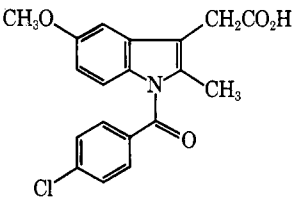
Rigid Analogs of Indomethacin†

Douglas R. Olson, William J. Wheeler, and Jack N. Wells*

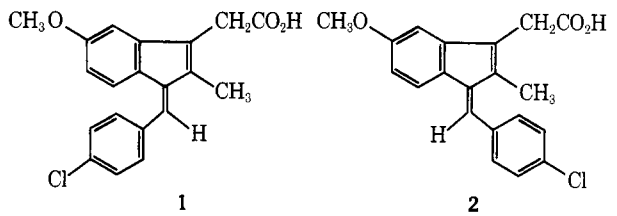
Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907. *Received August 27, 1973*

10-Chloro-2-methoxy-5-methyl-7*H*-pyrrolo[3,2,1-*de*]phenanthyrid-7-one-4-acetic acid and its deschloro analog were synthesized as rigid analogs of indomethacin. The chloro analog was found to be inactive in a standard *in vivo* guinea pig uv-erythema assay.

A hypothetical antiinflammatory "receptor" has been proposed by Shen[1] for the indomethacin type nonsteroidal antiinflammatory agents. The "receptor" requires that the molecule bind to the receptor with the aroyl moiety "cis" to the indole nucleus and tilted out of the plane of the rest of the molecule. This conception is supported by evidence concerning the preferred conformation of indomethacin from X-ray crystallographic as well as uv and nmr data.



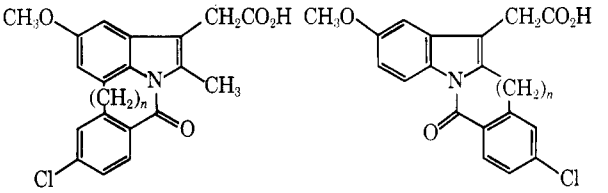
indomethacin



1 2

Additional support for the binding of the cisoid conformation is provided by the relative activities of the *cis*- and *trans*-indene analogs of indomethacin[2] (1 and 2). The cis isomer 1 is about one-half as active as indomethacin while the trans isomer 2 is about one-tenth as active. However, this would seem to be an equivocal test of the conformational requirements of the "receptor" since one-tenth of the activity of the extremely potent indomethacin still represents good activity. This would indicate that 2 can still bind quite well to the receptor surface.

In an attempt to provide a less equivocal test of the conformational requirements of the indomethacin receptor, we proposed to prepare and test compounds of the series 3 and 4. In these series the aroyl moiety would be fixed in either a cisoid or transoid conformation and could be tilted out of the plane to a predictable degree by variation of *n*. Compound **3a** was synthesized and tested for biological activity.

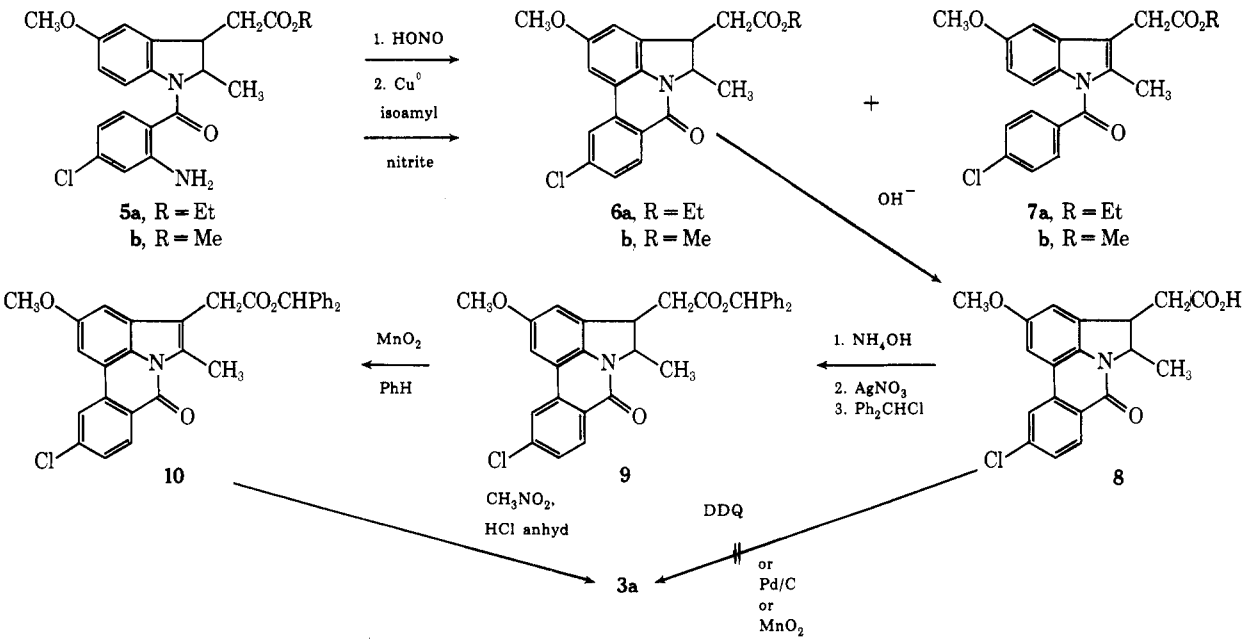


3a, $n = 0$
b, $n = 1$
c, $n = 2$
d, $n = 3$

4a, $n = 1$
b, $n = 2$

It was decided to approach the synthesis of **3a** (Scheme I) through preparation of a 1-(2-aminobenzoyl)indoline **5** followed by a Pschorr cyclization step to provide the phenanthridone nucleus. The use of the Pschorr reaction to prepare phenanthridones has been reported.[3-5] The aroylindoline was utilized to circumvent the problem of the reported acid and base lability of aroylindoles.[6]

Scheme I



5a, R = Et
b, R = Me

6a, R = Et
b, R = Me

7a, R = Et
b, R = Me

10 **9** **8** **3a**

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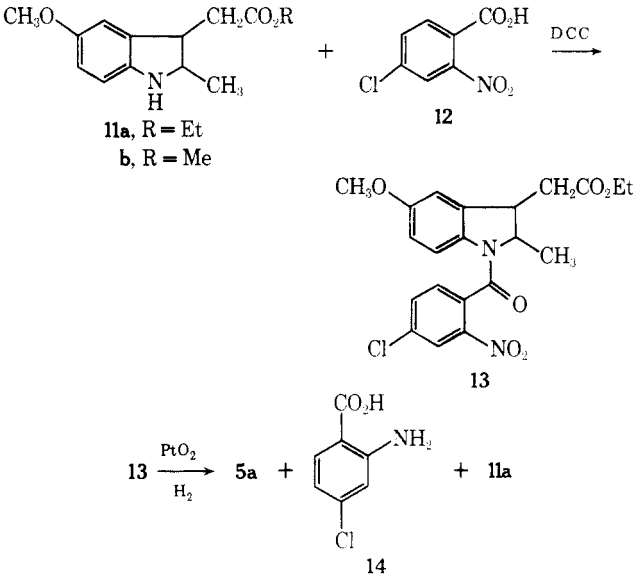
*Address correspondence to this author at the Department of Physiology, School of Medicine, Vanderbilt University, Nashville, Tenn. 37232.

Synthesis of the amine **5** was accomplished by two different methods. One approach involved the synthesis of the corresponding (2-nitrobenzoyl)indoline **13** and subsequent catalytic reduction to the amine **5a**. The latter step proved to be a low yield process due to an unexplained cleavage of the benzoyl group to yield 4-chloroanthranilic acid (**14**) and the indoline **11a**.



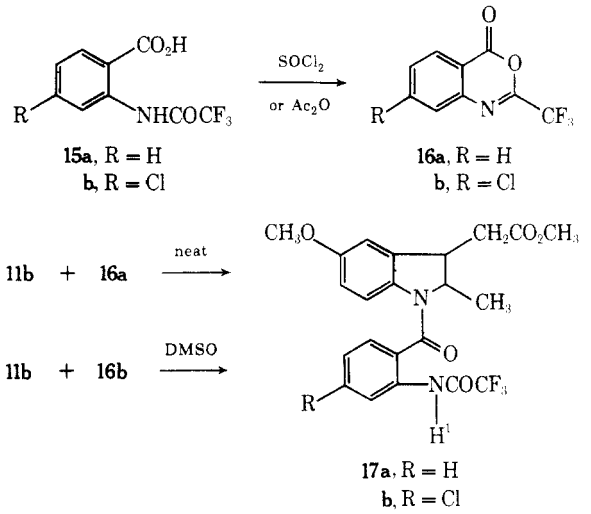
The need for a high yield route to the amine **5a** and the difficulty encountered with the preceding reduction step indicated that acylation of the indoline **11b** with an N-protected anthranilic acid was advisable. The use of the easily hydrolyzed trifluoroacetyl moiety as an O- and N-protecting group has been documented.[7,8] Also, 2-alkyl-4*H*-3,1-benzoxazin-4-ones have been shown to typically react with amines at the 4 position to yield *N*-acylanthranilamides.[9] The condensation of indolemagnesium bromide with 7-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one to yield 1-(2-acetamido-4-chlorobenzoyl)indole has also been reported.[10]

The benzoxazones **16a,b** were prepared by the cyclization of the corresponding *N*-trifluoroacetylanthranilic acids **15a,b**. It was found that thionyl chloride proved to be a more convenient cyclizing reagent than acetic anhydride[11] due to the ease of removal of by-products (SO_2 and HCl) and excess reagent.

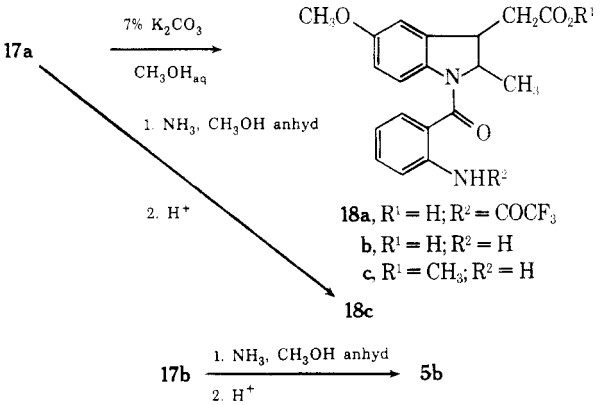
Fusion of **16a** with the indoline **11b** gave good yields of the (2-trifluoroacetamidobenzoyl)indoline **17a**. Condensation of **16b** with **11b** under similar conditions gave a decidedly lower yield of the acylindoline **17b**. However, when the condensation was carried out in dimethyl sulfoxide (DMSO) good yields were again obtained.

Newman[7] describes the mild hydrolysis of *N*-trifluoroacetamides with 7% K_2CO_3 in aqueous methanol. Attempts to hydrolyze **17a** under similar conditions led to partial hydrolysis of the amide and complete hydrolysis of the methyl ester **18a,b**. The slow rate of hydrolysis of the amide was undoubtedly due to anion formation on the trifluoroacetamide group by the base. The resultant anion would be more resistant to hydrolysis.[12] An indication of the acidity of H^1 was given by its chemical shifts in the nmr which were δ 10.5 ppm for **17a** and δ 10.95 ppm for **17b**.

It was decided to use a less basic nucleophile in anhydrous solvent to effect cleavage of the trifluoroacetyl group. Anhydrous ammonia in dry methanol seemed best suited for this purpose. Ammonolysis of **17a** at room temperature under these conditions gave good yields of the



corresponding amine **18c** isolated as the hydrochloride salt. Treatment of **17b** under the same conditions gave decidedly lower yields of the amine **5b**. The increased acidity of H^1 on **17b** due to the added electron-withdrawing effect of the chlorine probably accounts for this fact. For this reason[13] and the fact that the rate of methoxide displacement from the methyl ester by ammonia is decreased in the absence of water,[14] ammonia in freshly dried methanol gave the best results.

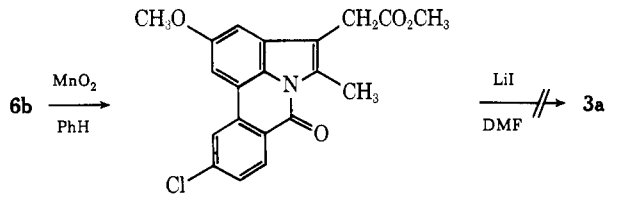


Isolation of the free amines **5b** and **18c** from the corresponding amine hydrochlorides lowered the yields considerably. However, use of the above system allows one to recycle the recovered starting amides **17a,b**.

It was found that cyclization of the amine **5a,b** to the phenanthridone **6a,b** (Scheme I) could be effected by decomposition of the corresponding diazonium salt with copper or by treatment of the free amine with isoamyl nitrite at elevated temperatures.[15] In each case similar results were obtained. In addition to the desired phenanthridone **6a,b**, a second fraction of material was obtained which proved to be the appropriate ester of 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (**7a,b**). Forbes and Gray[3] reported formation of 1-benzoylindoles from the thermal decomposition of the diazonium salt of 1-(2-aminobenzoyl)indolines. They attributed this observation to a hydride transfer from the 2 position of the indoline to the 2′ position of the benzoyl moiety. In the case of the cyclization with isoamyl nitrite, it is possible that the 1-benzoylindole is arising *via* free-radical hydrogen abstraction rather than hydride transfer. Work by Gragerov and Levit[16,17] demonstrated the presence of aryl free radicals in the arylation reaction with free amines and isoamyl nitrite. It is not unreasonable then to envision a competition between arylation (cyclization) and hydrogen

abstraction from the 2 position of the indoline by the aryl free radical.

In view of the lability of aroylindoles to acid and base, the ester function was cleaved prior to attempts at dehydrogenation of **6a,b.** Dehydrogenation with dichlorodicyanobenzoquinone,[18] palladium on charcoal,[19] and activated manganese dioxide[20] met with little success. It was surmised that the difficulty with the latter two reagents was the extreme insolubility of 8 in organic solvents. However, even when a homogeneous system was obtained by dissolving 8 as the triethylamine salt in chloroform, activated manganese dioxide failed to effect the conversion to **3a.** When the soluble methyl ester **6b** was refluxed in benzene with activated manganese dioxide, conversion to **19** was accomplished. This is somewhat surprising in view of the number of acylindolines which have been reported to be resistant to dehydrogenation.[20-22] Attempts to cleave the methyl ester proved to be disappointing. Halogenolysis with lithium iodide in refluxing DMF[23] yielded only a minute amount of acidic material. However, cleavage of methyl 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate to indomethacin with lithium iodide in refluxing lutidine was reported in unstated yields.[24] Alkaline hydrolysis of **19** appeared to result in cleavage of the tertiary amide.



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In view of the above results the readily cleaved[25] diphenylmethyl ester **9** was prepared from **8.** Dehydrogenation was carried out as described for **6b.** Warming **10** in nitromethane containing dry HCl or simply allowing it to stand in the nitromethane–HCl solution readily provided **3a** in almost analytical purity.

Biological Activity. The antiinflammatory activity of **3a** was assessed by the standard *in vivo* guinea pig uv-erythema assay.[26] Each test was run on five animals with appropriate controls. The results are shown in Table I. The inactivity of **3a,** while disappointing, is consistent with the receptor site proposed by Shen[1] which requires the aroyl portion of the molecule to be noncoplanar with the indole nucleus. The tetracyclic ring of **3a** is definitely planar and therefore, according to the above criteria, should not be active. The test results of **3a** appear to support the hypothetical receptor as described. However, without testing data on the "trans" series **4,** one cannot state with assurance that the planarity of **3a** is responsible for the lack of activity. The view that conformation is of limited importance in the activity of *N*-arylanthranilic acids has recently been expounded by Westby and Barfknecht[27] in evaluating data from a series of planar and antiplanar *N*-arylanthranilic acid analogs. A receptor site, similar to that proposed by Shen, has been proposed by Scherer[28] based on the structure-activity relationship of the *N*-arylanthranilic acids. Although there is no evidence that the receptors proposed by Shen and Scherer are identical, the recent work of Vane[29] indicates that both these series of agents probably act at the same receptor.

Experimental Section

Melting points were determined in open capillary tubes using a Laboratory Devices Mel-Temp or a Büchi capillary melting point apparatus and are reported uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Midwest Microlabs, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical value. Ultraviolet spectra were determined on a Bausch and Lomb Model 505 or a Perkin-Elmer Coleman 124 recording spectrophotometer in 95% ethanol. Infrared spectra were obtained using a Perkin-Elmer Model 237B or Model 21 and a Beckman Model 33 infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60A or HA-100 and a Japan Electron Optics Laboratory MH-60II spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6A or a Consolidated Electronics Corporation Model 21-100 mass spectrometer. High-resolution mass spectra were obtained on the CEC 21-110.

Table I. Anti-Uv-Erythema Assay[a]

Compd	Route of admin	mg/kg	% inhibition
3a	po	1.0	0
	po	10.0	3
	sc	25.00	0
Indocin	po	1.0	20
	po	10.0	95

[a]Reference 26.

Ethyl and Methyl 5-Methoxy-2-methyl-2,3-dihydroindole-3-acetates (11a,b). A mixture of methyl 5-methoxy-2-methylindole-3-acetate[30] (45.6 g, 0.197 mol) and mossy tin (49.2 g, 0.416 g-atom) was refluxed in 6 *N* HCl (590 ml) for 24 hr. The reaction mixture was concentrated to a yellow oil which was dissolved in CH_3OH saturated with HCl (600 ml) and refluxed for 21 hr. The methanolic solution was cooled and neutralized with solid $NaCO_2$. The inorganic salts and solvent were removed. The resultant oil was taken up in Et_2O, washed with H_2O, dried, and concentrated to an oil; 35.5 g. The oil was distilled to yield 23.8 g (51.4%) of **11b,** bp 151–164° (0.2 mm). The nmr spectrum of this material indicated that it was a mixture of cis and trans isomers:[31] δ 1.05 (3, d, J = 6 Hz, *cis*-2-methyl) and 1.13 ppm (d, J = 6 Hz, *trans*-2-methyl).[32] The material was used without further purification.

The ethyl ester **11a** was prepared in a similar manner. The reduction and reesterification of ethyl 5-methoxy-2-methylindole-3-acetate (19.5 g, 79 mmol) yielded 10.8 g (55%) of **11a,** bp 143–173° (0.25 mm).

4-Chloro-*N*-trifluoroacetylanthranilic Acid (15b). Trifluoroacetic anhydride (Aldrich) (30.2 g, 0.14 mol) in anhydrous Et_2O (100 ml) was added dropwise over a period of 30 min to a cooled, stirred slurry of 4-chloroanthranilic acid[33] (**14,** 20.5 g, 0.12 mol) in anhydrous Et_2O (150 ml). The homogeneous reaction mixture was allowed to warm to room temperature and stirred for an additional 2.5 hr. The Et_2O solution was poured into 500 ml of $CHCl_3$ and ice. This mixture was washed with H_2O and dried (Drierite). The solvents were removed and the resulting solid was recrystallized (benzene) to yield 22.9 g (72%) of **15b,** mp 177.5–178.5°. *Anal.* ($C_9H_5ClF_3NO_3$) C, H.

2-Trifluoromethyl-4*H*-3,1-benzoxazin-4-one (16a). (A) *N*-Trifluoroacetylanthranilic acid[11] (**15a,** 20.0 g, 86 mmol) was dissolved in Ac_2O (90 ml) and the mixture distilled until most of the Ac_2O and acetic acid were removed. The solid residue was recrystallized (*n*-hexane) to afford 12.3 g (67%) of **16a,** mp 49–51° (lit.[11] mp 53–54°).

(B) A mixture of **15a** (9.2 g, 40 mmol) and $SOCl_2$ (5.9 g, 49 mmol) in dry benzene (100 ml) was refluxed for 21.5 hr. The benzene and excess $SOCl_2$ were removed and the solid residue was recrystallized (*n*-hexane) to yield 7.15 g (84%) of **16a,** mp 49.5–51°. An additional 0.2 g (86.5% combined) of **16a** was obtained from the mother liquor: mp 50.5–52°.

7-Chloro-2-trifluoromethyl-4*H*-3,1-benzoxazin-4-one (16b). A solution of 4-chloro-*N*-trifluoroacetylanthranilic acid (**15b,** 23.9 g, 90 mmol) and $SOCl_2$ (13.1 g, 112 mmol) in dry benzene (200 ml) was refluxed for 12 hr. The benzene and excess $SOCl_2$ were removed and the solid residue was recrystallized (*n*-hexane) to give 20.8 g (93%) of **16b,** mp 54.2–54.8°. *Anal.* ($C_9H_3ClF_3NO_2$) C, H.

Methyl 1-(2-Trifluoroacetamidobenzoyl)-5-methoxy-2-methyl-2,3-dihydroindole-3-acetate (17a). A mixture of 2-trifluoromethyl-4*H*-3,1-benzoxazin-4-one[11] (**16a,** 7.15 g, 33 mmol) and **11b** (7.8 g, 33 mmol) was fused on a steam bath for 2.5 hr. The re-

sulting solid was triturated with Et_2O, collected, and recrystallized ($EtOH-H_2O$) to yield 13.1 g (88%) of **17a**, mp 165–166°. The nmr spectrum indicated that this was a mixture of cis and trans isomers: δ, 1.1 (3, d, J = 6 Hz, *cis*-2-methyl) and 1.27 ppm (3, d, J = 7 Hz, *trans*-2-methyl). *Anal.* ($C_{22}H_{21}F_3N_2O_5$) C, H.

Methyl 1-(2-Trifluoroacetamido-4-chlorobenzoyl)-5-methoxy-2-methyl-2,3-dihydroindole-3-acetate (17b). (A) A mixture of 7-chloro-2-trifluoromethyl-4*H*-3,1-benzoxazin-4-one (**16b**, 8.9 g, 36 mmol) and **11b** (8.4 g, 36 mmol) was fused on a steam bath for 3 hr. The cooled reaction mixture was dissolved in Et_2O and extracted with dilute HCl. The Et_2O layer was dried (Drierite) and concentrated to an oil which was triturated with Et_2O to afford 6.6 g (38%) of **17b**, mp 137.5–138.5°. A second set of doublets for the *trans*-2-methyl group was not evident in the nmr of **17b**. *Anal.* ($C_{22}H_{20}ClF_3N_2O_5$) C, H.

(B) A solution of **11b** (19.1 g, 81 mmol) and **16b** (20.0 g, 81 mmol) in DMSO (100 ml) was heated on a steam bath for 12 hr. The cooled reaction mixture was poured into 1500 ml of H_2O and ice and the resulting precipitate collected. The residue was dissolved in benzene and the solution washed with H_2O (500 ml), saturated $NaHCO_3$, and saturated NaCl solutions. The benzene layer was dried and concentrated to a brown oil, 39 g. Recrystallization ($EtOH-H_2O$) gave 32.3 g (82%) of **17b**, mp 127–133°. An additional 1.0 g (85% combined) of **17b** was obtained from the mother liquor.

Methyl 1-(2-Aminobenzoyl)-5-methoxy-2-methyl-2,3-dihydroindole-3-acetate (18c). (A) A solution of **17a** (1.0 g, 2.2 mmol) in a 7% CH_3OH-H_2O (1:1) solution was stirred at room temperature for 15 hr. The methanol solution was neutralized with 6 *N* HCl and concentrated to a small volume which was diluted with H_2O (100 ml) and extracted with $CHCl_3$. The $CHCl_3$ was dried (Drierite) and removed to yield a light tan solid (0.5 g) which was recrystallized (benzene–hexane) to afford a solid (mp 122–125°) which appeared to be a mixture of **18a** and **18b** (1:2.2): nmr δ 8.24 (0.4, d, J = 8 Hz, 3′-H) and 10.38 ppm (s, H^1 on **19a**); ir 2.9, 2.97 (NH_2 str), and 5.81 μ (acid C=O).

(B) A solution of **17a** (10.0 g, 22.3 mmol) in 400 ml of CH_3OH [distilled from $Mg(OCH_3)_2$] and NH_3 (9.3% w/w) was sealed in a pressure vessel and maintained at room temperature for 37 hr with occasional shaking. The CH_3OH and NH_3 from two combined batches were removed and the resulting oil was taken up in dry Et_2O, cooled to 0°, filtered, and treated with dry HCl. The precipitate was collected and dried under a N_2 stream to yield 16.3 g (94%) of **18c** as the hydrochloride salt. This material was characterized as the free base which was best liberated by the following procedure.

Dilute NH_4OH was added to a rapidly stirred suspension of **18c** hydrochloride in Et_2O. The layers were separated and the H_2O layer was extracted once with Et_2O. The combined Et_2O layers were washed with H_2O and saturated NaCl solution, dried, and concentrated, and the solid was recrystallized ($EtOH-H_2O$) to afford 10.0 g (63%) of **18c**, mp 118–119°. *Anal.* ($C_{20}H_{22}N_2O_4$) C, H.

Ethyl 1-(4-Chloro-2-nitrobenzoyl)-5-methoxy-2-methyl-2,3-dihydroindole-3-acetate (13). An EtOAc solution (25 ml) of dicyclohexylcarbodiimide (2.45 g, 11.8 mmol) was added dropwise to a solution of **11a** (3.0 g, 11.8 mmol) and 2-nitro-4-chlorobenzoic acid[34] (**12**, 2.37 g, 11.8 mmol) in 125 ml of EtOAc which was cooled to −10°. Stirring was continued at −10° for 2 hr after the addition was complete. The precipitated dicyclohexylurea [2.4 g, mp 232–234° (lit.[35] mp 229–230°)] and EtOAc were removed and the residue was crystallized from Et_2O to yield 3 g (61%) of **13**, mp 91–92.5°. *Anal.* ($C_{21}H_{21}ClN_2O_6$) C, H.

Ethyl and Methyl 1-(2-Amino-4-chlorobenzoyl)-5-methoxy-2-methyl-2,3-dihydroindole-3-acetates (5a,b). (A) A solution of **13** (9.1 g, 21.1 mmol) in 45 ml of benzene was hydrogenated over PtO_2 (150 mg) under 50 psi of H_2. After an uptake of the theoretical amount of H_2 (53 psi), the catalyst and a precipitate were removed and the benzene solution was washed with 6 *N* HCl and H_2O and dried (Drierite). The benzene was removed and the resulting oil triturated with Et_2O to yield 2.61 g (31%) of **5a**, mp 128–128.5°. *Anal.* ($C_{21}H_{23}ClN_2O_4$) C, H.

The catalyst was washed with EtOAc which was evaporated to yield 4-chloroanthranilic acid (**14**, 1.13 g), mp 238–240° (lit.[33] mp 240°).

(B) A solution of **17b** (12.2 g, 25 mmol) in 350 ml of CH_3OH [distilled from $Mg(OCH_3)_2$], saturated in the cold with NH_3, was maintained in a sealed reaction vessel at room temperature for 48 hr. The CH_3OH and NH_3 from two combined batches were removed to yield a yellow oil which was dissolved in anhydrous Et_2O, cooled to 0°, filtered, and treated with Et_2O–HCl. The precipitate was collected and dried under a stream of N_2 to yield **5b** hydrochloride, 17.0 g (79%). This material was characterized as the free base which was liberated in the same manner as **5a**. Typically, 6.0 g of **5b** hydrochloride yielded 3.7 g of crude amine which was recrystallized ($EtOH-H_2O$) to afford 2.71 g (49% recovery) of **5b**, mp 154.5–155°. *Anal.* ($C_{20}H_{21}ClN_2O_4$) C, H.

An additional 0.36 g (56% combined recovery) of **5b** was obtained from the mother liquor. A small quantity of Et_2O-insoluble material was also obtained which appeared from spectral data to be methyl 1-(2-amino-4-chlorobenzoyl)-5-methoxy-2-methyl-2,3-dihydroindole-3-acetamide, 0.5 g, mp 211–213°.

Ethyl and Methyl 10-Chloro-2-methoxy-5-methyl-4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthrid-7-one-4-acetates (6a,b). (A) An aqueous solution of $NaNO_2$ (220 mg, 3.2 mmol) in 2 ml of H_2O was added dropwise to a mixture of **5a** (1.2 g, 2.9 mmol), concentrated H_2SO_4 (1 ml), and acetone (75 ml) which was cooled to −10°. After the addition of the $NaNO_2$ was complete, stirring was continued for 0.5 hr. The diazonium salt was decomposed by the portionwise addition of freshly prepared Cu[36] (2.4 g) and the mixture was then stirred at 0° for 10 hr. The inorganic material and solvents were removed and the resulting semisolid was recrystallized (EtOH) to yield ethyl 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate (**7a**, 181 mg, 14.7%), mp 93–95° (lit.[37] mp 97–98°, mmp with authentic **7a** was not depressed).

Concentration of the mother liquors and recrystallization (EtOH) yielded 234 mg (19%) of **6a**, mp 141–142°. *Anal.* ($C_{21}H_{20}ClNO_4$) C, H.

(B) Isoamyl nitrite (MCB) (1.29 g, 11.0 mmol) was added to a stirred suspension of **5b** (3.0 g, 7.9 mmol) in dry benzene (15 ml). The reaction mixture immediately turned red and, upon warming to 35°, proceeded spontaneously with vigorous evolution of gas. When gas evolution began to diminish the solution was refluxed for an additional 15 min. The solvent was removed to yield a dark red oil. Crystallization (EtOH) afforded 0.75 g (26.6%) of **6b**, mp 164.8–165.2°. *Anal.* ($C_{20}H_{18}ClNO_4$) C, H.

Concentration of the mother liquor from **6b** and crystallization (EtOH) gave 0.43 g (15%) of methyl 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate (**7b**), mp 86–88° [mmp (with authentic **7b**) 84–86°].

10-Chloro-2-methoxy-5-methyl-4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthrid-7-one-4-acetic Acid (8). A solution of **6b** (0.5 g, 1.35 mmol) in 90% CH_3OH-H_2O (20 ml) and NaOH (65 mg, 1.62 mmol) was boiled for 15 min to about one-half the original volume. The CH_3OH solution was diluted with H_2O (50 ml), extracted with Et_2O, and acidified with dilute HCl. The resulting precipitate was collected and air-dried to yield 0.39 g (81%) of **8**, mp 296–298°.

Diphenylmethyl 10-Chloro-2-methoxy-5-methyl-4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthrid-7-one-4-acetate (9). An aqueous solution of $AgNO_3$ was added dropwise to a solution of **8** (200 mg, 0.56 mmol) in dilute NH_4OH until precipitation was complete. The silver salt was collected, washed with H_2O, and dried to yield 270 mg (100%) of a white solid. The silver salt was finely ground and suspended in $CHCl_3$ (15 ml) with stirring. Diphenylchloromethane (Eastman) (125 mg, 0.57 mmol) in $CHCl_3$ (5 ml) was added to the suspension and the mixture was allowed to stir at room temperature for 10 hr and then at reflux for 2 hr. The $CHCl_3$-insoluble material was collected by filtration [150 mg (80 mg, theory)] and washed several times with $CHCl_3$. The combined $CHCl_3$ filtrates were concentrated *in vacuo* to a yellow oil, 200 mg. Crystallization (EtOH) gave 120 mg (41%) of **9**: mp 162–164°; ir 5.76 (ester C=O) and 6.08 μ (amide C=O); nmr δ 6.79–8.38 ppm [16, m, aromatic, $(C_6H_5)_2CH$].

Et_2O–HCl (1 ml) was added to a solution of **9** (15 mg, 28.7 μmol) in CH_3NO_2 (3 ml) which was warmed to 40° for 30 min. The resulting solid was collected, washed (EtOH), and air-dried to give 5 mg (49%) of **8**, mp 297–298.5°.

Methyl 10-Chloro-2-methoxy-5-methyl-7*H*-pyrrolo[3,2,1-*de*]phenanthrid-7-one-4-acetate (19). A mixture of **6b** (0.64 g, 1.73 mmol) and activated MnO_2 (Winthrop Laboratories) (2.56 g) was stirred in refluxing benzene for 34 hr (subsequent work indicated that this was an excessive amount of time). The reflux condenser was fitted with a Dean-Stark trap to collect the water formed. The MnO_2 was removed by filtration and washed several times with hot $CHCl_3$. The benzene filtrate and $CHCl_3$ washings were combined and concentrated *in vacuo* to a solid residue, 0.49 g. This material was chromatographed ($CHCl_3$) over neutral alumina to afford 0.33 g (52%) of **19**, mp 193–197°. Recrystallization ($CHCl_3$) gave a purer sample of **19**: mp 201°; ir 5.75 (ester C=O) and 5.96 μ (amide C=O); nmr δ 2.7 (3,5, ring methyl) and 3.6

(2,5, ring methylene). *Anal.* Calcd for $C_{20}H_{16}ClNO_4$: C, 64.96; H, 4.36. Found: C, 64.51; H, 4.74.

10-Chloro-2-methoxy-5-methyl-7*H*-pyrrolo[3,2,1-*de*]phenanthrid-7-one-4-acetic Acid (3a). A mixture of **9** (120 mg, 0.23 mmol) and activated MnO_2 (500 mg) was stirred in benzene under reflux for 12 hr. The MnO_2 was removed, boiled in $CHCl_3$ (50 ml), refiltered, and washed with an additional 20 ml of $CHCl_3$. The combined benzene filtrate and $CHCl_3$ washings were concentrated *in vacuo* to a yellow oil, 110 mg. Chromatography over neutral alumina ($CHCl_3$) and evaporation of solvent yielded 60 mg (50%) of **10**: ir 5.75 (ester C=O) and 5.96 μ (amide C=O); nmr δ 2.73 (3,5, ring CH_3) and 3.73 ppm (5,5, OCH_3 and ring CH_2).

Et_2O-HCl (1.5 ml) was added to a filtered CH_3NO_2 (6 ml) solution of **10** (60 mg, 0.115 mmol). The solution was warmed to 40–50° for 45 min. The resulting solid was collected, washed with EtOH and hot $CHCl_3$, and dried to give 23 mg (56%) of **3a**, mp 250–252°. *Anal.* ($C_{19}H_{14}ClNO_4$) C, H.

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