Synthesis of 7,8,9,10-Tetrahydropyrimido[1,2-*b*]indazole-4(1*H*)one and 2(1*H*)one Derivatives

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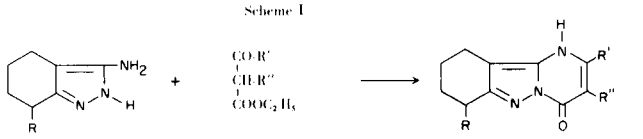
In connection with some work under way in these laboratories (1), we were interested in synthesizing a number of tetrahydropyrimido[1,2-*b*]indazole-4(1*H*)ones and 2(1*H*)ones, in order to study the biological properties of these compounds. A review of the literature indicated that these products apparently have not been previously synthesized. We found that fusion of 3-amino-4,5,6,7-tetrahydroindazoles (I and II) with β-ketoesters in an oil bath at 200° afforded crystalline products which were assigned the 4(1*H*)one structure (Scheme I) and fusion of

Scheme I



I, R = H
II, R = CH_3

III, R' = C_6H_5, R'' = H
IV, R' = CH_3, R'' = H
V, R' = R'' = CH_3

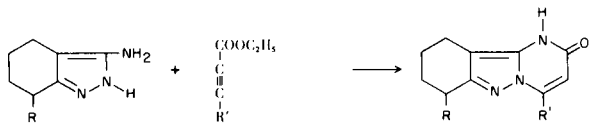
VIa, b, c, d, e, f

a, R = R'' = H, R' = C_6H_5
b, R = R'' = H, R' = CH_3
c, R = H, R' = R'' = CH_3
d, R = CH_3, R'' = H, R' = C_6H_5
e, R = R' = CH_3, R'' = H
f, R = R' = R'' = CH_3

3-amino-4,5,6,7-tetrahydroindazoles (I and II) with propiolic esters at 100° gave products which were assigned the 2(1*H*)one structure (Scheme II). Assignment of structure of the condensation products was made on the basis of elemental and spectral analyses (uv, ir, nmr). The uv spectra were similar to those of 7-oxo and 5-oxo pyrazolo[1,5-*a*]pyrimidine derivatives, respectively (2,3). Ir spectra determined in potassium bromide disks indicated a ν C=O at 1680 cm^{-1} and multiple bands in the 3μ region due to the intermolecular bonded NH stretching. Nmr spectra exhibited, besides other signals for alicyclic and substituents protons, a broad singlet (1H) at *ca.* 12 δ (NH). The conclusive proof of structure was afforded by an unambigous synthesis of VIa and VId (Scheme III).

Recently Reimlinger and his coworkers reported (4)

Scheme II



I, R = H
II, R = CH_3

VIII, R' = C_6H_5
IX, R' = CH_3
X, R' = H

XIa, b, c, d, e

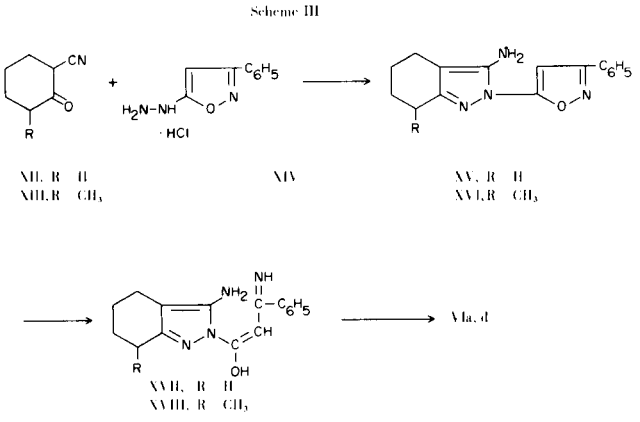
a, R' = C_6H_5, R = H
d, R = CH_3, R' = C_6H_5

b, R' = CH_3, R = H
e, R = CH_3, R' = H

c, R = R' = H

that reaction of 3-aminoindazole with propiolic acid methyl ester in ethanol gave a product melting at 335-339° for which it was not possible to assign one of the two alternative structures XX and XXI. We believe this product to be XXI due to the fact that it was obtained by dehydrogenation of XIc with Pd-C (10%) in decalin (Scheme IV). Compound XXI was identified by a mixed melting point and comparison of the spectroscopic data (uv, ir, nmr).

Scheme III



XII, R = H
XIII, R = CH_3

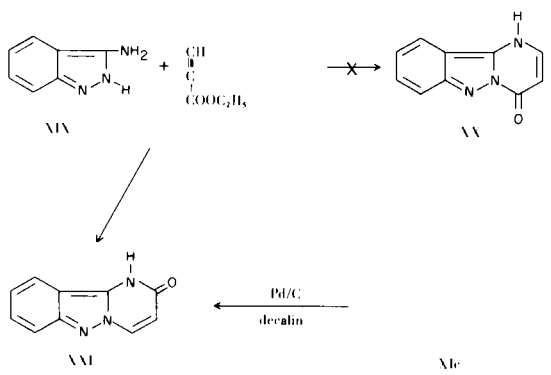
XIV

XV, R = H
XVI, R = CH_3

XVII, R = H
XVIII, R = CH_3

VIa, d

Scheme IV



EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Ir spectra were determined in nujol mull (unless otherwise specified) with a Perkin-Elmer infracord 137 spectrophotometer; uv spectra were determined in methanol solution with a Beckmann DB recording spectrophotometer. The nmr spectra were obtained with a Jeol C-60H spectrometer (TMS as internal reference).

General Procedure for the Tetrahydropyrimido[1,2-*b*]indazol-4(1*H*)one.

A mixture of I or II (5) and a slight excess of III, IV, or V was heated at 200° for 15 minutes. The crystalline products were recrystallized to yield 50-55% of the desired products VI.

7,8,9,10-Tetrahydro-2-phenylpyrimido[1,2-*b*]indazol-4(1*H*)one (VIa).

The product melted at 273-276° (ethanol); uv λ max nm log ε 328 (3.60), 250 (4.60); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.50-2.90 δ (m, overlapped, $-CH_2(CH_2)_2-CH_2$) 5.88 δ (s, 1H, -CH=), 7.50-8.00 δ (m, 5H, C_6H_5), *ca.* 12.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.33; H, 5.63; N, 15.76.

7,8,9,10-Tetrahydro-2-methylpyrimido[1,2-*b*]indazol-4(1*H*)one (VIb).

The product melted at 335-340° (ethanol): uv λ max nm log ε 300 (3.80), 264 (4.00), 254 sh (4.00); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.50-2.80 δ (m, overlapped by solvent signals, $-CH_3$ and $-CH_2(CH_2)_2CH_2$), 5.42 δ (q, 1H, -CH=, J = 0.7 Hz), *ca.* 12.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.34; H, 6.32; N, 21.04.

7,8,9,10-Tetrahydro-2,3-dimethylpyrimido[1,2-*b*]indazol-4(1*H*)one (VIc).

The product melted at > 350° (ethanol); uv λ max nm log ε 304 (3.80), 264 (4.00), 256 sh (3.90); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.60-2.90 δ (m, overlapped by solvent signals, 2 x CH_3 and $-CH_2(CH_2)_2CH_2$), 11, 68 δ (broad 1H, NH).

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.59; H, 6.89; N, 19.55.

7,8,9,10-Tetrahydro-7-methyl-2-phenylpyrimido[1,2-*b*]indazol-4(1*H*)one (VId).

The product melted at 318-320° (methanol): uv λ max nm log ε 328 (3.70), 250 (4.70); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.32 δ (d, 3H, CH_3, J = 6.8 Hz); 1.40-3.00 δ (m, overlapped by solvent signals, $(CH_2)_3CH$), 5.88 δ (s, 1H, CH=), 7.40-8.00 δ (m, 5H, C_6H_5), 12.10 δ (broad 1H, NH).

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 73.47; H, 6.13; N, 15.35.

7,8,9,10-Tetrahydro-2,7-dimethylpyrimido[1,2-*b*]indazol-4(1*H*)one (VIe).

The product melted at 270-272° (ethanol-water): uv λ max nm log ε 305 (3.69), 265 (3.99), 258 sh (3.83); ir (potassium bromide): 1680 cm^{-1} δ (CO); nmr (DMSO-d_6): 1.25 δ (d, 3H, CH_3 at C_7 J = 6.8 Hz), 1.40-3.00 δ (m, overlapped by solvent signals, $(CH_2)_3CH$); 2.28 δ (d, 3H, CH_3, J ~ 0.7 Hz), 5.47 δ (q, 1H, -CH=, J ~ 0.7 Hz), *ca.* 12.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.73; H, 6.93; N, 19.56.

7,8,9,10-Tetrahydro-2,3,7-trimethylpyrimido[1,2-*b*]indazol-4(1*H*)-one (VIf).

The product melted at 347-350° (ethanol); uv λ max nm log ε 312 (3.75), 268 (3.95), 260 sh (3.88); ir: (potassium bromide) 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.28 δ (d, 3H, CH_3, J = 6.8 Hz), 1.95 δ (s, 3H, CH_3 at C_3), 2.30 δ (s, 3H, CH_3 at C_2), 1.40-3.00 δ (m, overlapped by solvent signals, $(CH_2)_3CH$), *ca.* 12.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.83; H, 7.28; N, 18.15.

General Procedure for Tetrahydropyrimido[1,2-*b*]indazol-2(1*H*)-one.

A mixture of I or II (5) and a slight excess of VIII, IX, or X was heated at 100° for 45 minutes. After cooling, trituration with ethanol gave crystalline products, yield 40-45%.

7,8,9,10-Tetrahydro-4-phenylpyrimido[1,2-*b*]indazol-2(1*H*)one (XIa).

The product melted at 292-296° (ethanol); uv λ max nm log ε 294 (4.00), 242 (4.50); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.50-2.90 δ (m, overlapped by solvent signals, $-CH_2(CH_2)_2CH_2$), 5.90 δ (s, 1H, CH=), 7.40-8.00 δ (m, 5H, C_6H_5), 12.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.43; H, 5.71; N, 15.95.

7,8,9,10-Tetrahydro-4-methylpyrimido[1,2-*b*]indazol-2(1*H*)one (XIb).

The product melted at 279-281° (ethanol); uv λ max nm log ε 282 (3.87), 243 (4.24); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.50-2.80 δ (m, overlapped by solvent signals, $-CH_2(CH_2)_2CH_2$ and CH_3), 5.68 δ (q, 1H, -CH=, J ~ 0.7 Hz) 11.78 δ (broad, 1H, NH).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.38; H, 6.46; N, 20.51.

7,8,9,10-Tetrahydropyrimido[1,2-*b*]indazol-2(1*H*)one (XIc).

The product melted at 290-294° (ethanol); uv λ max nm log ε 284 (3.85), 244 (4.24); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.50-2.80 δ (m, $-CH_2(CH_2)_2CH_2$ overlapped by solvent signals), 5.77 δ (d, 1H, H_3, J = 7.8 Hz), 8.24 δ (d, 1H, H_4, J = 7.8 Hz), 11.90 δ (broad, 1H, NH).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21.

Found: C, 63.61; H, 5.89; N, 22.04.

7,8,9,10-Tetrahydro-7-methyl-4-phenylpyrimido[1,2-*b*]indazol-2-(1*H*)one (XId).

The product melted at 260-262° (methanol); uv λ max nm log ε 289 (3.95), 246 (4.48); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.19 (d, 3H, CH_3, J = 6.8 Hz), 1.40-3.00 δ (m, overlapped by solvent signals, $(CH_2)_3CH$-), 5.93 δ (s, 1H, -CH=), 7.40-8.10 δ (m, 5H, C_6H_5), *ca.* 12.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 73.17; H, 5.99; N, 15.05.

7,8,9,10-Tetrahydro-7-methylpyrimido[1,2-*b*]indazol-2(1*H*)one (XIe).

The product melted at 221-223° (ethanol); uv λ max nm log ε 283 (3.92), 245 (4.38); ir (potassium bromide): 1680 cm^{-1} (CO); nmr (DMSO-d_6): 1.23 δ (d, 3H, CH_3, J = 6.8 Hz), 1.40-3.00 δ (m, overlapped by solvent signals, $(CH_2)_3CH$), 5.80 δ (d, 1H, H_3, J = 7.8 Hz), 8.33 δ (d, 1H, H_4, J = 7.8 Hz), *ca.* 12.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.39; H, 6.38; N, 20.64.

General Procedure for 2-(5-Isoxazolyl)-2*H*-indazoles.

Equimolar amounts of 5-(3-phenylisoxazolyl)hydrazine hydrochloride (7 mmoles) (XIV) (1) and of XII or XIII (6) (7 mmoles) in ethanol (25 ml.) were refluxed for 1 hour. After cooling, addition of water gave the title compounds, yield 70-75%.

3-Amino-4,5,6,7-tetrahydro-2-(3-phenyl-5-isoxazolyl)-2*H*-indazole (XV).

The product melted at 207-210° (ethanol); ir 3430, 3300, 3140 cm^{-1} (NH_2); nmr (DMSO-d_6): 1.50-2.80 δ (m, overlapped by solvent signals, $-CH_2(CH_2)_2CH_2$), 5.32 δ (s, 2H, ONH_2), 7.12 δ (s, isoxazole H), 7.38-8.00 δ (m, 5H, C_6H_5).

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.72; H, 5.84; N, 19.91.

3-Amino-4,5,6,7-tetrahydro-7-methyl-2-(3-phenyl-5-isoxazolyl)-2*H*-indazole (XVI).

The product melted at 185-187° (methanol); ir: 3430, 3300, 3140 cm^{-1} (NH_2); nmr (deuteriochloroform): 1.22-2.80 δ (m, 10H, $-CH_3$ and $-(CH_2)_3CH$-), 4.80 δ (s, 2H, NH_2), 6.48 δ (s, isoxazole H), 7.40-8.00 δ (m, 5H, C_6H_5).

Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.04. Found: C, 69.81; H, 6.29; N, 19.39.

General Procedure for Hydrogenation of the 2-(5-Isoxazolyl)-2*H*-indazoles.

A mixture of 3 mmoles of XV or XVI, 300 ml. of ethanol and *ca.* 2 g. of W_2 Raney-Nickel (7) was hydrogenated in a Parr apparatus at 45-50 psi for 3 hours at room temperature. Removal of the catalyst and evaporation of ethanol yielded 75-80% of product after recrystallization.

3-Amino-α-(benzimidoylmethylene)-4,5,6,7-tetrahydro-2*H*-indazole-2-methanol (XVII).

The product melted at 208-212° (ethanol); ir: 3400, 3280, 3200 (broad) cm^{-1} (NH, NH_2); nmr (DMSO-d_6): 1.48-2.80 δ (m, overlapped by solvent signals, $-CH_2(CH_2)_2CH_2$), 6.12 δ (s, 1H, -CH=), 6.30 δ (s, 2H, NH_2), 7.30-8.10 δ (m, 6H, C_6H_5 and OH), *ca.* 9.00 δ (broad, 1H, NH).

Anal. Calcd. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.85. Found: C, 68.05; H, 6.44; N, 20.03.

3-Amino-α-(benzimidoylmethylene)-4,5,6,7-tetrahydro-7-methyl-2*H*-indazole-2-methanol (XVIII).

The product melted at 198-202° (ethanol); ir: 3400, 3280, 3200 (broad) cm^{-1} (NH, NH_2); nmr (deuteriochloroform): 1.12-2.80 δ (m, 10H, $-CH_3$ and $-(CH_2)_3CH$-), 5.22 δ (s, 2H, NH_2), 6.24 δ (s, 1H, -CH=), 7.20-7.60 δ (m, 6H, C_6H_5 and OH), *ca.* 9.80 δ (broad, 1H, NH).

Anal. Calcd. for $C_{17}H_{20}N_4O$: C, 68.89; H, 6.80; N, 18.91. Found: C, 69.16; H, 6.81; N, 18.92.

Cyclization of XVII and XVIII, 7,8,9,10-Tetrahydro-2-phenylpyrimido[1,2-*b*]indazol-4(1*H*)one (VIa), 7,8,9,10-Tetrahydro-7-methyl-2-phenylpyrimido[1,2-*b*]indazol-4(1*H*)one (VId).

To a solution of 4 mmoles of either XVII or XVIII in 30 ml. of ethanol was added 2 ml. of ethanol saturated with hydrochloric acid. After refluxing 1 hour, the ethanol was removed under vacuum and the residue was mixed with water (60 ml.). The precipitate was collected and recrystallized, yield 75-80%. The products, m.p. 273-276° and 318-320°, respectively, were identical with Va and Vd, respectively, obtained by above method (mixed m.p., ir, uv, nmr).

Pyrimido[1,2-*b*]indazol-2(1*H*)one (XXI).

A mixture of 10 mmoles of XIc and 1 g. of 10% palladium on charcoal suspended in 120 ml. of decalin was heated under reflux for 10 hours. The reaction mixture was filtered and on cooling, 0.92 g. (50%) of a crystalline product precipitated, m.p. 334-337° (lit. 335-339°) (acetic acid). This product was identical (mixed m.p., ir, uv, nmr) with a sample synthesized by an independent route (4).

Anal. Calcd. for $C_{10}H_7N_3O$: N, 22.69. Found: N, 22.57.

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