Stereoselective Reduction of Some Indoles with Triethylsilane–Trifluoroacetic Acid[1]

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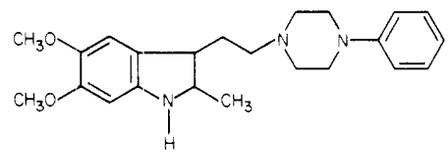
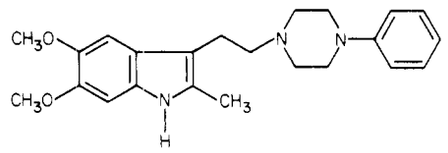
The completely stereoselective reduction of indoles to *cis*-indolines by triethylsilane–trifluoroacetic acid is demonstrated. A rationalization of this stereoselectivity is offered. The precursor indoles were prepared by the Fisher indole condensation with levulinic acid (**7**). 3,4-Dimethoxyhydrazine (**6a**) gave only the 5,6-dimethoxyindole **8a** while 3,4-dichlorohydrazine (**6d**) gave a 1:1 mixture of the isomeric chloroindoles **8d** and **8e** which were separated by preparative liquid chromatography.

cis-5,6-Dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]indoline (**1a**)[2] has undergone clinical



1a

trials as an antipsychotic agent. We wish to report a new synthesis of **1a** and its congeners by the completely stereoselective reduction of the indoles, such as **2a**,[3] using triethylsilane–trifluoroacetic acid (TES–TFA).[18]



2a

There has been much interest recently in new methods for the reduction of indoles with various boron hydrides and a proton source.[4-9] These methods usually give *cis*-hexahydrocarbazole from tetrahydrocarbazole and give a mixture of *cis*- and *trans*-indoline from 2,3-dimethylindole, although Berger's BH_3/HCl system is reported to yield only trans 2,3-disubstituted indolines.[5]

The older methods[10] involve reduction in strong aqueous acid either by the use of dissolving metals[11] or by catalytic hydrogenation.[12] The catalytic reduction of 2,3-dimethylindole is reported to be reversible, with the equilibrium favoring the indole.[13] In fact, 2,3-dimethylindole is reduced at very high pressure to *trans*-2,3-dimethylindoline,[14] and in several 2,3-disubstituted cases the benzene ring of an indole has been reduced in preference to the pyrrole ring.[15] The dissolving-metal reduction of 2,3-dimethylindole gives a mixture of *cis*- and *trans*-indolines in a ratio of 2:1, but the yield is variable.[11,14,18] The TES–TFA reduction appears to be the first general method for the completely stereoselective cis reduction of indoles in high yield.

Table I. Reductions and Attempted Reductions of Indole 2a

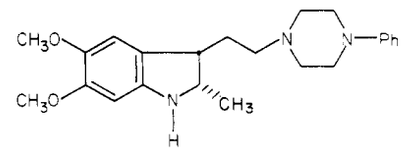
reagent	% yield[a] cis isomer	trans isomer	recovd starting matl
TES-TFA[18]	80	0	0
Sn/HCl[14]	48	5	2
H_2/Cu-Cr,[14] 11 000 psi	1.4	0.6	98[b]
BH_3/$NaOCH_3$[4]	60	40	0
Zn/H_3PO_4[11]	0	0	100
H_2/PtO_2/HBF_4[12]			0[c]
$NaBH_3CN$/TFA[6]	37	47	16[b]
BH_3/HCl[8]	35	58	7[b]
BH_3·NMe_3/HCl[5]	0	0	100
BH_3/TFA[9]	19	48	33

[a] The cis/trans ratio was determined by measuring the height of the two outside peaks of the two methyl doublets. [b] Estimated by ^{1}H NMR. [c] Decomposition.

Results and Discussion

Reduction of the Indoles. Reduction of indole **2a** with tin and hydrochloric acid gave a 53% yield of a 10:1 mixture of isomeric indolines as determined by ^{1}H NMR. The major isomer exhibited a methyl doublet at δ 1.17 (J = 6.5 Hz) and the minor isomer a methyl doublet at δ 1.23 (J = 6.0 Hz). Fractional crystallization and partition chromatography gave a purer sample of the major isomer, and it was unambigously shown to be the cis isomer **1a** by single-crystal X-ray diffraction analysis. A view of the *cis*-indoline **1a** is shown in Figure 1.

We have been unable to separate the minor isomer from the reaction mixture, but we have assigned it the *trans*-indoline structure **3** on the basis of the downfield shift and



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(1) A part of this work has been described in U.S. Patent 4 089 853.
(2) G. R. Allen, F. J. McEvoy, V. G. DeVries, D. B. Moran, and R. L. Littell, U.S. Patents 3 751 416 and 3 900 563 (1973).
(3) S. Archer, U.S. Patent 3 188 313 (1965).
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(9) B. E. Maryanoff and D. F. McComsey, *J. Org. Chem.*, **43**, 2733 (1978).
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(12) (a) A. Smith and J. H. P. Utley, *Chem. Commun.*, 427 (1965); (b) *J. Chem. Soc. C*, 1 (1970).
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(14) A. R. Bader, R. J. Bridgewater, and P. R. Freeman, *J. Am. Chem. Soc.*, **83**, 3319 (1961).
(15) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, 1967, p 373.

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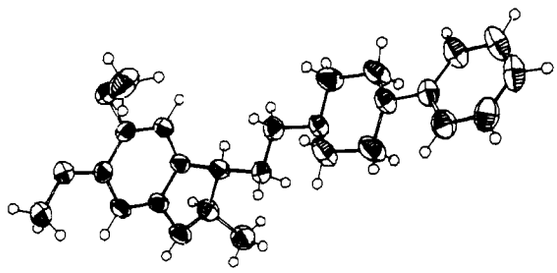
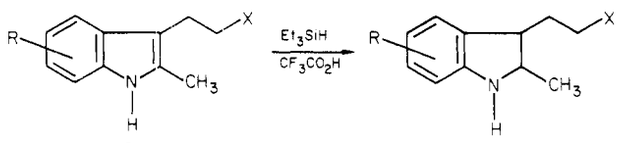


Figure 1. ORTEP drawing of indoline **1a**. The hydrogen atoms are shown as spheres 0.25 Å in diameter.

Table II. Reduction of Indoles with Triethylsilane-Trifluoroacetic Acid



2 1

indoline	mp, °C	% yield[a]	indoline	mp, °C	% yield[a]
1a	112-113	80	1f	102-110[b]	46
1b	106-108	25	1g	232 dec[b]	58
1c	110-125[b]	32	1h	230-232[b]	52
1d	190 dec[b]	14			

[a] Yield of isolated crystalline product. Except for 1a these yields have not been optimized. These indolines give hydroscopic, air-sensitive hydrochloride salts. The ^{1}H NMR spectra of the crude reaction mixtures reveal yields, in general, of 60-80%. [b] HCl salt.

smaller coupling constant of the C-2 methyl group in the ^{1}H NMR.[16]

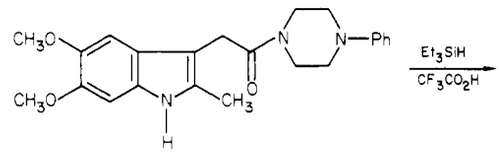
This stereochemical assignment was strengthened by examining the H(2)–H(3) coupling constants of the indoline mixture, which were 8 Hz and 0 Hz, respectively, for the major and minor isomers.[16,17]

Triethylsilane Reduction. Attempts to maximize the selectivity of the reduction of **2a** with various reducing agents are summarized in Table I. None of these were stereoselective, and we then turned to the hydrosilation method of Parnes,[18] who had obtained a 42:58 mixture of the *cis*- and *trans*-indoline isomers in the reduction of 2,3-dimethylindole. Reduction of **2a** with triethylsilane in trifluoroacetic acid (TES–TFA) gave **1a** in 80% yield with no detectable amount of trans isomer by ^{1}H NMR analysis. The indoline obtained by TES–TFA reduction was spectroscopically identical with that used for the X-ray structure determination and gave an undepressed mixture melting point.

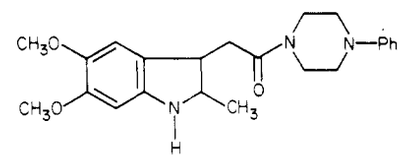
The reduction of indole **2a** with TES–TFA is completely stereoselective and proceeds in higher yield than all other methods we have tried (Table I). We have reduced a number of 2-methyl-3-substituted indoles (Table II) with TES–TFA and in all cases the reaction is stereoselective. In addition, indole **2c**, which was recovered unchanged from tin and hydrochloric acid, was reduced smoothly with TES–TFA.

The mechanism of this reduction has been shown to entail the initial protonation of the indole at C-3[19] by the trifluoroacetic acid, followed by the transfer of hydride from the triethylsilane to C-2.[18a,20] This general mechanism was first proposed by Smith and Utley[12] for the catalytic reduction of indoles in strong acid, and the stereochemical consequences of such a mechanism have been discussed by Monti.[4]

The stereoselectivity of the TES–TFA reduction of 3-(piperazinylethyl)indoles must be due either to steric control by the piperazinylethyl side chain or to internal delivery of the reducing agent by the basic nitrogen atom in the side chain, a concept discussed by Berger.[8] We have ruled out the latter possibility on the basis of the following experiment. Reduction of the indole amide **4a** with



4a



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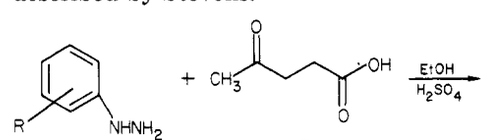
TES–TFA gave a single *cis*-indoline amide **5**. The stereochemistry of **5** was assigned on the basis of the ^{1}H NMR spectrum (C-2 Me, δ 1.11, J = 6.5 Hz). The assignment was confirmed by lithium aluminum hydride (LAH) reduction of **5** which gave the authentic cis compound **1a**.

The reason for the stereoselectivity of reductions with silicon hydrides compared to the boron hydrides or to tin is speculative. Since triethylsilane is a less reactive reducing agent than borane ($\Delta\Delta H$ = +11 kcal), the corollary to Hammond's postulate[21] suggests that reduction of the indolium ion by silicon hydride involves a later, more productlike transition state than boron hydride reduction. This more indoline-like transition state should have more sp^3 character at C-2 and a shorter C–H bond, both factors which should increase the steric control of the C-3 side chain on the direction of approach of a bulky hydride donor.

Synthesis of the Indoles. The new indoles were obtained by a Fisher-indole cyclization with the appropriate hydrazine, levulinic acid in ethanol, and sulfuric acid as described by Stevens.[22]



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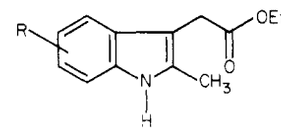

8

Cyclization of 3,4-dichlorophenylhydrazine (**6d**) gave a 1:1

(16) F. A. L. Anet and J. M. Muchowski, *Chem. Ind. (London)*, 81 (1963).
(17) We wish to thank G. Morton, spectroscopy group, Analytical Research and Methods Development Department, for this experiment.
(18) (a) Z. N. Parnes, V. A. Budylin, E. Yu. Beilinson, and A. N. Kost, *J. Org. Chem. USSR (Engl. Transl.)*, 8, 2613 (1972); (b) D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 633 (1974).
(19) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, 84, 2534 (1962).
(20) A. E. Lanzilotti and R. L. Littel, *J. Labelled Compd.*, in press.
(21) (a) G. S. Hammond, *J. Am. Chem. Soc.*, 77, 334 (1955); (b) D. Farcasiu, *J. Chem. Educ.*, 52, 76 (1975).
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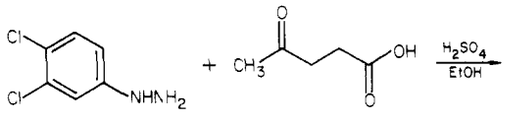
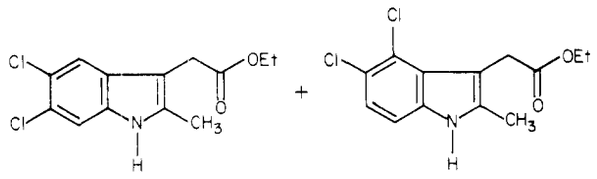
mixture of 4,5- and 5,6-dichloroindoles. These were sep-

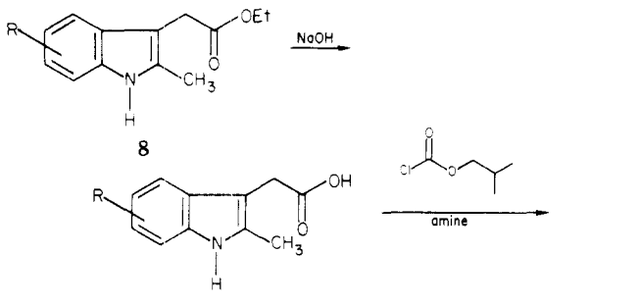


6d 7



8d 8e

arated by preparative liquid chromatography. 3,4-Dimethoxyphenylhydrazine (**6a**) cyclized to give only a single isomer. Saponification of the esters **8** gave the acids **9**



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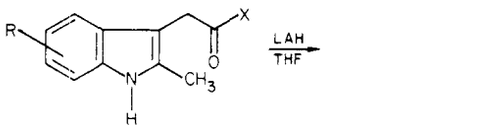
9



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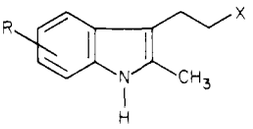

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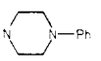
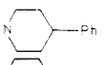
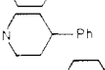
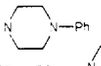
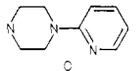
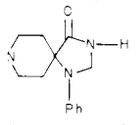
a, R = 5-OCH_3, 6-OCH_3; X = 

b, R = 5-Br; X = 

c, R = 5-F; X = 

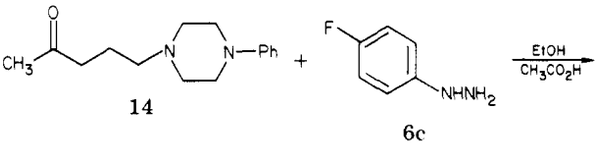
d, R = 5-Cl, 6-Cl; X = 

f, R = 5-OCH_3, 6-OCH_3; X = 

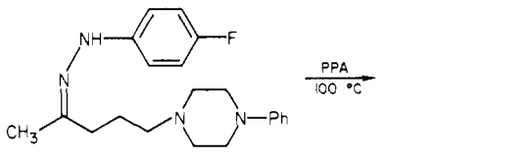
g, R = 5-OCH_3, 6-OCH_3; X = 

which were coupled with the appropriate secondary amines (**10**–**13**) by using isobutylchloroformate[3] to give the amides **4**. Reduction of these amides with LAH gave the indoles **2**. Lithium aluminum hydride reduction of the bis amide **4g** selectively reduced only the tertiary amide to give the lactam **2g**.

The indole **2h** was prepared from the piperazinylpentanone **14**[23] by a Fischer indole cyclization of the derived hydrazone **15** in polyphosphoric acid. This convergent route, although shorter, was not always reproducible, and the other phenylhydrazines either failed to react with



14 6c



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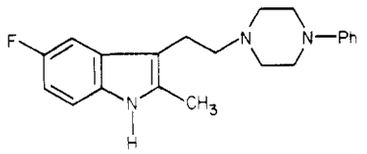

2h

14 or the derived hydrazones **15** could not be cyclized.

Summary

We have found that triethylsilane–trifluoroacetic acid is a stereospecific system for the reduction of indoles substituted with a bulky group at C-3 to *cis*-indolines. The chemical yields range from 14 to 80%, but indoles that cannot be reduced by other standard methods do react with TES–TFA. The stereochemistry of the indoline **1a** has been unambiguously assigned by single-crystal X-ray diffraction.

Experimental Section

General Methods. Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are not corrected. Infrared, UV, ^{1}H NMR, and mass spectra were run on Perkin-Elmer 21 or Nicolet 7000, Cary 14, Varian EM-360 or HA-100, and AEI MS 9 spectrometers, respectively. Starting materials were obtained from Aldrich Chemical Co. except for triethylsilane which was purchased from Chemicals Procurement Laboratories. Tetrahydrofuran was freshly distilled from lithium aluminum hydride prior to use.

The phrase "solvent workup procedure" means the reaction mixture was cooled to room temperature, diluted with water, and extracted several times with the indicated solvent. The combined extracts were washed with water, dried over anhydrous sodium sulfate, and filtered, and the solution was concentrated in vacuo by using a rotary evaporator. Ether solutions were washed with saturated brine prior to the aforementioned drying over sodium sulfate.

Elemental compositions of new compounds were determined by combustion analysis or by high-resolution mass spectroscopy. The combustion data agreed with calculated values within ±0.4%.

***cis*-5,6-Dimethoxy-2-methyl-3-[2-(4-phenylpiperazinyl)-ethyl]indoline (1a) by Tin and Hydrochloric Acid Reduction.** A mixture of 3.79 g (9.99 mmol) of **2a**[3] and 19 g (160 mmol) of mossy tin in 50 mL of ethanol and 55 mL of concentrated hydrochloric acid was stirred at 75–80 °C for 6 h and at 65 °C overnight. The cooled reaction mixture was decanted from unreacted tin into 200 mL of 2 N NaOH solution and then filtered. The filter cake was suspended in 400 mL of hot ethyl acetate and refiltered. Usual workup of the organic filtrate gave 4 g of a dark oil. The oil was crystallized from ethyl acetate–ether to give 2.00 g (52.5% yield) of a white solid, mp 105–107 °C (lit.[2] mp 112–113 °C). ^{1}H NMR spectroscopy, as described in the text, revealed this solid to be a 10:1 mixture of isomers.

X-ray Crystal Structure of 1a. A sample of **1a** suitable for X-ray analysis was purified by partition chromatography on Celite using a heptane–methanol system,[24] and it was then crystallized

(23) S. C. Laskowski, French Patent 1 551 082 (1968).

(24) We wish to thank P. A. Bonenfant, chromatography group, Analytical Research and Methods Development Department, for carrying out this separation.

from heptane–ethanol by slow evaporation in the cold. The irregularly shaped crystals of this racemic compound are monoclinic, space group $P2_1/a$ (centrosymmetric). The cell dimensions, based on diffractometer measurements for 25 strong reflections in the range $20° < \theta < 40°$ are a = 18.989 (10) Å, b = 6.489 (3) Å, c = 20.217 (10) Å, β = 122.93 (3)°. For one molecule in the asymmetric unit the calculated density is 1.219 g cm^{-3}; the observed value, by flotation in aqueous potassium iodide, is 1.22 g cm^{-3}. Three-dimensional data collection on the CAD-3 diffractometer with nickel-filtered Cu Kα radiation (λ 1.5418 Å) yielded 3486 independent reflections in the range $2.5° < \theta < 60.0°$ of which 2615 were classified as observed by the criterion $I(h) > 1.5\sigma(I)$.

The structure was solved by an application of the MULTAN[25] phase-determining program to the set of 483 reflections with normalized structure factors $E(h) > 1.5$. In space group $P2_1/a$ reflections for three phases may be chosen arbitrarily; in addition, five other reflections were selected automatically and used to yield 32 trial phase sets. The set corresponding to the highest absolute figure of merit (1.06) was used to prepare an electron-density map that contained peaks corresponding to all nonhydrogen atoms of the molecule.

Isotropic refinement of the trial structure with atom types assigned on the basis of the chemical structure gave a final discrepancy factor R = 0.15 between observed and calculated structure factors. Further anisotropic refinement gave R = 0.11; at this stage an electron density difference map was calculated and was found to contain peaks at positions appropriate to all the hydrogen atoms. The atomic parameters are listed in Tables III and IV, and the bond distances and angles are given in Table V (see supplementary material).

Triethylsilane–Trifluoroacetic Acid Reduction. General Procedure. The indole **2** (7.0 mmol) was dissolved in 25 mL of trifluoroacetic acid and heated to 50 °C (oil bath temperature). To this stirred solution was added 2.2 mL (14 mmol) of triethylsilane, and the resulting solution was heated at 50 °C for 64 h. The progress of the reaction was monitored by TLC. The cooled reaction mixture was made basic (pH 9) with aqueous KOH, and the chloroform workup procedure gave the crude free base.

In most cases the free base was dissolved in ethyl acetate and made acidic with HCl gas. The white precipitate which was collected by filtration, deliquesced upon exposure to air and resolidified after a few days at room temperature to give a tan solid.

Indoline 1a by Triethylsilane–Trifluoroacetic Acid Reduction. An 80% yield of the free base was obtained from **2a** after recrystallization from 2-propanol, mp 112–113 °C (lit.[2] 112–113 °C).

***cis*-5-Bromo-2-methyl-3-[2-(4-phenylpiperidino)ethyl]-indoline (1b).** A 25% yield of the free base was obtained from **2b** after recrystallization from acetonitrile; mp 106–108 °C.

***cis*-5-Fluoro-2-methyl-3-[2-(4-phenylpiperidino)ethyl]-indoline dihydrochloride (1c)** was prepared in 32% yield from **2c**; mp 110–125 °C.

***cis*-5,6-Dichloro-2-methyl-3-[2-(4-phenyl-1-piperazinyl)-ethyl]indoline hydrochloride (1d)** was prepared in 14% yield from **2d** and recrystallized from ethanol; mp 190 °C dec. A molecule of ethanol of solvation was detected in the ^{1}H NMR spectrum.

***cis*-5,6-Dimethoxy-2-methyl-3-[2-[4-(2-pyridyl)-1-piperazinyl]ethyl]indoline hydrochloride (1f)** was prepared in 46% yield from **2f**; mp 102–110 °C.

***cis*-8-[2-(5,6-Dimethoxy-2-methyl-3-indolinyl)ethyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one hydrochloride (1g)** was prepared in 58% yield from **2g**; mp 232 °C dec.

***cis*-5-Fluoro-2-methyl-3-[2-(4-phenyl-1-piperazinyl)-ethyl]indoline hydrochloride (1h)** was prepared in 52% yield from **2h**; mp 230–232 °C.

***cis*-[(5,6-Dimethoxy-2-methyl-3-indolinyl)acetyl]-4-phenylpiperazine (5).** Reduction of **4a** was carried out by the general procedure except that after 83 h there was starting material remaining as determined by TLC. The crude free base was subjected to preparative liquid chromatography on a Waters Prep LC500 using silica gel as the stationary phase and 5% 2-propanol in ethyl acetate as the mobile phase. Indole **5** (k' = 3.67) was isolated in 59.2% yield as a brown glass. Trituration with isopropyl ether gave the reference sample as a brown solid, mp 69–75 °C.

LAH Reduction of 5. A mixture of 880 mg (2.22 mmol) indoline **5** and 100 mg (2.63 mmol) of $LiAlH_4$ in 40 mL of THF was stirred overnight at room temperature and then at reflux for 15 min. The cooled reaction mixture was quenched with saturated aqueous Na_2SO_4 solution, filtered, and evaporated to give 720 mg of brown gum. Trituration with 2-propanol gave a white solid identical in all respects (including mixture mp) with **1a**.

Indole Cyclization of Levulinic Acid (7). General Procedure. The phenylhydrazine hydrochloride (0.3 mol), levulinic acid (0.3 mol), and 30 mL of concentrated H_2SO_4 in 400 mL of ethanol were heated at reflux for 24 h. The progress of the reaction was monitored by TLC. The cooled reaction mixture was poured onto 1 L of ice and the resulting mixture stirred overnight at room temperature. Filtration and drying gave the crystalline indole esters **8**.

Ethyl 5,6-Dimethoxy-2-methyl-3-indoleacetate (8a). From **6a**[26] a 38.7% yield was obtained after recrystallization from ether–hexane; mp 70–73 °C (lit.[27] mp 81.5–83 °C).

Ethyl 5-Bromo-2-methyl-3-indoleacetate (8b). From **6b** a 56.3% yield was obtained after recrystallization from chloroform–hexane; mp 87–90 °C (lit.[22] mp 83.5–84 °C).

Ethyl 5-Fluoro-2-methyl-3-indoleacetate (8c). From **6c** a 51.0% yield was obtained after recrystallization from chloroform–hexane; mp 57–61 °C (lit.[28] no melting point given).

Ethyl 5,6-Dichloro-2-methyl-3-indoleacetate (8d) and Ethyl 4,5-Dichloro-2-methyl-3-indoleacetate (8e). From **6d** a 55.9% yield of a mixture of isomers **8d** and **8e** was obtained after recrystallization from chloroform–hexane; mp 108–111 °C. The mixture was separated by preparative liquid chromatography on a Waters Prep LC500 using silica gel as the stationary phase and dichloromethane as the mobile phase. Indole ester **8d** (k' = 1.88) was isolated in 25.8% overall yield, mp 125–130 °C, and ester **8e** (k' = 3.21) was isolated in 21.0% overall yield; mp 147–150 °C.

Recrystallization of **8d** from chloroform–hexane gave the reference sample, mp 131–134 °C.

Recrystallization of **8e** from chloroform gave the reference sample, mp 153–155 °C.

Hydrolysis of the Indole Esters 8. General Procedure. A mixture of 30 mmol of the ester in 35 mL of aqueous 3 N NaOH was heated at reflux for 3 h. The cooled reaction mixture was made acidic with concentrated HCl. Ether workup gave the crude acid which was recrystallized from acetonitrile.

5,6-Dimethoxy-2-methyl-3-indoleacetic Acid (9a). From **8a** an 88.2% yield was obtained; mp 146–152 °C.

5-Bromo-2-methyl-3-indoleacetic acid (9b) was prepared in 45% yield from **8b**; mp 189–191 °C (lit.[29] mp 188–189 °C).

5-Fluoro-2-methyl-3-indoleacetic acid (9c) was prepared in 81% yield from **8c**; mp 179–182 °C.

5,6-Dichloro-2-methyl-3-indoleacetic acid (9d) was prepared in 69% yield from **8d**, mp 244–246 °C.

Preparation of the Amides 4. General Procedure. To a cooled (dry ice–carbon tetrachloride bath), stirred mixture of 15.4 mL (140 mmol) of *N*-methylmorpholine, 240 mL of tetrahydrofuran, and 64 mmol of a 2-methylindole acetic acid (**9**) was added a tetrahydrofuran solution of 95 mL (64 mmol) of isobutyl chloroformate, dropwise during 30 min, under nitrogen. Following this addition, 64 mmol of a 4-substituted piperidine or of *N*-phenylpiperazine was added slowly. The reaction was allowed to warm to room temperature and stirred 16 h at room temperature. Chloroform workup gave a solid amide which was purified by recrystallization.

1-[(5,6-Dimethoxy-2-methyl-3-indolyl)acetyl]-1-phenylpiperazine (4a). From **9a** and *N*-phenylpiperazine (**10**) a 79.1%

(25) G. Germain, P. Main, and M. H. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970); *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

(26) J. J. Delucia, J. W. Dehn, Jr., and R. A. Pizzanello, U.S. Patent 3 366 619 (1968).

(27) S. I. Sallay and S. J. Childress, U.S. Patent 3 294 805 (1966).

(28) T.-Y. Shen, U.S. Patent 3 316 260 (1967).

(29) F. J. Stevens and D. H. Higginbotham, *J. Am. Chem. Soc.*, **76**, 2206 (1954).

yield was obtained; mp 125–129 °C, after recrystallization from ether–hexane.

1-[(5-Bromo-2-methyl-3-indolyl)acetyl]-4-phenylpiperidine (4b). From **9b** and 4-phenylpiperidine (**11**) a 64% yield was obtained, mp 175–180 °C, after recrystallization from chloroform–hexane.

1-[(5-Fluoro-2-methyl-3-indolyl)acetyl]-4-phenylpiperidine (4c). From **9c** and 4-phenylpiperidine (**11**) a 75% yield of **4c** was obtained, mp 165–166 °C, after recrystallization from acetonitrile.

1-[(5,6-Dichloro-2-methyl-3-indolyl)acetyl]-4-phenylpiperazine (4d). From **9d** and *N*-phenylpiperazine (**10**) a 28% yield was obtained, mp 209–219 °C, after recrystallization from acetonitrile.

1-[(5,6-Dimethoxy-2-methyl-3-indolyl)acetyl]-4-(2-pyridyl)piperazine (4f). From **9a** and *N*-(2-pyridyl)piperazine (**12**) a 35% yield was obtained, mp 172–174 °C, after recrystallization from ethanol.

8-[(5,6-Dimethoxy-2-methyl-3-indolyl)acetyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (4g). From **9a** and 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (**13**) a 42% yield was obtained, mp 250–254 °C, after recrystallization from ethanol.

Reduction of the Amides 4. General Procedure. To a stirred mixture of 0.49 g (13 mmol) of lithium aluminum hydride and 200 mL of tetrahydrofuran was added a tetrahydrofuran solution of 5 mmol of an indolylamide **4** dropwise during 10 min under nitrogen at room temperature. The reaction was stirred at room temperature for 16 h, and then the excess hydride was decomposed by the cautious addition of saturated aqueous sodium sulfate. Filtration and ether workup gave the crude indole **2**.

5-Bromo-2-methyl-3-[2-(4-phenylpiperidino)ethyl]indole (2b). From **4b** a 61% yield was obtained after recrystallization from acetonitrile; mp 138–141 °C.

5-Fluoro-2-methyl-3-[2-(4-phenylpiperidino)ethyl]indole (2c). From **4c** a 21% yield was obtained after recrystallization from acetonitrile; mp 132–134 °C.

5,6-Dichloro-2-methyl-3-[2-(4-phenyl-1-piperazinyl)-ethyl]indole (2d). From **4d** a 87% yield was obtained after recrystallization from acetonitrile; mp 196–199 °C.

5,6-Dimethoxy-2-methyl-3-[2-[4-(2-pyridyl)-1-piperazinyl]ethyl]indole Hydrochloride (2f). The crude indole from **4f** was dissolved in ethanol and made acidic with ethanolic HCl. Addition of ether produced a white crystalline precipitate which was collected by filtration. The salt deliquesced upon exposure to air and resolidified after a few days in the air to give a gray solid, mp 220 °C dec, in 35% yield.

8-[2-(5,6-Dimethoxy-2-methyl-3-indolyl)ethyl]-1-phenyl-1,3,4-triazaspiro[4.5]decan-4-one (2g) was prepared in 16% yield from **4g** after recrystallization from acetonitrile; mp 238–241 °C.

5-(4-Phenyl-1-piperazinyl)-2-pentanone(4-fluorophenyl)hydrazone (15). A solution of 7.5 g (60 mmol) of (4-fluorophenyl)hydrazine, 19.7 g (80 mmol) of 5-(phenyl-1-piperazinyl)-2-pentanone,[23] and 10 drops of glacial acetic acid in 100 mL of ethanol was heated under reflux for 90 min. The clear solution was concentrated in vacuo, and the residue was recrystallized from ethanol to give 6.4 g (30%) of cream-colored crystals, mp 80–85 °C. A 1.0-g sample was recrystalized from ethanol to give 0.45 g of white crystals, mp 98–103 °C.

5-Fluoro-2-methyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]-indole (2h). A mechanically stirred portion of 175 g of polyphosphoric acid was heated to 100 °C (oil bath temperature), and 16.9 g (50 mmol) of **15** was added in portions during 2 min. The stirred mixture was heated at 100 °C for 5 min and then poured onto a mixture of chopped ice and 250 mL of concentrated NH_4OH. A brown precipitate formed and was collected. This solid was partially dissolved in 600 mL of hot chloroform and filtered. The chloroform solution was concentrated to give 7.6 g (45%) of a brown glass.

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Registry No. **1a**, 71987-48-9; **1b**, 72016-61-6; **1c**·2HCl, 72016-62-7; **1d**·HCl, 71987-49-0; **1f**·HCl, 72016-63-8; **1g**·HCl, 71987-50-3; **1h**·HCl, 71987-51-4; **2a**, 153-87-7; **2b**, 71987-52-5; **2c**, 71987-53-6; **2d**, 71987-54-7; **2f**·HCl, 71987-55-8; **2g**, 72016-64-9; **2h**, 71987-56-9; **4a**, 71987-57-0; **4b**, 71987-58-1; **4c**, 71987-59-2; **4d**, 71987-60-5; **4f**, 71987-61-6; **4g**, 72016-66-1; **5**, 72016-67-2; **6a**·HCl, 20329-82-2; **6b**·HCl, 41931-18-4; **6c**·HCl, 40594-35-2; **6d**·HCl, 71987-62-7; **7**, 123-76-2; **8a**, 13697-78-4; **8b**, 72016-68-3; **8c**, 17536-39-9; **8d**, 71987-63-8; **8e**, 71987-64-9; **9a**, 71987-65-0; **9b**, 71987-66-1; **9c**, 71987-67-2; **9d**, 71987-68-3; **10**, 92-54-6; **11**, 77-10-1; **12**, 34803-66-2; **13**, 1021-25-6; **14**, 25699-21-2; **15**, 71987-69-4; triethylsilane, 617-86-7; trifluoroacetic acid, 76-05-1; **3**, 72016-65-0.

Supplementary Material Available: Table III, nonhydrogen coordinates and anisotropic temperature parameters for **1a**; Table IV, hydrogen coordinates and isotropic temperature parameters for **1a**; Table V, bond distances and angles of osculant atoms; Table VI, spectral data for the new compounds (11 pages). Ordering information is given on any current masthead page.

Efficient Reduction of Polycyclic Quinones, Hydroquinones, and Phenols to Polycyclic Aromatic Hydrocarbons with Hydriodic Acid

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A series of polyarene quinones, hydroquinones, and phenols (or their esters or methyl ethers) undergo reduction directly to the corresponding fully aromatic hydrocarbons in high yield on treatment with hydriodic acid alone or in refluxing acetic acid. Phosphorus is generally not required (except for 1-hydroxynaphthalene) and has a deleterious effect through promotion of undesired hydrogenation of the aromatic products.

Although reduction of several polycyclic quinones with phosphorus and hydriodic acid was described over a century ago,[1] this reagent has never gained wide acceptance and is rarely employed today. Reasons for neglect include the high temperatures (>200 °C) traditionally employed and the complex mixtures of phenols and polyhydrogenated products frequently obtained.[2] We recently

(1) The earliest example of this reaction described in the literature appears to be the reduction of anthraquinone with HI/P to afford anthrone, anthracene, dihydroanthracene, and further hydrogenation products. Cf.: Graebe, C.; Liebermann, C. *Justus Liebigs Ann. Chem., Suppl.* **1870**, *7*, 287. Liebermann, C.; Topf, A. *Chem. Ber.* **1876**, *9*, 1201. Liebermann, C. *Justus Liebigs Ann. Chem.* **1882**, *212*, 1.

(2) Clar states: "The reduction of quinones with hydriodic acid and red phosphorus at 200 °C yields mostly hydrogenated hydrocarbons. These can be dehydrogenated by sublimation over copper at 400 °C." Clar, E. "Polycyclic Hydrocarbons"; Academic Press: New York, 1964; Vol. I, p 171.

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