with water and alkalinized with a 20% solution of sodium hydroxide. The precipitate was filtered, washed with water and recrystallized from acetic acid to give 175 mg. (80%) of the polyazasteroidal compound **8a**, m.p. > 300°; ms: m/e (relative intensity) M^+ 219 (100), M-CHN 192 (40), M-CHN_2 178 (20), M-CHN_3 164 (18).

Compounds **8b** and **8c** were prepared similarly using acetic and propionic acids respectively instead of formic acid (see Table I).

β-4-Quinolylacrylyl Azide (**11**).

To a stirring solution of 19.9 g. (0.1 mole) of β-4-quinolylacrylic acid (**10**) (9) in 180 ml. of acetone and 10 ml. of triethylamine, a solution of 12 g. (0.11 mole) of ethylchloroformate in 30 ml. of acetone was slowly added. The temperature was kept at 0°. To the reaction mixture, a solution of 9.1 g. (0.14 mole) of sodium azide in 30 ml. of water was dropwise added. The solution was stirred for an hour at 0°, and an hour at room temperature. Addition of ice water produced a precipitate, 14.1 g. (63%) of the azide **11**, m.p. 76-78°; ir (potassium bromide): 2068 cm^{-1} azide. The azide was used in the next step without further purification, after drying at room temperature.

β-8-Quinolylacrylyl Azide (**19**).

The title compound was prepared from β-8-quinolylacrylic acid (**18**) (12), as described for compound **11**. The yield was 51%, m.p. 73-75°; ir (potassium bromide): 2063 cm^{-1}, azide.

Benzo[*c*][2,7]naphthyridin-5-(6*H*)one (Perlolidine) (**12**).

A solution of 11 g. β-4-quinolylacrylyl azide (**11**) in 40 ml. of dichloromethane was added dropwise to 150 ml. of diphenyl ether preheated at 230° in a distillation apparatus. Dichloromethane was gradually distilled off. The reaction mixture was kept at 230° for an additional hour then cooled. Addition of diethyl ether precipitated the crude perlolidine which was recrystallized from alcohol to give 7.6 g. (81%) of perlolidine (**12**), m.p. 336-340°; ms: m/e (relative intensity) M^+ 196 (100), M-CO 169 (73), M-C_2H_2NO 140 (52). This compound was identical with a sample prepared by known method (10).

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.46; H, 4.08; N, 14.28. Found: C, 73.33; H, 4.14; N, 14.09.

1,8-Phenanthrolin-7-(8*H*)one (**20**).

It was prepared from β-8-quinolylacrylyl azide (**19**) similar to the preparation of compound **12**. The compound was recrystallized from ethanol. The yield of the purified compound was 63%, m.p. 280-282°; ms: m/e (relative intensity) M+ 196 (100), M-CO 168 (79), M-C_2H_2NO 149 (43).

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.46; H, 4.08; N, 14.28. Found: C, 73.50; H, 4.22; N, 13.88.

Benzo[*c*][2,7]naphthyridine-5-(6*H*)thione (**13**).

A mixture of benzo[*c*][2,7]naphthyridin-5-(6*H*)one (**12**), and 1 g. of powdered sulfur pentasulfide in 10 ml. of dry pyridine was refluxed for 3 hours. After evaporation of the solvent under reduced pressure, the residue was decomposed with water. The precipitate was recrystallized from dimethylformamide to give 750 mg. of a yellow crystalline powder (69%), m.p. 229-232°; molecular weight by mass spectroscopy m/e 212.

Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.92; H, 3.77; N, 13.20. Found: C, 68.09; H, 3.59; N, 13.26.

1,8-Phenanthroline-7-(8*H*)thione (**21**).

This compound was prepared from 1,8-phenanthrolin-7-(8*H*)one (**20**); similar to the compound **13**, m.p. 254-256°; molecular weight by mass spectroscopy m/e 212.

Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.92; H, 3.77; N, 13.20. Found: C, 67.68; H, 3.80; N, 13.21.

4-Methylthiobenzo[*c*][2,7]naphthyridine (**14**).

Benzo[*c*][2,7]naphthyridine (**13**), 636 mg. (3 mmoles), was dissolved in a solution of 1 g. of potassium hydroxide in 20 ml. of ethanol. To the stirring solution obtained, 1 ml. (excess) of methyl iodide was added at room temperature. After 4 hours the reaction mixture was refrigerated. The white precipitate formed was recrystallized from alcohol to give 590 mg. (86%) of **14**, m.p. 149-151°; molecular weight by mass spectroscopy m/e 226; nmr (deuteriochloroform): 2.75 (s, 3H, CH_3), 7.71-8.80 (m, 7H, aromatics).

Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.02; H, 4.42; N, 12.38. Found: C, 68.89; H, 4.21; N, 12.44.

7-Methylthio-1,8-phenanthroline (**22**).

This compound was prepared from 1,8-phenanthroline-7-(8*H*)thione (**21**) as described for the preparation of methylthio **14** (79% yield), m.p. 122-124°; molecular weight by mass spectroscopy m/e 226; nmr (deuteriochloroform): 3.15 (s, 3H, CH_3), 6.92-8.71 (m, 7H, aromatics).

Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.02; H, 4.42; N, 12.38. Found: C, 69.10; H, 4.56; N, 12.40.

REFERENCES AND NOTES

(1) For Article II see I. Lalezari and S. Sadeghi-Milani, *J. Heterocyclic Chem.*, **16**, 707 (1979). This work was in part presented at the 7th International Congress of Heterocyclic Chemistry, August 1979, Tampa, Florida, USA.

(2) Former Research Associate, Department of Chemistry, College of Pharmacy, Tehran University, Tehran, Iran.

(3) I. Lalezari and S. Sadeghi-Milani, *J. Heterocyclic Chem.*, **15**, 501 (1978).

(4) F. Eloy and A. Deryckere, *ibid.*, **7**, 1191 (1970).

(5) B. Y. West, *J. Am. Chem. Soc.*, **42**, 1664 (1920).

(6) S. W. Schneller and B. G. Bartholomew, *J. Heterocyclic Chem.*, **15**, 439 (1978).

(7) Gy. Hajos and A. Messmer, *ibid.*, 463 (1978).

(8) K. T. Potts and C. R. Surapaneni, *ibid.*, **7**, 1019 (1970).

(9) G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1241 (1939).

(10) M. A. Akhtar, W. G. Brower, A. D. Jeffers, C. W. Gemenden, W. I. Taylor, R. N. Seelye and D. W. Stanton, *J. Chem. Soc. C* 859 (1967).

(11) V. M. Rodionov and M. A. Berkengeim, *J. Gen. Chem., USSR*, **14**, 330 (1944); *Chem. Abstr.*, **39**, 4076 (1945).

(12) R. Gall and H. Erlenmeyer, *Helv. Chim. Acta*, **38**, 1421 (1955).