The Synthesis of Substituted 1,7*H*-Pyrindine Acetic Esters

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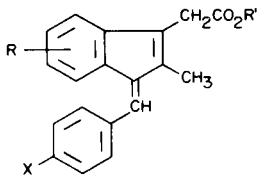
As an extension of our work on substituted indene acetic acid derivatives (**1**) as nonsteroidal anti-inflammatory agents (1) it became of interest to investigate an aza isoster such as 1,7*H*-pyrindine acetic ester of the general type (**2**) which also represent the previously unknown azabenzofulvene system.



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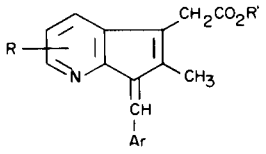

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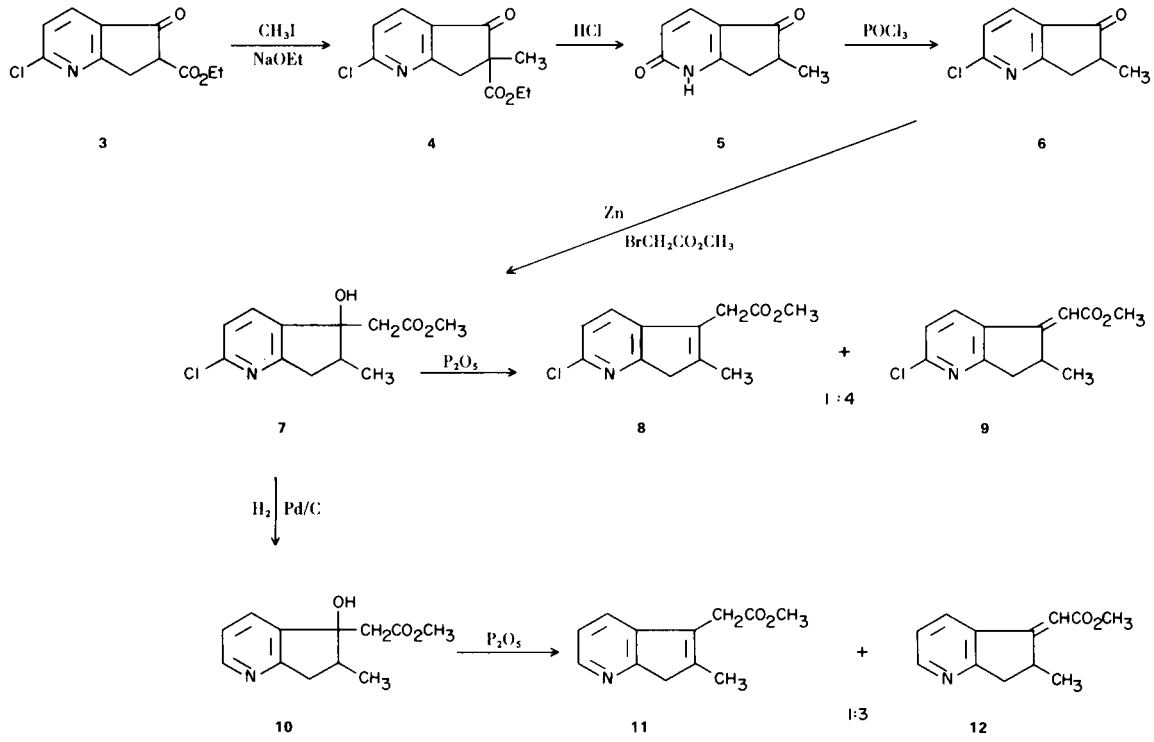
The preparation of 1,5*H*-pyrindine was accomplished in 1958 by Robison (2) using the rearrangement of pyrindane *N*-oxide with acetic anhydride followed by elimination of acetic acid with sulfuric acid. While this method offers a direct route to the parent heterocycle, it is not satisfactory for the preparation of substituted members of this class. The only other report of a pyrindine has been made by Ramirez (3) who synthesized a 2-hydroxy-6-alkyl-1,5*H*-pyrindine from 2-chloro-5-oxo-6-carbethoxy-6,7-dihydro-1,5*H*-pyrindine (**3**). We have made further use of this intermediate in the synthesis of functionally substituted pyrindines, and in addition condensed these pyrindines with aromatic aldehydes to the desired products (**2**).

The key intermediate of this study was the preparation of methyl 6-methyl-1,7*H*-pyrindinyl-5-acetate (**11**). The synthesis was accomplished as shown in Scheme I. Methylation of the keto ester **3** proceeded smoothly to give compound **4**. Decarboxylation of crude **4** in concentrated hydrochloric acid was accompanied by hydrolysis of the

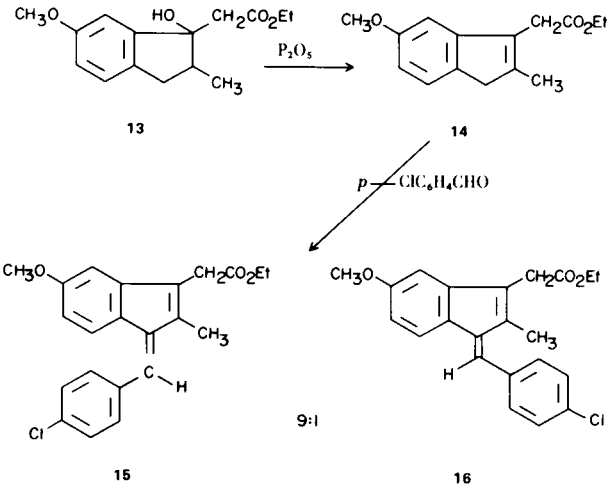
SCHEME I



3 4 5 6 7 8 9 10 11 12

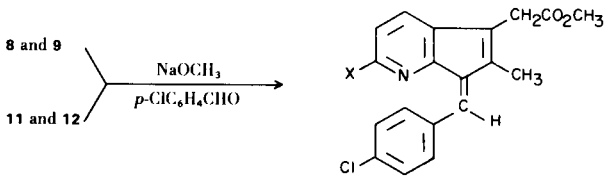
chloropyridine moiety giving rise to pyrindinedione **5**. Careful treatment of this ketone with phosphorus oxychloride led to regeneration of the desired pyrindine system **6**. A Reformatsky reaction on **6** gave the hydroxy ester **7**, which was obtained as a syrup and possibly a mixture of diastereoisomers. This product could not be induced to crystallize, but its mass spectrum gave the correct molecular ion for the desired alcohol. Dehydration of **7** utilizing phosphorus pentoxide resulted in the formation of both *exo*cyclic and *endo*cyclic isomers in the ratio of 4:1 as indicated by the nmr spectrum (deuteriochloroform) of the oily product: 8.65 (d, J = 6 Hz), 7.88 (s), 6.4-7.5 (m), 6.32 (s), 6.25 (s), 3.80 (m, isomers $=CHCO_2CH_3$), and 2.0-2.9 τ (m). Integration of the two methyl resonances indicated that the mixture contained 80 ± 3% of **9** and 20 ± 3% of **8**. Additional spectral data verified the assigned structures for **8** and **9**. Thus, the infrared spectrum showed bands at 5.78 and 5.85 μ indicative of ester and α,β-unsaturated ester functions, while the mass spectrum exhibited the following values; m/e = 237 (parent) 206, 178, 152, 142 and 114.

Hydrogenation of **7** gave the dechlorinated hydroxy ester **10** also as an oil which, after dehydration, led to a similar mixture of *endo* and *exo* isomers (**11** and **12**), characterized in the same manner as above. In this case the ratio was 3:1. The finding that both *exo* and *endo* isomers were obtained in the dehydration reaction is interesting in view of the fact that under identical conditions, the carbocyclic congener, ethyl (1-hydroxy-2-methyl-6-methoxyindanyl) acetate (**13**), (4) gave almost



exclusively the *endo*cyclic isomer **14**. Furthermore, the conversion of **13** to **14** was completed in *ca.* 15 minutes while the dehydration of **7** or **10** required many hours. These results seem to indicate a protonated species is involved in the dehydration of the hydroxy pyrindanes **7** and **10**, which tends to destabilize carbonium ion formation at the tertiary alcohol center.

Reaction of the pyrindines, as a mixture of *exo* and *endo* isomers, with *p*-chlorobenzaldehyde in the presence of sodium methoxide led to the formation of the aza-



17a, X = Cl
17b, X = H

benzofulvenes **17**. It was reported previously that base catalyzed condensation of **14** with *p*-chlorobenzaldehyde gave both **15** and **16** (5), but no stereoisomers of **17** were detected in these experiments. The configuration of **17** was determined from the chemical shift of the 6-methyl substituent (6) by analogy with the indene system. The anisotropic effect of the phenyl ring adjacent to the methyl group can be seen from the values in Table I.

TABLE I

NMR Spectra ($CDCl_3$)

Compound	τ (CH_3)	τ ($-C_6H_4Cl$)
15	7.88	2.49
16	8.20	2.54
17a	7.80	
17b	7.87	

The nmr spectra of **17a** and **17b** are distinguished from the carbocyclic series by a downfield shift of nearly 1 ppm of the protons *meta* to the benzylidene chlorine. This very large displacement cannot arise primarily from conventional steric pressures since no unusual chemical shifts are observed in the spectra of 7-substituted indenyl analogs (7). The implication is that this phenomenon results from long-range interaction by the nitrogen lone pair (8). Such a proposal requires that the deshielding effect should be voided by the nonavailability of a lone electron pair on the heterocyclic ring. An attempt to demonstrate this relationship by adding deuterium chloride to a DMSO solution of **17b** cannot be considered conclusive. Nonetheless, the appearance in the acidified solution of a new, relatively intense singlet near 2.14 τ constitutes supportive evidence for the hypothesis since both the chemical shift and absence of fine structure are characteristic of the *p*-chlorobenzylidene protons in the indenyl series (Table I).

EXPERIMENTAL

Infrared spectra were determined with a Perkin-Elmer Model 137 spectrometer. Nmr spectra were obtained on a Varian A60 and HA-100 spectrometer in deuteriochloroform unless otherwise specified. Melting points were measured with a Thomas-Hoover capillary apparatus and are uncorrected. Ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer.

6,7-Dihydro-6-methyl-1,5*H*-pyrindin-2,5-dione (**5**).

Compound **3**, (3) 2.4 g. (0.01 mole) was dissolved in 50 ml. of a freshly prepared solution of sodium ethoxide (0.01 mole). The deep red solution was stirred for 10 minutes at room temperature and then 20 ml. of methyl iodide was added. The mixture was refluxed for one hour and most of the solvent removed *in vacuo*. Water, 50 ml., was added and the ketone (**4**) extracted with two portions of methylene chloride, dried over magnesium sulfate, and isolated as a red oil, 2.4 g. after removal of solvent, λ max (neat), 5.72 (ester) and 5.79 (ketone) μ.

The crude ketone **4**, 2.4 g. (9.5 mmoles) was dissolved in 30 ml. of concentrated hydrochloric acid and the solution refluxed for 16 hours. The solvent was removed under reduced pressure to leave a solid. Recrystallization from 2-propanol gave 1.4 g. (92%) of white needles, m.p. 236-238°; λ max (nujol), 2.9 (sh), 3.1 (broad), 6.0 (sh), and 6.1 μ; nmr (DMSO), 7.8 (d, 3, J = 7 Hz), 6.6-7.7 (m), 3.65 (d, 1, J = 8 Hz), and 2.48 τ (d, 1, J = 8 Hz).

Anal. Calcd. for $C_9H_9NO_2$: C, 66.31; H, 5.57; N, 8.59. Found: C, 66.53; H, 5.48; N, 8.69.

2-Chloro-5-oxo-6-methyl-6,7-dihydro-1,5*H*-pyridine (**6**).

A mixture of 0.5 g. (3.0 mmoles) of **5** and 20 ml. of phosphorus oxychloride was stirred while the temperature was gradually raised. When a homogeneous solution was obtained the reaction mixture was cooled and the excess phosphorus oxychloride was removed under diminished pressure. The residue was treated carefully with cold water, and the precipitate was filtered and dried to leave 0.4 g. (75%) of product. The analytical sample was prepared by vacuum sublimation to give colorless needles, m.p. 72-74°; λ max (nujol) 5.8 μ; nmr, 8.61 (d, 3, J = 5.5 Hz), 6.3-7.4 (m, 3), 2.63 (d, 1, J = 7 Hz) and 2.2 τ (d, 1, J = 7 Hz); mass spectrum; m/e = 181 (parent), 166, 152.

Anal. Calcd. for C_9H_8ClNO: C, 59.51; H, 4.46; N, 7.74. Found: C, 59.50; H, 4.29; N, 8.04.

Methyl 2-Chloro-5-hydroxy-6-methyl-6,7-dihydro-1,5*H*-pyrindinyl-5-acetate (**7**).

A well-stirred mixture of 0.90 g. (5.0 mmoles) of **6**, 0.6 g. (5.2 mmoles) of methyl bromoacetate, 400 mg. of zinc dust, and a crystal of iodine in 30 ml. of dry benzene was refluxed for 20 hours. Approximately 30 ml. of water was added to the cooled mixture and after stirring for 10 minutes the organic layer was separated and dried over magnesium sulfate. Removal of solvent left 0.7 g. of brown oil; λ max (neat), 2.9 (OH), and 5.8 (ester) μ; m/e = 255 (parent), 237, 196, 182, 166, 152, 117.

Methyl 2-Chloro-6-methyl-1,7*H*-pyrindinyl-5-acetate (**8**) and Methyl 2-Chloro-6-methyl-6,7-dihydro-1,5*H*-pyrindinylidene-5-acetate (**9**).

A solution of 1.0 g. (3.9 mmoles) of **7** in 50 ml. of dry benzene and 5.0 g. of phosphorus pentoxide was refluxed for 18 hours. Excess phosphorus pentoxide was decomposed with water and the benzene layer separated and dried (magnesium sulfate). Evaporation of solvent *in vacuo* left 0.4 g. (43%) of dehydrated material. Tlc (silica gel, dichloromethane) showed one major and one minor spot. The mass spectrum (see text) verified the presence of a molecular ion at m/e = 237.

Methyl 5-Hydroxy-6-methyl-6,7-dihydro-1,5*H*-pyrindinyl-5-acetate (**10**).

A solution of 3.2 g. (0.013 mole) of **7** in 50 ml. of methanol was hydrogenated at 45 psi using 0.3 g. of 10% palladium on carbon catalyst until the theoretical uptake of hydrogen was observed. The catalyst was filtered and the filtrate evaporated to dryness. The residual orange oil was dissolved in a small volume of water. The acid solution was extracted with methylene chloride to give 0.9 g. of recovered **7**. The aqueous phase was made basic with potassium carbonate solution and extracted with three portions of methylene chloride and dried over magnesium sulfate. Evaporation left 2.0 g. (99% based on recovered starting material) of hydroxy ester **10** as an oil; λ max (neat), 2.95 (sh), 3.18 (v.s.), and 5.80 μ; nmr, 8.81 (d, 3, J = 6 Hz), 6.7-7.9 (m, 5), 2.1-3.0 (m, 2), and 1.58 τ (m, 1).

Methyl 6-Methyl-1,7*H*-pyrindinyl-5-acetate (**11**) and Methyl 6-Methyl-6,7-dihydro-1,5*H*-pyrindinylidene-5-acetate (**12**).

A mixture of 2.0 g. (0.01 mole) of alcohol **10** and 4.0 g. of phosphorus pentoxide in 75 ml. of benzene was refluxed for 26 hours. The benzene layer was decanted from the gummy mass and this residue carefully decomposed with water. The aqueous solution was made basic with 10% potassium hydroxide solution and the mixture extracted four times with methylene chloride. After drying (magnesium sulfate), removal of solvent left 0.55 g. (26%) of tan oil; λ max (neat), 5.78 (ester) and 5.85 (α,β-unsaturated ester) μ; nmr, 8.76 (m, *cis* and *trans* isomers present), 7.88 (s), 6.7-7.5 (m), 6.34 (s), 6.25 (s), 3.74 (m, *cis* and *trans* isomers $=CHCO_2CH_3$), 2.1-3.0 (m), and 1.35-1.8 τ (m). Integration of the methyl resonances gave the proportion of **11** and **12** as 25 ± 3% and 75 ± 3%, respectively.

Methyl 2-Chloro-6-methyl-7-*p*-chlorobenzylidene-1,7*H*-pyrindinyl-5-acetate (**17a**).

A solution of 0.24 g. (1.0 mmole) of the mixture of isomers **8** and **9** (approximately 0.2 mmole *endo*cyclic isomer), 0.14 g. (1.0 mmole) of *p*-chlorobenzaldehyde and 0.10 g. (2.0 mmoles) of sodium methoxide in 15 ml. of anhydrous methanol was placed under an atmosphere of nitrogen and refluxed for 3 hours. The mixture was poured into water and made weakly acid with dilute hydrochloric acid. The aqueous phase was extracted three times with methylene chloride and dried over magnesium sulfate. Evaporation of solvent left an oil. The oil was dissolved in 25 ml. of dry methanol and one drop of concentrated sulfuric acid added. The solution was refluxed for 12 hours. The methanol was stripped off under reduced pressure and the residue chromatographed on silica gel using methylene chloride as eluent. The orange fractions were combined and evaporated to give 15 mg. of yellow crystals, m.p. 156-157°; λ max (nujol), 5.85 μ; nmr, 7.75 (s, 3), 6.46 (s, 2), 6.35 (s, 3), 2.8 (s, 1), 2.6-3.0 (m, 4), and 1.75 τ (d, 2, J = 8 Hz); λ max (ethanol), 355 (11,700), 338 (14,600), 308 (11,600) and 225 (17,800) mμ; m/e = 359 (parent), 300, 285, 264, 250, 228.

Anal. Calcd. for $C_{19}H_{15}Cl_2NO_2$: N, 3.89. Found: N, 3.81.

Methyl 6-Methyl-7-*p*-chlorobenzylidene-1,7*H*-pyrindinyl-5-acetate (**17b**).

A solution of 0.5 g. (2.4 mmoles) of the mixture of **11** and **12** in 15 ml. of methanol, 0.28 g. (2.0 mmoles) of *p*-chlorobenzaldehyde and 0.2 g. (4.0 mmoles) of sodium methoxide were reacted as described for **17a**. The final yield of crystalline orange ester was 19 mg. recrystallized from *n*-hexane, m.p. 88-90°; λ max (nujol), 5.88 μ; λ max (ethanol), 344 sh (9650), 333 (11,700), 308 sh

(8850), and 226 (10,000) mμ; nmr, 7.87 (s, 3), 6.42 (s, 2), 6.34 (s, 3), 2.5-3.0 (m, 5), and 1.6-1.9 τ (m, 2); DMSO, aromatic region, 2.16-2.70 (m, 4), 1.53 (m, 1), and 1.27 τ (d, 2, J = 8 Hz); DMSO-deuterium chloride, aromatic region, 1.1-2.3 τ (m, 5 - sharp spike 2.14 τ).

Anal. Calcd. for $C_{19}H_{16}ClNO_2$: C, 70.00; H, 4.95; N, 4.30. Found: C, 69.89; H, 5.06; N, 4.06.

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