Azasteroids. V. Approaches to the 14,16-Diazasteroidal Ring System (1,2)

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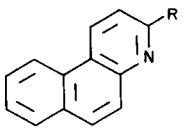
Making use of Reissert compound II and Reissert compound analogue VI, benzo[*f*]quinoline has been converted into the 14,16-diazasteroidal ring system. A number of reactions in this ring system are discussed.

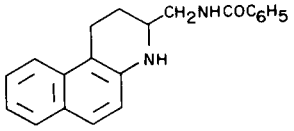
The diamine I would appear to be a convenient intermediate for the preparation of 14,16-diazasteroidal systems. This diamine should be potentially available (3) from benzo[*f*]quinoline via the appropriate Reissert compound (II).

The conversion of II to benzo[*f*]quinoline-3-carboxylic acid (III, R = CO_2H) has previously been reported (4). This acid was converted via its acid chloride to the corresponding amide (III, R = $CONH_2$) which could also be obtained together with the nitrile (III, R = CN) by treatment of II with phosphorus pentachloride. Attempted reduction of the amide (III, R = $CONH_2$) failed to yield any usable amounts of the tetrahydroamide needed to prepare II. An alternate route from II to I was available, however, through the high pressure hydrogenation of II. This sequence gave an oil (probably IV) which was hydrolyzed and reacted with carbon disulfide to give a low yield of the cyclic thiourea (V) (a 3-desoxy-18-nor-14,16-diazaequilenin ring system).

Although the preceding sequence gave the desired product, the low yield made it desirable to find an alternative route to the 14,16-diazasteroidal ring system. The Reissert analogue VI (5) was catalytically hydrogenated in the presence of hydrogen chloride to give a good yield of the monourethane hydrochloride VII. When heated with base VII was converted into the cyclic urea (VIII, R = H). When the hydrogenation was carried out in the absence of hydrogen chloride the free base of VII was obtained as an oil which was characterized as its hydro-



III



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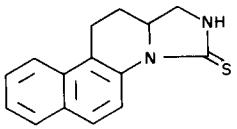

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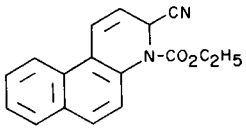

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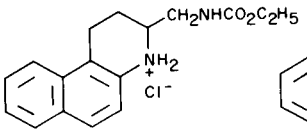
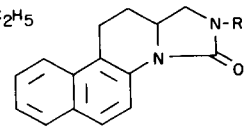
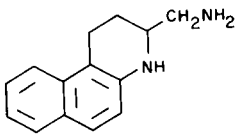


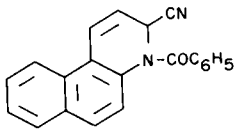
VII



VIII



I



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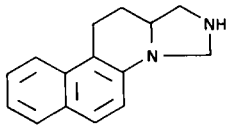
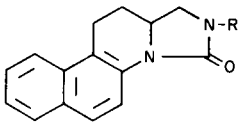


IX

TABLE I



RX	M.p.	Analyses					
		Calcd.			Found		
		C	H	N	C	H	N
CH_3I	148-150	76.16	6.40	11.10	76.09	6.40	11.03
$C_6H_5CH_2Br$	196-197	80.50	6.13		80.35	6.30	
C_6H_5COCl	195-197	77.25	5.30		77.31	5.40	
C_2H_5OCOCl	196-200	69.70	5.84	9.02	69.61	5.89	8.96
$H_2NCO(CH_2)_2Cl$	222-224	69.88	6.19	13.57	69.90	6.29	13.63

chloride or hydrolyzed without further purification to give VIII (R = H). The cyclization probably proceeds through an isocyanate intermediate which cyclizes spontaneously.

The cyclic urea (VIII, R = H) was converted to the cyclic thiourea (V) by reaction with phosphorus pentasulfide. Compound VIII (R = H) was reduced with lithium aluminum hydride to give the amine (IX) which was characterized as its perchlorate and hydrochloride. A variety of halo compounds were allowed to react with VIII (R = H) in dimethylformamide to give the corresponding 16-substituted-14,16-diazasteroids (VIII) indicated in Table I.

EXPERIMENTAL (6)

3-Cyano-4-benzoyl-3,4-dihydrobenzo[*f*]quinoline (II).

This compound was prepared from benzo[*f*]quinoline, benzoyl chloride, and potassium cyanide in methylene chloride-water as previously described (7).

Benzo[*f*]quinoline-3-carboxylic Acid (III, R = CO_2H).

This compound was prepared from II as previouslv described (4).

Benzo[*f*]quinaldamide (III, R = $CONH_2$).

A solution of 14.0 g. (0.063 mole) of anhydrous acid (III, R = CO_2H) and 100 g. of thionyl chloride was refluxed for 3 hours and the thionyl chloride removed *in vacuo* to give 13.6 g. (93%) of solid. This material was recrystallized from benzene and 1.46 g. (0.0065 mole) was added to 50 ml. of concentrated ammonium hydroxide in an ice bath. The mixture was stirred for 10 minutes and filtered to yield 1.15 g. (79.5%) of a solid, m.p. 233-235°, after washing with water, and ether. This material was identical with that described below.

Reaction of II with Phosphorus Pentachloride.

To 11.5 g. (0.0384 mole) of II in 50 ml. of refluxing anhydrous chloroform was slowly added 10 g. of phosphorus pentachloride. Refluxing was continued for 2 hours and 250 ml. of water was added. Sodium carbonate was added until no more carbon dioxide was evolved and a solid was obtained. Chromatography of this solid on alumina yielded upon elution with benzene a 44.5% yield of the nitrile (III, R = CN), m.p. 149-152°, and a 26.1% yield of the amide (III, R = $CONH_2$), m.p. 236-238°. These same two products could also be isolated from the reaction by fractional recrystallization. Recrystallization of the amide from aqueous ethanol gave m.p. 238-240° (reported (8) m.p. 240-243°) and recrystallization of the nitrile from hexane gave m.p. 151-153°; IR: 2230 cm^{-1} (potassium bromide).

Anal. Calcd. for $C_{14}H_8N_2$: C, 82.35; H, 3.94; N, 13.71. Found: C, 82.32; H, 4.01; N, 13.75.

1,11,12,12a-Tetrahydrobenz[*f*]imidazo[1,5-*a*]quinolin-3(2*H*)-thione (V).

A mixture of 21.25 g. (0.0685 mole) of II, 250 ml. of ethanol and about 10 g. of Raney nickel was hydrogenated under a pressure of 106 atmospheres at 100° for 24 hours. The mixture was filtered and the solvent removed to yield 21 g. of oil. The oil was dissolved in ether, washed with base and water, and the solvent evaporated. The oil was then refluxed for 48 hours with 25% hydrochloric acid, the solution was made basic and extracted with ether. Evaporation of the ether gave 16.6 g. of oil. A solution of 8.3 g. of this oil in a mixture of 400 ml. of ethanol and 50 ml. of water was refluxed with 10 ml. of carbon disulfide for 1 hour and 4 ml. of concentrated hydrochloric acid was added. The mixture was refluxed for 12 hours and concentrated to 200 ml. to yield 0.57 g. (7%) of V, m.p. 235-239°. This material was identical to that described below. Further concentration of the solution gave unidentifiable materials.

Ethyl 3-Cyanobenzo[*f*]quinoline-4(3*H*)-carboxylate (VI).

To a mixture of 18 g. (0.1 mole) of benzo[*f*]quinoline in 140 ml. of methylene chloride and 22 g. of potassium cyanide in 50 ml. of water was added with stirring 21.56 g. (0.2 mole) of ethyl chloroformate. The mixture was stirred for 5.5 hours and extracted with methylene chloride. The extract was washed with water, dilute hydrochloric acid, water, dilute sodium hydroxide, and water and dried over magnesium sulfate. Concentration gave 24.8 g. (89%) of white solid, m.p. 137-140°. Recrystallization from ethanol gave m.p. 145-146°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.40; H, 5.07; N, 10.01. Found: C, 73.33; H, 5.12; N, 9.89.

Hydrogenation of VI (Preparation of VII).

A solution of 1.4 g. (0.005 mole) of VI, 0.1 g. of platinum oxide, 0.55 g. of concentrated hydrochloric acid, and 100 ml. of ethanol was hydrogenated under a pressure of 4 atmospheres. After three hours the reaction was heated to 40° and then allowed to slowly cool. After a total of 20 hours the take up of hydrogen had ceased. It is of interest to compare the relative ease of reduction of the Reissert analogue VI with the Reissert compound II. The mixture was filtered and the solvent evaporated to give 1.6 g. of solid. Recrystallization from benzene gave 1.05 g. (65%) of white crystals, m.p. 182-186°. Further recrystallization from benzene gave m.p. 184.5-185.5°; IR: 3425, 1668, 1050 cm^{-1} (potassium bromide).

Anal. Calcd. for $C_{17}H_{21}ClN_2O_2$: C, 63.70; H, 6.59; N, 8.74. Found: C, 64.77; H, 6.54; N, 8.74.

1,11,12,12a-Tetrahydrobenz[*f*]imidazo[1,5-*a*]quinolin-3(2*H*)-one (VIII, R = H).

A mixture of 5.56 g. (0.02 mole) of VI, 0.4 g. of platinum oxide, and 100 ml. of glacial acetic acid was hydrogenated under a pressure of 4 atmospheres for 12 hours. Acetic acid was removed *in vacuo* to yield a clear oil. A small amount of this oil was treated with hydrogen chloride to yield VII identical with that obtained above. The remaining oil was placed in water and made basic with sodium hydroxide. After heating on a steam bath a solid was obtained and was recrystallized from ethanol to yield 3.0 g. (59%) of solid, m.p. 252-258°. Further recrystallization from ethanol gave m.p. 254-258°; IR: 3200, 3090, 1695 cm^{-1} (potassium bromide).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.52; H, 6.01; N, 11.69.

VIII (R = H) was also prepared by heating 0.065 g. of VII in 5 ml. of 50% sodium hydroxide on a steam bath for 20 minutes. Filtration gave 0.035 g. (69%) of solid identical with that obtained above.

Alkylation of VIII (R = H) (Preparation of 2-Substituted Analogues).

To a solution of 0.28 g. (0.0012 mole) of VIII (R = H) in 10 ml. of dry dimethylformamide was added slowly 0.3 g. (0.0022 mole) of 30% sodium hydride in mineral oil. The mixture was stirred and 0.002 mole of a halo compound was added. After 30 minutes of stirring the solution was poured onto 200 g. of ice and allowed to stand overnight. The solid was filtered, washed with water and dried. Recrystallization from ethanol gave the compounds shown in Table I in approximately quantitative yield.

Conversion of VIII (R = H) to V.

A suspension of 0.7 g. of phosphorus pentasulfide and 0.48 g. (0.002 mole) of VIII (R = H) in 100 ml. of dry xylene was refluxed for 3 hours. The mixture was extracted with 40 ml. of 12.5% sodium hydroxide and the xylene phase was evaporated to yield 0.04 g. (8%) of solid, m.p. 232-235°. Recrystallization from ethanol gave a solid, m.p. 236-237°, identical with that described above.

Anal. Calcd. for $C_{15}H_{14}N_2S$: C, 70.85; H, 5.55; N, 11.00. Found: C, 70.70; H, 5.49; N, 10.86.

1,2,311,12,12a-Hexahydrobenz[*f*]imidazo[1,5-*a*]quinoline (IX).

To a suspension of 0.3 g. (0.006 mole) of lithium aluminum hydride in 75 ml. of refluxing tetrahydrofuran was added 1.0 g. (0.004 mole) of VIII (R = H) and the mixture was refluxed with stirring for 14 hours. The mixture was concentrated to about 20 ml. and water, 20% sodium hydroxide, and water were added and a precipitate was obtained. Extraction of the precipitate with ether and concentration of the ether extract gave 0.96 g. (72%) of an oil. Treatment of a portion of this oil with perchloric acid gave an 80% yield of the perchlorate, m.p. 196-197° from *n*-butanol containing a small amount of hexane.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_4$: C, 55.45; H, 5.28; N, 8.62; Cl, 10.90. Found: C, 55.29; H, 5.64; N, 8.57; Cl, 10.64.

Treatment of the above oil in hexane with dry hydrogen chloride gave a white solid, m.p. 241-243° from ethanol.

Anal. Calcd. for $C_{15}H_{17}ClN_2 \cdot \frac{1}{2}H_2O$: C, 66.80; H, 6.75; N, 10.38. Found: C, 66.74; H, 7.15; N, 10.20.

REFERENCES

(1) Part IV: F. D. Popp, W. R. Schleigh, P. M. Froehlich, R. J. Dubois, and A. C. Casey, *J. Org. Chem.*, 33, 833 (1968).

(2) This work was supported in part by a grant from the American Cancer Society. Presented at 155th National A. C. S. Meeting.

(3) See L. E. Katz and F. D. Popp, *J. Heterocyclic Chem.*, 4, 635 (1967), for a similar sequence in the isoquinoline series.

(4) F. D. Popp and W. R. Schleigh, *ibid.*, 1, 107 (1964).

(5) The preparation and reactions of Reissert compound analogues of this type will be discussed in detail in a future paper.

(6) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. All melting points are in capillaries and are corrected.

(7) F. D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.*, 26, 4930 (1961).

(8) M. Haring, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, 37, 1339 (1954).

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