Evidence for the Structures of Steroidal *N*-Phenyl[3,2-*c*]pyrazoles. Attempted Dehydrogenation to Indazoles

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19-Nor-1′-phenyl-4,17(20)-pregnadieno[3,2-*c*]pyrazole (**4**) and 19-nor-2′-phenyl-2,4,17(20)-pregnatrieno[3,2-*c*]pyrazole (**5**) were dehydrogenated with dichlorodicyanobenzoquinone to afford 19-nor-1′-phenyl-4,6,17(20)-pregnatrieno[3,2-*c*]pyrazole (**10**) and 19-nor-2′-phenyl-1(10)-2,4,17(20)-pregnatetraeno[3,2-*c*]pyrazole (**9**), respectively. The ultraviolet spectrum of **9** resembles very much that of 3-methyl-1-phenylindazole (**6**) and is definitely different from that of 2-phenylindazole (**7**) so that the correctness of the structural assignments is confirmed.

Steroids with a pyrazole ring fused to ring A have been reported to possess unusually high biological activities.[1,2] In general, they are prepared by condensing a 3-keto steroid at the 2 position with an ester. The resultant β-dicarbonyl compound is then reacted with a monosubstituted hydrazine. Two isomeric pyrazoles, 1′-substituted steroidal [3,2-*c*]pyrazole (**1**), and 2′-substituted steroidal [3,2-*c*]pyrazole (**2**), are obtained. The two pyrazoles show distinctive spectral characteristics.

Thus, of the two pyrazoles, **1** and **2** (Δ^4, R = C_6H_6, R′ = H, R^2 = CH_3), one absorbs maximally at ~300 mμ (ε ~32,000) while the other shows maximal absorption at ~260 mμ (ε ~17,000).[2] Hirschmann, *et al.*,[2] proposed that the pyrazole which absorbs at 300 mμ has structure **1** while that absorbing at 260 mμ has structure **2**. On the basis of the difference in ultraviolet absorption of the two pyrazoles and on the basis of the similarity in the nmr splitting pattern of the phenyl protons of aniline to the phenyl protons of the pyrazole which absorbs maximally at the greater wavelength, they concluded that the pyrazole which absorbs at 260 mμ exhibits steric inhibition of resonance. Therefore, its structure must be **2**, for in **2** there is steric interaction between the ortho hydrogen of the phenyl ring and the C-4 hydrogen of the steroid nucleus.[3] The mechanism by which the pyrazole ring is formed was advanced as additional evidence in support of this conclusion.

Although the interpretation of Hirschmann, *et al.*, is not unreasonable, there is, nevertheless, a need for more conclusive evidence.

Recent publications on the preparation of 1-aryl- and 2-arylindazoles from aromatic ketones and aldehydes[4] suggested to us the possibility of providing independent support for the structures of the *N*-aryl steroidal pyrazoles by comparing the ultraviolet spectra of the indazoles derived from the dehydrogenation of steroidal *N*-aryl-19-nor[3,2-*c*]pyrazoles with the spectra of appropriate 1-aryl- and 2-arylindazoles prepared from the aromatic carbonyl compounds.

This report describes the preparation and dehydrogenation of the two isomeric steroidal *N*-phenylpyrazoles, **4** and **5**, obtained from 19-norpregna-4,17(20)-dien-3-one (**3**)[5] and the comparison of the spectra of their dehydrogenated products with the spectra of 3-methyl-1-phenylindazole (**6**)[4a,6] [λ_{max} 251 mμ (ε 34,050), 304–307 (13,500)] and 2-phenylindazole (**7**)[4a,b] [λ_{max} 235–236 mμ (ε 21,700), 294–295 (15,800)].

19-Nor-1′-phenyl-4,17(20)-pregnadieno[3,2-*c*]pyrazole (**4**) and 19-nor-2′-phenyl-2,4,27(20)-pregnatrieno[3,2-*c*]-pyrazole (**5**) were synthesized from **3** by the method described by Hirschmann, *et al.*[2] One of the pyrazoles absorbs at 297–298 mμ (ε 28,000) while the other absorbs at 259–261 mμ (ε 16,750). The phenyl protons of the pyrazole which absorb at 297–298 mμ appear as a complex multiplet between 429 to 463.5 cps (downfield with respect to internal tetramethylsilane at 60 Mc in deuteriochloroform) in the nmr spectrum while the same protons of the isomeric pyrazole appear as a single peak at 446 cps. In addition, the vinyl proton at C-4 of the pyrazole absorbing at 297–298 mμ resonates at 382 cps while that of the pyrazole absorbing at 259–261 mμ resonates at 373 cps. In accordance with the interpretation of Hirschmann, *et al.*,[2] the pyrazole absorbing at 297–298 mμ is assigned structure **4** and that absorbing at 259–261 mμ is assigned structure **5**. In **4**, the phenyl ring is in the plane of the pyrazole ring so that the ortho protons of the phenyl ring are more deshielded than the meta and para protons. This gives rise to the multiplet that is observed in the region of 429–463.5 cps. In contrast, the phenyl ring of **5** is out of the plane of the pyrazole ring because of steric repulsion. The time-averaged magnetic field effect on the phenyl protons due to the pyrazole ring is such that these protons appear to be equivalent.[7] Since the phenyl ring of **5** is not coplanar with the pyrazole ring, the C-4 proton of **5** is more apt to be shielded than the corresponding proton of **4**. Consequently, the C-4 proton of **5** would be expected to resonate at a higher field than that of **4**. Experimentally, this is, indeed, what is observed.

Dehydrogenation of **4** and **5** was achieved with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in acetone. We had expected that the elimination of 1 mol equiv of hydrogen from **4** and **5** would give the indazoles, 19-nor-1′-phenyl-1(10),4,17(20)-pregnatrieno[3,2-*c*]pyrazole (**8**) and 19-nor-2′-phenyl-1(10)-2,4,17(20)-pregnatetraeno-

(1) (a) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Amer. Chem. Soc.*, **83**, 1478 (1961); (b) R. O. Clinton, R. L. Clarke, F. W. Stonner, A. J. Manson, and K. F. Jennings, *J. Org. Chem.*, **27**, 2800 (1962).

(2) R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H. Fried, R. Ellis, G. J. Kent, and M. Tishler, *J. Amer. Chem. Soc.*, **86**, 1520 (1964).

(3) *Cf.* S. Tabak, I. I. Grandberg, and A. N. Kost, *Tetrahedron*, **22**, 2703 (1966).

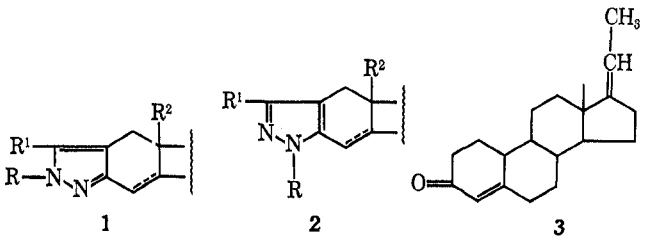
(4) (a) W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.*, 3048 (1965); (b) L. Krbechek and H. Takimoto, *J. Org. Chem.*, **29**, 1150 (1964); (c) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, 4831 (1965).

(5) F. B. Colton, L. Nysted, B. Riegel, and A. L Raymond, *J. Amer. Chem. Soc.*, **79**, 1123 (1957).

(6) Kindly supplied by Professor R. O. C. Norman, to whom we are indebted.

(7) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

[3,2-*c*]pyrazole (**9**), respectively. Because one of the indazoles has an *o*-quinoid structure while the other has a benzenoid structure, the two indazoles were expected to be distinguishable by spectroscopic means.[8]



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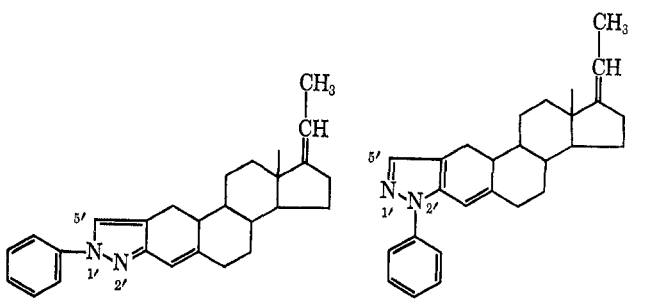

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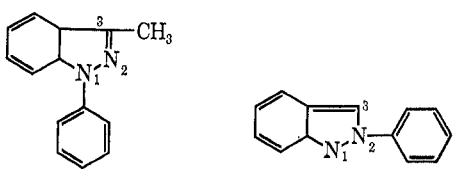

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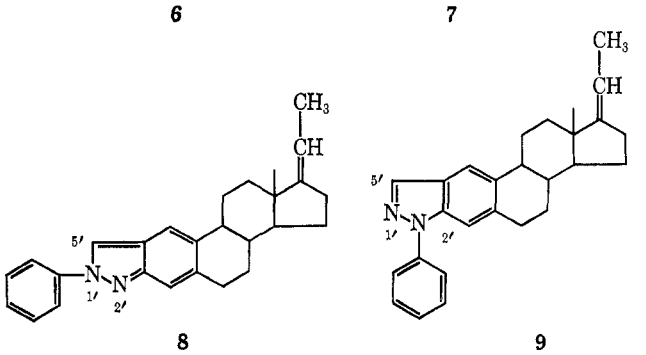

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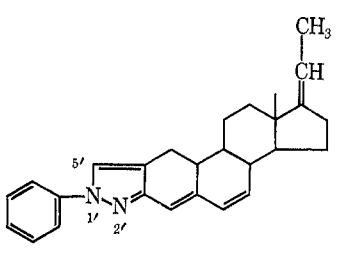

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Instead of **8**, the dehydrogenated product obtained from **4** proved to be 19-nor-1′-phenyl-4,6,17(20)-pregnatrieno[3,2-*c*]pyrazole (**10**). Besides the protons at C-5′ and -20, its nmr spectrum reveals the presence of three additional vinyl protons. These protons appear as a singlet at 385 cps and a pair of doublets centered at 351 and 375 cps. Each of the doublets exhibits a spin–spin coupling constant of 10 cps. The singlet is assigned to the C-4 proton and the pair of doublets are assigned to the protons at C-6 and -7. The extremely high levorotation, which this product displays, is a further indication that the newly introduced double bond is located at the 6,7 position.[1a] The ultraviolet spectrum of **10** shows maximal absorption at 246.5–248.5 mμ (ε 9030) and 320–321 (37,700), and it is clearly different from the spectrum of 3-methyl-1-phenylindazole (**6**) and that of 2-phenylindazole (**7**).

Dehydrogenation of **5** gives the expected product **9**. Its nmr spectrum shows no vinyl protons other than those at C-5′ and -20. The ultraviolet spectrum of **9** shows maximal absorption at 256.5 mμ (ε 28,450) and 306 (7900). This spectrum resembles greatly that of 3-methyl-1-phenylindazole (**6**), and it differs distinctly from that of 2-phenylindazole (**7**).

These results indicate that the structures of the two isomeric pyrazoles obtained from **3** are correctly formulated. Hence, Hirschmann, *et al.*, were correct in their conclusion.[2] However, in view of the study of Tensmeyer and Ainsworth,[7] the inference which the former drew[2] from a comparison of the nmr splitting pattern of the phenyl protons of the pyrazoles with that of the phenyl protons of aniline is worth noting. In aniline, the ortho protons are shifted upfield by resonance while, in an unhindered phenylpyrazole, the same protons are shifted downfield because of the deshielding effect of the pyrazole ring.[7] Consequently, the similarity that they observed[2] in the phenyl proton region of the nmr spectra between aniline and the steroidal 1′-phenyl[3,2-*c*]pyrazole must be attributed to an interaction of the nitrogen atom with the aromatic protons, an interaction which is diminished in the 2′-phenylpyrazole as a result of the lack of coplanarity.

Experimental Section[9]

2-(Hydroxymethylene)-19-norpregna-4,17(20)-dien-3-one.—To a mixture of 2.5 g of 19-norpregna-4,17(20)-dien-3-one,[5] 10 ml of dry benzene and 2 ml of ethyl formate, stirred in an ice bath, was added 1.2 g of a 56% dispersion of sodium hydride in mineral oil. The reaction mixture was stirred in the ice bath for 2.5 hr, the ice being allowed to melt. The resultant brown paste was carefully diluted with water and then with benzene. The benzene phase was separated and extracted successively with water and 5% sodium hydroxide. The combined aqueous, alkaline phases were acidified by addition to a mixture of ice and 5% hydrochloric acid. The mixture was extracted with methylene chloride. The methylene chloride extract was dried (Na_2SO_4) and distilled to dryness to afford the product as a viscous yellow-brown oil, which imparted a purple-brown color to an alcoholic solution of ferric chloride.

19-Nor-1′-phenyl-4,17(20)-pregnadieno[3,2-*c*]pyrazole (4) and 19-Nor-2′-phenyl-2,4,17(20)-pregnatrieno[3,2-*c*]pyrazole (5).—The aforementioned crude hydroxymethylene compound was dissolved in 30 ml of 95% ethanol. After 1 ml of phenylhydrazine was added, the reaction mixture was heated under reflux in a nitrogen atmosphere for 1 hr. Then the reaction mixture was distilled to dryness under reduced pressure. The residue was dissolved in methylene chloride. The methylene chloride solution was washed with water, dried (Na_2SO_4), and distilled to dryness to afford a brown tarry product.

The tar was chromatographed on 300 g of neutral alumina. Elution of the column with 20% hexane in benzene gave in succession 0.41 g of **4** and 1.06 g of **5**. Crystallization of **4** from ether–hexane gave 0.25 g of a colorless crystalline product, mp 138–141.5°. Another crystallization from ether–hexane raised the mp to 141.5–143.5°; $[\alpha]^{26}D$ −34°; (*c* 1, $CHCl_3$); λ_{max}^{MeOH} 297–298 mμ (ε 28,000); λ_{min} 253–255 mμ (ε 5120); λ_{max}^{KBr} 3.28,

(8) *Cf.* V. Rosseau and H. G. Lindwell, *J. Amer. Chem. Soc.*, **72**, 3047 (1950); J. Elguero, A. Fruchlier, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 2075 (1966).

(9) Melting points were taken on a Fisher-Johns melting block and are corrected. The nmr spectra were determined in deuteriochloroform on a Varian A-60 instrument with tetramethylsilane as an internal standard.

6.12, 6.25, 6.35 μ; nmr 429–463.5 (m), 382 (s), 304 (q, J = 6.5 cps), 93 (d, J = 6.5 cps), 48 cps (s).

Anal. Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.29. Found: C, 84.60; H, 8.30; N, 7.68.

Crystallization of **5** from ether–hexane gave 0.66 g of a yellow crystalline product: mp 156–160°; $[\alpha]^{26}D$ +26° (*c* 1, $CHCl_3$); λ_{max}^{MeOH} 259–261 mμ (ε 16,750); λ_{min} 234.5–235.5 mμ (ε 8725); λ_{max}^{KBr} 3.25, 6.15, 6.22 μ; nmr 446 (s), 442 (s), 373 (s), 303 (q, J = 7 cps), 93 (d, J = 7 cps), 45 cps (s).

Anal. Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.29. Found: C, 84.52; H, 8.30; N, 7.32.

19-Nor-2′-phenyl-1(10)-2,4,17(20)-pregnatetraeno[3,2-*c*]pyrazole (9).—To a warm solution of 0.48 g of 19-nor-2′-phenyl-2,4,17(20)-pregnatrieno[3,2-*c*]pyrazole (**5**) in 40 ml of acetone was added portionwise with stirring over a period of 1 hr 0.35 g of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. The reaction mixture, which contained a crystalline product, was allowed to stand at room temperature for an additional hour. Then the colorless, crystalline product was collected, washed with acetone, and dried, yield 0.27 g, mp 198.5–200.5°. The combined filtrate and washings were concentrated to 25 ml. On standing at room temperature for 15 hr, the resultant mixture afforded an additional 0.04 g of **9**, mp 196.5–201.5°. Crystallization of the first crop from acetone raised the mp to 201.5–204.5°; $[\alpha]^{26}D$ +15° (*c* 1, $CHCl_3$); $\lambda_{max}^{CHCl_3-MeOH}$ 256.6 mμ (ε 28,450), 306 (7900); λ_{min} 232.5–233.5 mμ (ε 8860), 283.5–286 (5175); λ_{max}^{KBr} 3.27, 6.12, 6.13 μ; nmr 485.5 (s), 442.5–461 (m), 307 (q, J = 7 cps), 180 (t, J = 5 cps), 95 (d, J = 6.5 cps), 47.5 cps (s).

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.70; H, 7.82; N, 7.61.

19-Nor-1′-phenyl-4,6,17(20)-pregnatrieno[3,2-*c*]pyrazole (10).—To a warm solution of 1.01 g of 19-nor-1′-phenyl-4,17(20)-pregnadieno[3,2-*c*]pyrazole (**4**) in 30 ml of acetone was added portionwise with stirring over a period of 1 hr 0.78 g of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. The reaction mixture was allowed to stand at room temperature for 16 hr and then treated with a dilute solution of sodium sulfite. The reaction mixture was concentrated. The residue was diluted with ice water. The resultant brown solid was collected, washed with water, and dried. It was chromatographed on 100 g of neutral alumina. Elution of the column with 30% hexane in benzene gave 0.33 g of a pale yellow crystalline product, mp 183–186°. Crystallization from acetone gave **10** as colorless crystals, mp 187.5–190°. Admixed with **9**, it melted at 168–177°; $[\alpha]^{26}D$ −514° (*c* 0.25, $CHCl_3$); $\lambda_{max}^{CHCl_3-MeOH}$ 246.5–248.5 mμ (ε 9030), 320–321 (37,700); λ_{min} 237.5–239 mμ (ε 8500), 271–273 (5550); λ_{max}^{KBr} 3.28, 6.24, 6.38 μ; nmr 435.5–453.5 (m), 377 (d, J = 10 cps), 351 (d, J = 10 cps), 303.5 (*q*, J = 65 cps), 184 (d, J = 7 cps), 93 (d, J = 6.5 cps), 47.5 cps (s).

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 85.03; H, 7.99; N, 7.45.

Ultraviolet Absorption Maxima and Minima of 3-Methyl-1-phenylindazole (6):[4a,6] λ_{max}^{MeOH} 251 mμ (ε 34,050), 304–307 (13,500); λ_{min} 229–231 mμ (ε 8400), 278 (5080).

Ultraviolet Absorption Maxima and Minima of 2-Phenylindazole (7).—This substance was prepared according to the procedure of Krbechek and Takimoto;[4b] λ_{max}^{MeOH} 235–236 mμ (ε 21,700), 294–295 (15,800), λ_{min} 257 mμ (ε 2290).

Registry No.—**4**, 28504-58-7; **5**, 28504-59-8; **6**, 1575-29-7; **7**, 3682-71-1; **9**, 28504-62-3; **10**, 28504-63-4.

Synthesis of 1,10,11,11a-Tetrahydro-11a-methyl-2*H*-naphth[1,2-*g*]indol-7-ol, an Equilenin-Like 15-Aza Steroid[1]

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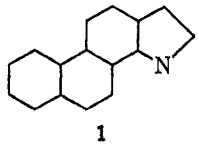
This study reports the synthesis and characterization of the 15-azaequilenin derivative 1,10,11,11a-tetrahydro-11a-methyl-2*H*-naphth[1,2-*g*]indol-7-ol (**6a**) as well as the methyl ether **6b** of the above compound and the novel model compound 3,3a,4,5-tetrahydro-3a-methyl-2*H*-benz[*g*]indole (**7**).

Steroids which have nitrogen incorporated in the cyclopentaphenanthrene nucleus have been shown to possess a wide range of physiological activities.[3–5] Interestingly, naph[1,2-*g*]indoles or 15-aza steroids of general formula **1** represent an almost totally neglected area of organic synthesis despite the fact that these compounds combine the steroid and indole nuclei in a single structure and may be expected to demonstrate significant biological activity.



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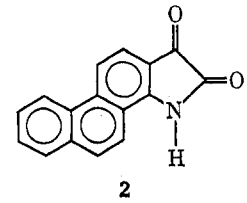
A literature search revealed only four examples of 15-monoaza steroid structures. Naphthisatin **2** was synthesized in the 1930's as a "synthetic decarboxylase,"[6] and compounds **3–5** were intermediates in steroid–terpene structure correlations.[7] No pharmacological data on the aforementioned compounds are available.



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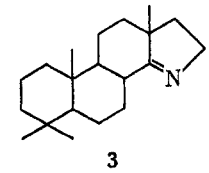

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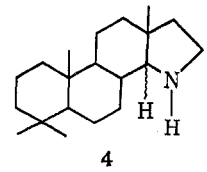

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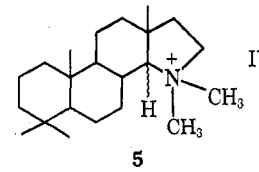

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