Syntheses of Some Indazoles Structurally Related to Equilenin (1)

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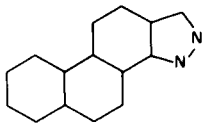
This study reports the complete synthesis and characterization of the 15,16-diazaequilenin derivative 10,11-dihydro-3*H*-naphth[1,2-*g*]indazol-7-ol (**2b**) as well as the methyl ether **2a** of the above compound and the novel "model" compound 4,5-dihydro-1*H*-benz[*g*]indazol-7-ol (**3b**). Indazoles **2a** and **3a** have demonstrated *in vitro* activity against a variety of microorganisms.

A number of physiologically active azasteroids have been obtained by fusing the pyrazole ring to the A or D ring of a naturally occurring steroid (3-5). In addition, a number of 15,16-diazasteroids or naphth[1,2-*g*]indazoles of general formula **1** have been the products of *de-novo* syntheses and contain a D ring which is either a pyrazole function or else derived therefrom (6-11). Very little biological testing of this latter class of compounds is recorded in the literature.



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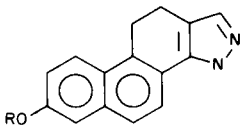
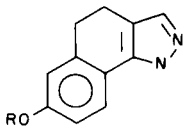
This study reports the complete synthesis and characterization of the novel 15,16-diazasteroid, 10,11-dihydro-3*H*-naphth[1,2-*g*]indazol-7-ol (**2b**) and the precursor methyl ether **2a**. In addition a "model" compound, 4,5-dihydro-1*H*-benz[*g*]indazol-7-ol (**3b**) was synthesized.

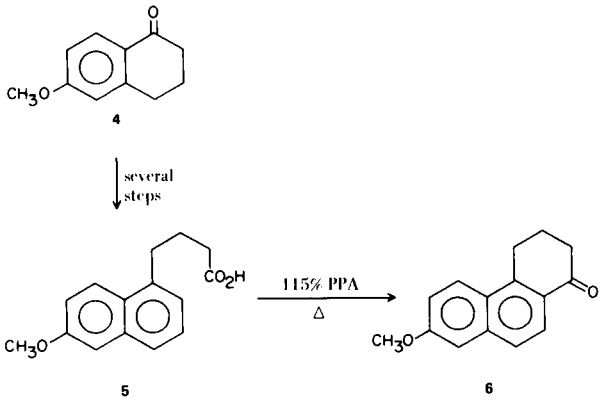


2a R = CH_3
2b R = H

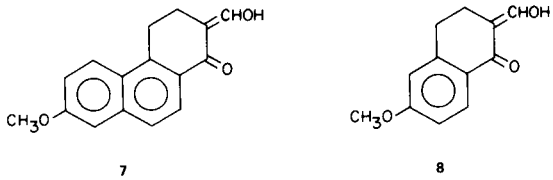


3a R = CH_3
3b R = H

3,4-Dihydro-7-methoxy-1(2*H*)-phenanthrone (**6**) was prepared by the polyphosphoric acid (PPA) cyclization (12) of 4-(6-methoxy-1-naphthalene)-butyric acid (**5**). The acid **5** was prepared from the commercially available 6-methoxy-1-tetralone (**4**) and ethyl 4-bromo-2-butenoate by the method of Stork (13) (Scheme I). The method of cyclization of **5** → **6** is unique to our study though not wholly novel.



Phenanthrone **6** was condensed with ethyl formate to yield the known hydroxymethylene ketone **7** (14). Crude **7** was then condensed with hydrazine to yield **2a**, and the methyl ether function of **2a** was cleaved with boiling 48% hydrobromic acid to yield **2b**.



In a pilot series of reactions, the benzindazol **3a** was prepared by known procedure (15) from **4**, ethyl formate, and hydrazine. When the intermediate hydroxymethylene derivative **8** was treated with boiling 48% hydrobromic acid, a highly colored polymeric material resulted. The benzindazol **3a**, itself, however, when so treated, yielded the expected novel **3b** in good yield without isomerization or degradation of the pyrazole function.

Compounds **2a**, **2b**, **3a**, and **3b** are colorless, crystalline, high-melting solids. The methoxy compounds **2a** and **3a** demonstrate very low water solubility and are apparently indefinitely stable in air. The indazolols **2b** and **3b** show a tendency to discoloration on long standing and basic aqueous solutions rapidly darken. Compound **3b** shows a slight but appriciable water solubility, and may be recrystallized from boiling water.

In accordance with the observed low basicity for pyrazoles and indazoles, (16,17) the above compounds form water soluble salts with concentrated aqueous hydrobromic acid or with anhydrous hydrogen chloride in non-aqueous solvents. These salts are rapidly hydrolyzed on dilution, however, with precipitation of the free base.

Compounds **2a**, **2b**, **3a**, and **3b** were subjected to a testing program as antibiotics. Compounds **2a**, **3a**, and **3b** have demonstrated *in vitro* activity against a variety of microorganisms. These results will be reported in detail at a later date.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point device and are uncorrected. Infrared spectra were determined on a Beckman IR-5A spectrophotometer and proton nuclear magnetic resonance spectra were determined on a Varian A-60 high resolution spectrometer using tetramethylsilane as an internal standard. Microanalysis were performed by Galbraith Laboratories, Knoxville, Tennessee and by Midwest Microlabs, Inc., Indianapolis, Indiana.

Preparation of 3,4-Dihydro-7-methoxy-1(2*H*)-phenanthrone (**6**).

4-(6-Methoxy-1-naphthalene)butyric acid (**5**) was prepared according to the method of Stork (13) in 26% yield from 6-methoxy-1-tetralone (**4**) and ethyl 4-bromo-2-butenoate (Aldrich). The physical properties of **5** are: m.p. 151-152.5°, lit. (11) m.p. 151°; ir (potassium bromide) 1680 cm^{-1} (C=O); nmr (deuteriochloroform) δ 1.68-2.68 (m, 4H, CH_2), 2.90-3.27 (bt, 2H, benzylic CH_2), 3.91 (s, 3H, OCH_3), 7.01-8.11 (m, 6H, aromatic H), and 10.9 (s, 1H, CO_2H).

Acid **5** (7.5 g., 0.031 mole) was dissolved in aqueous sodium carbonate and precipitated with hydrochloric acid to yield a finely divided powder. Polyphosphoric acid (50 g. of 115% PPA) was heated to 110° in a 400 ml. beaker. Heating of the PPA was halted, the powdered **5** was added and the mixture was stirred for 15 minutes. An additional 50 g. of PPA was then added and the mixture was reheated to 110° and then allowed to cool to 60° with occasional stirring.

The resulting brown syrup was poured into ice water and the solid which separated was filtered, washed with water, air-dried, and dissolved in 50 ml. of benzene. The benzene solution was poured onto a 15 g. 5 cm. by 1 cm. column of alumina (Merck active aluminum oxide, neutral), and the column was washed with additional benzene until no further material was eluted. Evaporation of the benzene *in vacuo* yielded 5.0 g. (71%) of **6** [m.p. 97-99°, lit. (11) m.p. 98-100°; ir (potassium bromide) 1640 cm^{-1} (C=O); nmr (deuteriochloroform) δ 1.85-2.81 (m, 4H, CH_2), 2.92-3.28 (bt, 2H, benzylic CH_2), 3.83 (s, 3H, OCH_3), and 6.85-8.09 (m, 5H, aromatic H)].

Preparation of 10,11-Dihydro-7-methoxy-3*H*-naphth[1,2-*g*]indazole (**2a**).

Phenanthrone **6** (3.5 g., 0.0154 mole) was added to a stirred mixture of 1.7 g. (0.0315 mole) of sodium methoxide (Fisher, "Purified"), 2.3 g. (0.0312 mole) of ethyl formate (Matheson), and 50 ml. of benzene under nitrogen in a 100 ml., round bottom flask.

The mixture was stirred for 6 hours and then poured into one liter of ice water; the resulting mixture was extracted with 300 ml. of ether. The organic phase was washed with 500 ml. of aqueous 5% sodium hydroxide; the aqueous extracts were combined, and the combined extracts were acdiified with excess concentrated hydrochloric acid. The precipitated solid material was filtered out and vacuum-dried to yield 2.8 g. (72%) of 3,4-dihydro-2-(hydroxymethylene)-7-methoxy-1(2*H*)-phenanthrone (**7**) as a yellow powder.

Compound **7** (2.8 g., 0.011 mole) was dissolved in 300 ml. of methanol, and 3 ml. of 95% hydrazine was added. The solution was stirred 4 hours and then reduced to 50 ml. in volume by boiling on a hot plate. Upon cooling, 1.7 g. of **2a** (43% based on **6**) separated as feathery yellow needles (softened at 190°, m.p. 212-213°, s.t., vac.). This material was recrystallized from 200 ml. of benzene, yielding 1.1 g. (29% based on **6**) of **2a** as a white powder [m.p. 212.5-214°, s.t., vac.); uv λ max (ethanol) 266.5 mμ (log ε = 4.537); nmr (perdeuteriopyridine) δ 2.76-3.57 (m, 4H, CH_2), 3.81 (s, 3H, OCH_3), 7.17-8.85 (m, 6H, aromatic and vinyl H), and 13.5-14.9 (b, 1H, NH)].

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.88; H, 5.74; N, 11.02.

Preparation of 10,11-Dihydro-3*H*-naphth[1,2-*g*]indazol-7-ol (**2b**).

The methyl ether **2a** (0.50 g., 0.0020 mole) was boiled with 25 ml. of aqueous 48% hydrobromic acid for 12 hours under nitrogen purge. The mixture was cooled, made strongly alkaline with aqueous 10% sodium hydroxide, and filtered. The alkaline filtrate was neutralized with aqueous 10% sodium bicarbonate solution, and the resulting gray precipitate was filtered and sublimed at 240°/0.03 mm. to yield 0.4 g. (85%) of **2b** as a light orange crystalline solid [(m.p. 258-261°, s.t., vac.; uv λ max (sodium salt in water) 257.5 mμ (log ε = 4.594); nmr (perdeuteriopyridine) δ 2.70-3.59 (m, 4H, CH_2), 7.16-8.82 (m, 6H, aromatic and vinyl H), and 12.1-14.1 (b, 2H, OH and NH)]. Indazolol **2b** (0.2 g.) was recrystallized from 1:1:1 mixture of pyridine:benzene:cyclohexane and then sublimed again as above to yield 0.15 g. of a white, crystalline solid, m.p. unchanged. This material was submitted for analysis.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.52; H, 5.26; N, 12.00.

Preparation of 4,5-Dihydro-1*H*-benz[*g*]indazol-7-ol (**3b**).

4,5-Dihydro-7-methoxy-1*H*-benz[*g*]indazol (**3a**) was prepared by the method of Taylor and coworkers (15) [m.p. 162-163.5°, s.t., vac., lit., (14) m.p. 164-166°; uv λ max (ethanol) 270 mμ (log ε = 4.057); nmr (deuteriochloroform) δ 2.51-3.09 (m, 4H, CH_2), 3.72 (s, 3H, OCH_3), 6.51-7.74 (m, 4H, aromatic and vinyl H), and 10.8-11.4 (bs, 1H, NH)]. Compound **3a** (10.0 g., 0.0500 mole, m.p. 162-163.5°) was boiled with 250 ml. of aqueous 48% hydrobromic acid for 12 hours under nitrogen purge. The mixture was cooled and filtered and the resulting pink solid was dissolved in 200 ml. of aqueous 6% sodium hydroxide. The alkaline solution was filtered and neutralized with 10% sodium bicarbonate solution to yield 6.8 g. (73%) of off-white powder (**3b**) [m.p. 198-203°, s.t., vac.].

An analytical sample of **3b** was recrystallized from acetonitrile and sublimed (180°/0.03 mm.) to yield a white, hard, microcrystal-

line solid [m.p. 206.5-208°, s.t., vac.; uv λ max (water) 270 mμ (log ε = 4.196); nmr (perdeuteriopyridine) δ 2.78 (bs, 4H, CH_2), 6.78-8.12 (m, 4H, aromatic and vinyl H), and 12.4 (bs, 2H, OH and NH)].

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.85; H, 5.37; N, 14.81.

REFERENCES

(1) We gratefully acknowledge support of this work by a grant to the Oklahoma State University from the American Cancer Society, Grant IN-91A. We thank the Merck, Sharp, and Dohme Company for partial support.

(2) Department of Chemistry: (a) NDEA Fellow 1966-69; This work is abstracted in part from the thesis submitted in partial fulfullment of the Doctor of Philosophy degree in the Oklahoma State University; (b) To whom inquiries should be addressed; (c) Department of Microbiology.

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