Notes

Synthesis of the 1,2,3,4-Tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one Ring System

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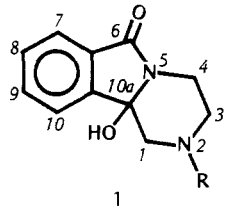
Several syntheses of 10b-hydroxy-substituted 1,2,3,4-tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one derivatives (**1**) by photolytic cyclization of ω-[(dialkylamino)ethyl]-phthalimides have been recently reported.[1,2] These



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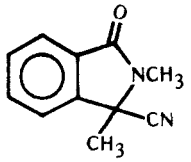
syntheses have produced the desired tricyclic heterocycles in only low to fair yields and in each case have given products bearing an angular hydroxyl group in the 10b position. In order to extend our work in related areas into the pyrazino[2,1-*a*]isoindole series, we wished to prepare 6-oxo compounds lacking the 10b-hydroxyl substituents but found that such derivatives had not been previously reported. While compounds incorporating the pyrazino-isoindole carbon skeleton have been reported,[3] the synthetic route is not amenable to synthesis of the 6-oxo species desired for the present work. We therefore needed to develop a route to these compounds which would not only permit the synthesis of the parent heterocycle but which would also allow structural variation within the series.

We envisioned synthesis of the desired compounds by one of the routes depicted in Scheme I. Among several reported routes to substituted 1-cyano-3-oxodihydroisoindoles,[4-6] that of Anderson et al.,[7] who had prepared 1-cyano-1,2-dimethyl-3-oxodihydroisoindole **2** as an intermediate in the synthesis of 3-oxodihydroisoindoles **3**, seemed most applicable. Thus, condensation of *o*-



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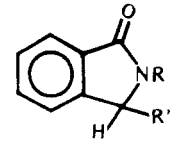

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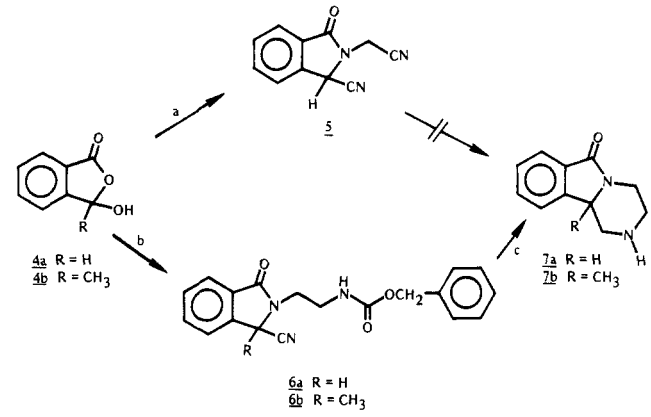
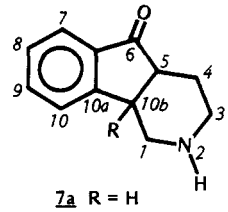
Scheme I



a) $H_2NCH_2CN \cdot HCl$, NaOAc, NaCN; b) $H_2NCH_2CH_2NHCOOCH_2C_6H_5 \cdot HCl$, NaOAc, NaCN; c) H_2, Pd/C, 50°C.

carboxybenzaldehyde (**4a**) or 2-acetylbenzoic acid (**4b**) with the requisite amine and NaCN yielded the desired intermediates **5** and **6a** or **6b**. Reduction of the dinitrile **5** over Raney nickel or 10% Pd/C at room temperature was quite slow. At elevated temperatures (50–70 °C) and higher pressures (45 psi) starting material was consumed, but a multicomponent mixture was formed. Although formation of the desired product should represent a terminal step from a variety of potential intermediates, the composition of this reaction mixture did not appear to change even with extended reaction times. Reduction of the protected amino nitrile **6a** also proved to be slow, but after 10 h at 40–50 °C over 10% Pd/C as a catalyst, a major product was formed which was shown to be the desired tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one (**7a**) by its spectral characteristics and by analysis.

The infrared spectrum of **7a** shows the expected loss of the Cbz carbonyl absorption but retains the isoindolin-1-one carbonyl absorption at 5.90 μm, slightly changed from that of the starting material at 5.81 μm. The mass



7a R = H
7b R = CH_3

spectrum displays a parent ion and the expected breakdown pattern. A 60-MHz NMR spectrum of the product gave, in addition to the expected four aromatic protons, a complex group of peaks in the aliphatic region. Assignment of the aliphatic proton signals was not straightforward even at 250 MHz, since only two of the three protons on positions 1 and 10b give resolved signals, the third overlapping one of the bands from the more complex four-proton system on positions 3 and 4. This problem was resolved by a double-resonance "tickling" experiment[8] which demonstrates that a signal at 4.42 ppm,

(1) Machida, M.; Takechi, H.; Kanaoka, Y. *Heterocycles* **1977**, 273.
(2) Coyle, J. D.; Newport, G. L. *Synthesis* **1979**, 381.
(3) Winn, M.; Zaugg, H. E. *J. Org. Chem.* **34**, 249 (1969).
(4) Spence, T. W. M.; Tennant, G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 835.
(5) Bayne, D. W.; Tennant, G.; Spence, T. W. M. *J. Chem. Soc., Chem. Commun.* **1972**, 849.
(6) Pfeiffer, P.; Jaensch, E. *J. Prakt. Chem.* **159**, 241 (1941).
(7) Anderson, P. S.; Christy, M. E.; Colton, C. D.; Shepard, K. C. *J. Org. Chem.* **43**, 3719 (1978).

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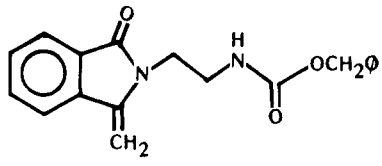
having two couplings of like sign, is due to the proton at position 10b and that the 2.31 and 3.63-ppm signals being of opposite sign and therefore geminal, are due to protons at C-1. The 250-MHz spectrum indicates that the structure of **7a** is as predicted by molecular models; that is, the piperazine ring exists in a typical chair conformation with the 10b proton axial and the aromatic portion of the molecule planar.

Application of the modified Strecker synthesis to 2-acetylbenzoic acid (**4b**) gave compound **6b**, the desired methyl-substituted homologue of **6a**, albeit in lower yield. This lower yield is interpreted in terms of the reduced reactivity of the ketone under the reaction conditions and to the presence of a substantial amount of a side product which was shown to be the methanophthalimide **8**. Catalytic reduction of **6b** gave, as expected, the desired **7b** but in low yield.



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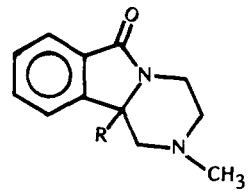
Analysis of the 250-MHz NMR spectrum of **7b** showed it to be very similar to that of the parent compound **7a** and confirms the assignment of the 10b proton in that spectrum. Both of the derivatives underwent methylation with formic acid and formaldehyde to give the *N*-methyl derivatives **9a** and **9b** as well as a variety of other acylation and alkylation reactions.



9a R = H
9b R = CH_3

Experimental Section

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian T-60 and Bruker WM-250 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department.

2-(Cyanomethyl)-1,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (5). A solution of 45.0 g (0.3 mol) of 2-carboxybenzaldehyde (**4a**) in 750 mL of glacial HOAc was mixed with 27.75 g (0.30 mol) of aminoacetonitrile hydrochloride and 29.4 (0.6 mol) of NaCN. The resulting suspension was treated with HCl gas for 5 min, causing some warming, and was then stirred at 25 °C overnight. The red-brown suspension was poured into 3 L of H_2O. The insoluble product was separated by filtration and washed well with water and with ether. After drying, the product weighed 28 g (47%), mp 198–200 °C, and was suitable for subsequent reactions without further purification: IR (KBr) 5.80, 6.77, 7.07, 7.22, 7.75, 8.75, 11.26, 13.49 μm; NMR (Me_2SO-d_6) δ 4.92 (2 H, s), 6.18 (1 H, s), 7.50–8.07 (4 H, m); mass spectrum, *m/e* 197 (100), 170, 143. An analytical sample, mp 198–200 °C, was prepared by recrystallization (twice) from hot CH_3OH. Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 66.64; H, 3.59; N, 21.12.

2-[2-[(Benzyloxycarbonyl)amino]ethyl]-1,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (6a). A suspension of 9.0 g (39 mmol) of (benzyloxycarbonyl)ethylenediamine hydrochloride[9] in 90 mL of absolute EtOH and 45 mL of glacial HOAc was treated with 3.2 g (39 mmol) of anhydrous NaOAc. The reaction mixture was stirred at room temperature for 10 min and 5.85 g (39 mmol) of 2-carboxybenzaldehyde (**4a**) and 1.9 g (39 mmol) of NaCN was added. The reaction mixture was stirred at room temperature for 18 h. Solvent was removed in vacuo to give a yellow slurry which was suspended in 100 mL of water. The product was extracted with two portions of EtOAc, and the extracts were combined, backwashed with $NaHCO_3$, and then dried over $MgSO_4$. Evaporation of solvent gave 6.1 g (47%) of a pale yellow oil: IR ($CHCl_3$) 2.90, 3.42, 5.76, 5.81, 6.62, 6.78, 7.14, 8.75, 9.98 μm; NMR ($CDCl_3$) δ 3.2–4.0 (4 H, m), 4.93 (2 H, s), 5.60 (1 H, s), 5.85 (1 H, t, *J* = 6 Hz), 7.18 (5 H, s), 7.33–7.82 (4 H, m); mass spectrum, *m/e* 335, 244, 228, 227, 200, 171 (100), 91. Analytically pure **6a**, mp 116–118 °C (ether), was separated from a minor, more polar impurity by column chromatography on silica gel, eluting with EtOAc. Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.04; H, 5.11; N, 12.53. Found: C, 68.05; H, 5.14; N, 12.66.

In like manner, 2-[2-[(benzyloxycarbonyl)amino]ethyl]-1,3-dihydro-3-oxo-1-methyl-1*H*-isoindole-1-carbonitrile (**6b**), mp 125–126 °C (EtOAc/petroleum ether) was prepared in 38% yield from 2-acetylbenzoic acid (**4b**): IR (KBr) 3.00, 5.92, 6.48, 7.24, 8.00, 8.82, 10.15, 13.11, 13.21, 14.45 μm; NMR ($CDCl_3$) δ 1.88 (3 H, s), 3.33–3.88 (4 H, m), 5.08 (2 H, s), 6.00 (1 H, br s), 7.30 (5 H, s), 7.30–7.93 (4 H, m); mass spectrum, *m/e* 349, 258, 242, 198, 185, 156, 91 (100). Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.49; H, 5.66; N, 11.80.

Also isolated from the preparation of **6b** was a 20% yield of **8**: mp 136–138 °C (EtOAc); IR (KBr) 3.02, 5.78, 5.94 μm; NMR (Me_2SO-d_6/CD_3OD, 1:1) δ 3.27 (2 H, t, *J* = 7 Hz), 3.80 (2 H, t, *J* = 7 Hz), 4.93 (2 H, s), 5.08 (1 H, d, *J* = 16 Hz), 5.13 (1 H, d, *J* = 16 Hz), 6.92 (5 H, s), 7.30–7.83 (4 H, m); mass spectrum, *m/e* 322, 231, 217, 216, 187, 172, 160, 158, 147, 130, 91 (100). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.47; H, 5.63; N, 8.63.

1,2,3,4-Tetrahydropyrazino[2,1-*a*]isoindol-6(2*H*)-one (7a). A solution of 17.0 g (51 mmol) of **6a** in 300 mL of absolute EtOH and 30 mL of concentrated HCl was hydrogenated over 5.0 g of 10% Pd/C at 50 °C and an initial pressure of 50 psi. After 6 h, the reaction mixture was filtered hot and the filtrate was concentrated to give 3.8 g of product, mp 305 °C dec. Additional washing of the catalyst with boiling CH_3OH, concentration, and filtration gave a further 3.5 g of **7a** (64% total yield): IR (KBr) 3.62, 5.90, 7.03, 7.76 μm; NMR ($CDCl_3$; free base at 250 MHz) δ 1.83 (1 H, s, NH), 2.31 (1 H, d of d, *J* = 11.9, 10.7 Hz, 1a), 2.62 (1 H, d of t, *J* = 11.9, 3.8 Hz, 3a), 3.07–3.27 (2 H, m, 4a, 3e), 3.63 (1 H, d of d, *J* = 11.9, 4.2, 1e), 4.36–4.49 (2 H, m, 4e, 10b), 7.40–7.60 (3 H, m, 8, 9, 10), 7.86–7.93 (1 H, d, *J* = 7 Hz, 7); mass spectrum, *m/e* 188 (100), 159, 146, 132, 131, 130, 117, 104. Anal. Calcd for $C_{11}H_{12}N_2O$·HCl: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.71; H, 5.78; N, 12.47.

In like manner, 5.25 g (15.0 mmol) of compound **6b** in 250 mL of absolute EtOH and 25 mL of concentrated HCl was reduced over 2 g of 10% Pd/C to give, after chromatography and HCl salt formation, 1.34 g (38%) of compound **7b**: mp 290–292 °C dec; IR (KBr) 3.45, 3.75, 5.90, 6.30, 6.82, 6.90, 7.12, 7.28, 7.75, 12.95 μm; NMR ($CDCl_3$; free base at 250 MHz) δ 1.59 (3 H, s, CH_3), 1.87 (1 H, s, NH), 2.39 (1 H, d, *J* = 12, 1a), 2.49–2.62 (1 H, d of t, *J* = 12, 4.5, 3a), 3.04–3.22 (2 H, m, 4a, 3e), 3.30 (1 H, d, *J* = 12, 1e), 4.28–4.39 (1 H, m, 4e), 7.37–7.60 (3 H, m, 8, 9, 10), 7.90 (1 H, d, *J* = 7, 7); mass spectrum, *m/e* 202 (100), 173, 159, 146. Anal. Calcd for $C_{12}H_{14}N_2O$·HCl: C, 60.37; H, 6.33; N, 11.73. Found: C, 59.98; H, 6.29; N, 11.38.

The free base of **7b** is a crystalline solid, mp 108.5–110.0 °C.

Preparation of 9a and 9b. Methylation of **7a** and **7b** was accomplished by heating 5 mmol of HCl salt in 10 mL of H_2O with 10 equiv of aqueous CH_2O and 25 equiv of 97% HCOOH solution for 2 h. The reaction mixture was then evaporated in

(8) Whipple, E. B.; Ruta, M.; Watts, V. S.; Goldstein, J. H. *J. Chem. Phys.* **45**, 4372 (1966).

(9) Lawson, W. B.; Leafer, M. D., Jr.; Tewes, A.; Rao, G. J. S. *Hoppe-Seyler's J. Physiol. Chem.* **349**, 251 (1968).

vacuo, dissolved in H_2O, and made alkaline with NaOH solution. The product was extracted into EtOAc, the extract was dried over $MgSO_4$ and solvent was evaporated. The HCl salts were formed in ether with HCl gas dissolved in ether to give **9a** in 48% yield, mp 286–287 °C (EtOH), and **9b** in 90% yield, mp >290 °C dec (CH_3CN/CH_3OH). Compound **9a**: IR (KBr) 4.32, 5.92, 6.80, 6.92, 7.10, 7.78, 13.60 μm; NMR (D_2O) δ 2.5–5.0 (7 H, m), 3.17 (3 H, s), 7.70 (4 H, s); mass spectrum, *m/e* 202 (100), 159, 130. Anal. Calcd for $C_{12}H_{14}N_2O$·HCl: C, 60.37; H, 6.33; N, 11.73. Found: C, 60.24; H, 6.43; N, 11.77. Compound **9b**: IR (KBr) 3.77, 5.88, 6.86, 7.17, 7.25, 7.37, 7.77, 13.15 μm; NMR (Me_2SO-d_6/D_2O, 1:1) δ 1.73 (3 H, s), 2.5–4.7 (6 H, m), 2.95 (3 H, s), 7.73 (4 H, m); mass spectrum, *m/e* 216, 173, 158, 104, 58 (100). Anal. Calcd for $C_{13}H_{16}N_2O$·HCl: C61.79; H, 6.81; N, 11.08. Found: C, 61.70; H, 6.72; N, 11.14.

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Registry No. 4a, 16859-59-9; **4b**, 1828-76-8; **5**, 80262-84-6; **6a**, 80262-85-7; **6b**, 80262-86-8; **7a**, 79016-59-4; **7a**·HCl, 80262-87-9; **7b**, 80262-88-0; **7b**·HCl, 80262-89-1; **8**, 80262-90-4; **9a**·HCl, 80262-91-5; **9b**·HCl, 80262-92-6; aminoacetonitrile hydrochloride, 6011-14-9; (benzyloxycarbonyl)ethylenediamine hydrochloride, 18807-71-1.

Stereoselective Protonation of Stable Carbanions Derived from 9,10-Dihydrophenanthrenes

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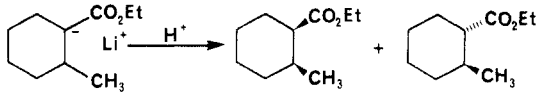
The stereochemistry of alkylation and protonation of stable carbanions remains a subject of current interest by virtue of its importance in organic synthesis.[1] Thermodynamic and kinetic control of protonation of cycloalkyl carbanions can yield products of different stereochemistry.[2,3] For example, Krapcho and Weimaster[2] report that protonation of **1** under equilibrating conditions favors the trans stereochemistry while kinetic control of protonation favors cis stereochemistry (eq 1). In cyclohexane ring



(1)

1	thermodynamic	24%	76%
	kinetic	72%	28%

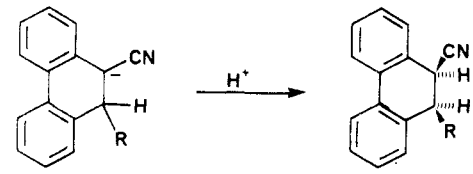
systems equatorial protonation is normally favored under kinetic control.[2] In contrast, kinetic control of protonation or methylation of carbanions derived from 9,10-dihydrophenanthrenes is reported to occur highly selectively from the axial direction.[4] Since the reactions of stable carbanions derived from 9,10-dihydrophenanthrenes have not previously been investigated, no comparisons of thermodynamic and kinetic product ratios have been reported for these systems. The 9,10-dihydrophenanthrenes represent a class of compounds with the unusual conformational property that substituents in the 9- and 10-positions preferentially occupy the pseudoaxial positions.[5,6] This preference leads to the prediction that thermodynamic and kinetic control of protonation should yield different stereoisomers.

Table I. Vicinal Coupling Constants for 9,10-Disubstituted 9,10-Dihydrophenanthrenes

compd	$J_{9,10}^{cis}$, Hz	$J_{9,10}^{trans}$, Hz
2	5.2	2.8
3	4.7	7.0
6[a]	4.5	
7[a]	4.9	
9,10-diphenyl-9,10-dihydrophenanthrene[b]	4.5	
9-acetoxy-10-chloro-9,10-dihydrophenanthrene[c]	4.0	3.2
10-methyl-9-phenyl-9,10-dihydrophenanthrene[d]	5.9	3.5

[a] From ref 7. [b] From ref 8a. [c] From ref 6d. [d] From ref 8b.

We report here our investigations of the carbanions derived from methyl 9,10-dihydro-10-methyl-9-phenthrenecarboxylate (**2c,t**) and 9,10-dihydro-10-methyl-9-phenanthrenecarbonitrile (**3c,t**). Our interest in the study of these carbanions was prompted by the observation that protonation of carbanions **4** and **5**, putative intermediates in the photochemical addition of 9-phenanthrenecarbonitrile and 2,3-dimethyl-2-butene in polar solvent, yields predominantly (>90%) a single isomer, **6** and **7** (eq 2).[7]



(2)

4 R = $CH_2C(CH_3)C(CH_3)_2$ 6

5 R = $C(CH_3)_2C(CH_3)_2OCH_3$ 7

Results

The dihydrophenanthrenes **2** and **3** were synthesized by Li/NH_3 reduction of the corresponding 9,10-disubstituted phenanthrenes (eq 3 and 4). The reduction yields a mixture of cis and trans isomers which are separable by chromatography. For both the ester and nitrile, the cis stereochemistry (**2c**, **3c**) predominates. Stereochemical assignments are made on the basis of comparison of the vicinal coupling constants for the benzylic hydrogens $J_{9,10}$, with literature values for 9,10-disubstituted 9,10-dihydrophenanthrenes (Table I).[6,8] The abnormally large trans coupling constant for **3t** reflects the unusual preference of the nitrile group for the pseudoequatorial position (see Discussion).

Base equilibration of **2c,t** and **3c,t** in 0.1 M sodium methoxide in refluxing methanol yields primarily the trans

(1) Posner, G. H.; Chapdelaine, M. J.; Lentz, C. M. *J. Org. Chem.* **1979**, *44*, 3661–3665.
(2) Krapcho, A. P.; Weimaster, J. F. *J. Org. Chem.* **1980**, *45*, 4105–4111.
(3) Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091–6096 and references therein.
(4) (a) Rabideau, P. W.; Harvey, R. G.; Stothers, J. B. *Chem. Commun.* **1969**, 1005–1006. (b) Rabideau, P. W.; Harvey, R. G. *J. Org. Chem.* **1970**, *35*, 25–30.
(5) Cohen, D.; Millar, I. T.; Heany, H.; Constantine, P. R.; Katritzky, A. R.; Semple, B. H.; Sewell, M. J. *J. Chem. Soc. B* **1967**, 1248–1250.
(6) (a) Cook, M. J.; Katritzky, A. R.; Pennington, F. C.; Semple, B. M. *J. Chem. Soc. B* **1969**, 523–526. (b) Cook, M. J. *Tetrahedron Lett.* **1969**, 2893–2896. (c) Cook, M. J.; Dassanayake, N. L. *J. Chem. Soc., Perkin Trans 2* **1972**, 1901–1905. (d) Burton, G. W.; Carr, M. D.; de la Mare, P. B. D.; Rosser, M. J. *Ibid.* **1972**, 710–715.
(7) Lewis, F. D.; DeVoe, R. J. *Tetrahedron*, in press.
(8) (a) Harvey, R. G.; Fu, P. P.; Rabideau, P. W. *J. Org. Chem.* **1976**, 41, 3722–3725. (b) Lapouyade, R.; Koussini, R.; Nourmamode, A.; Courseille, C. *J. Chem. Soc., Chem. Commun.* **1980**, 740–742.

0022-3263/82/1947-0888$01.25/0