The Synthesis of Three Indolizine Derivatives of Interest as Non-Isomerizable Analogues of Tamoxifen

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Three novel derivatives of indolizine **21**, **23**, and **25** have been prepared as analogues of the anti-cancer agent tamoxifen **1**. The compounds showed low relative binding affinity at the estrogen receptor.

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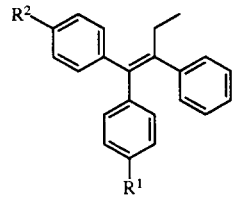
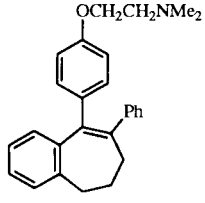
Tamoxifen, 1-[4-[2-dimethylaminoethoxy)phenyl]-1,2-diphenylbut-1-ene (**1**), is a synthetic anti-estrogen and is of current use in the treatment of breast cancer [1-3]. Only the *Z*-isomer is used because the *E*-isomer **2** is an estrogen agonist [4]. One of the human metabolites of tamoxifen is the 4-hydroxy derivative **3** and this has a higher potency *in vitro* than tamoxifen [5]. However, **3** is not suitable for use as an anti-cancer agent since it readily undergoes isomerization because of the conjugation between the olefinic bond and hydroxyl group through the aromatic nucleus. Thus, a mixture of the *Z* **3** and *E* isomers **4** is formed [6-8]. Some non-isomerizable analogues of tamoxifen are known, *e.g.* **5** [9], **6** [10], **7** [11] and **8** [12].

We sought to prepare the derivatives of indolizine **21**, **23** and **25** which cannot undergo isomerization but where the double bond character C(2)-C(3) of the aromatic indolizine nucleus is utilized to take the place of the olefinic bond in tamoxifen in a manner similar to the use of the C(2)-C(3) bond in **6** and **8**. The remainder of the indolizine nucleus constitutes a delocalised π electron system which, we hoped, would provide the equivalent of the space filling and binding character of the 1-phenyl nucleus in tamoxifen. It seemed possible that the high fluorescence of certain indolizines [13] might be utilized as a label of the estrogen binding site provided that a high binding affinity occurred.



1 $R^1 = OCH_2CH_2NMe_2$, $R^2 = H$
2 $R^1 = H$, $R^2 = OCH_2CH_2NMe_2$
3 $R^1 = OCH_2CH_2NMe_2$, $R^2 = OH$
4 $R^1 = OH$, $R^2 = OCH_2CH_2NMe_2$



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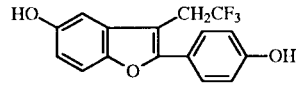

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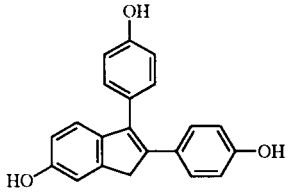

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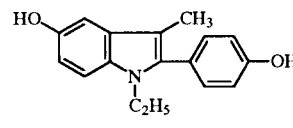

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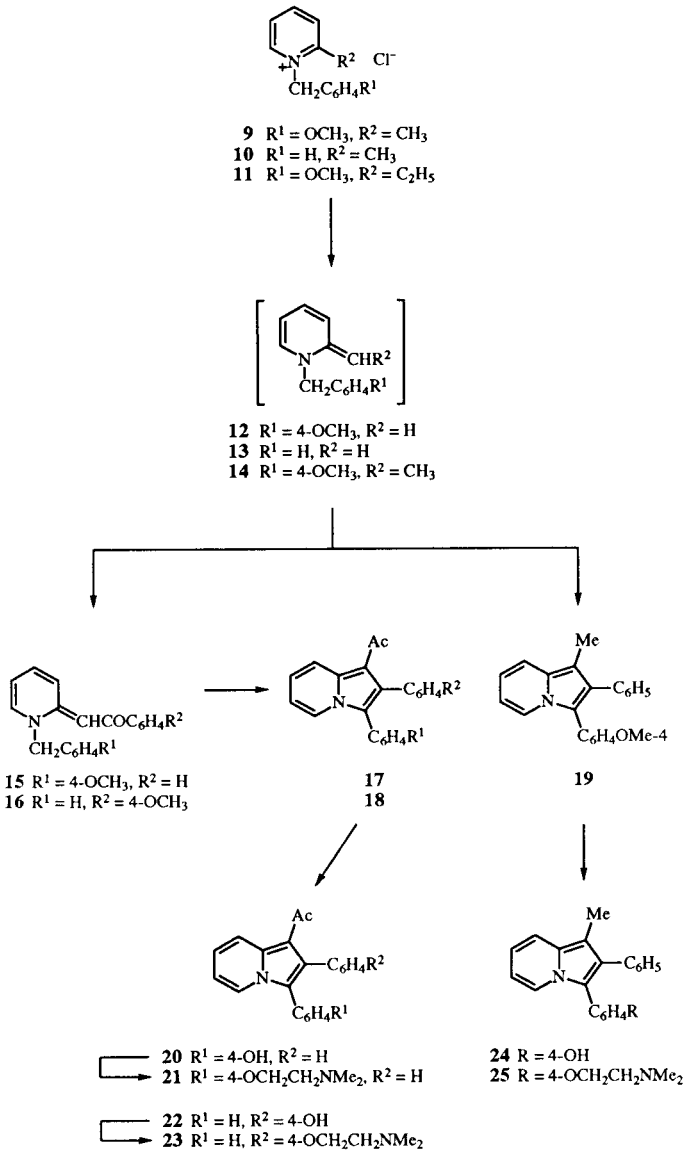
We chose to synthesize the target indolizine by using the method developed by Melton and Wibberley [14] from earlier observations of Baker and McEvoy [15] and Schneider *et al.* [16]. The quaternary salt **9**, obtained from 2-methylpyridine and 4-methoxybenzoyl chloride, on reaction with benzoyl chloride in the presence of aqueous sodium hydroxide yielded **15** *via* the intermediate **12** (Scheme 1). Treatment of **15** with acetic anhydride caused cyclization [14] and acetylation to give the indolizine **17**. The acetyl group in **17** was very labile in the presence of acid so the required demethylation to release the phenol **20** was achieved by use of sodium ethanethiolate [17]. An alkylaminoethane side chain, essential for antiestrogen activity in the triarylethenes [2] was introduced by a Williamson ether synthesis of the phenol and 2-dimethylaminoethyl chloride (liberated from its hydrochloride *in situ*) in the presence of potassium carbonate to give the amino ether **21**.

The isomer **23** was obtained in a similar series of reaction from the salt **10** by treatment with 4-methoxybenzoyl chloride to give **16** *via* the intermediate **13**. Cyclization and acetylation in the presence of acetic anhydride yielded **18** and this was converted to the phenol **22** and thence to the ether **23**.

Treatment of 2-ethylpyridine with 4-methoxybenzyl chloride yielded the salt **11**, which was reacted with benzoyl chloride to give the indolizine **19** and not the expected intermediate ketomethene **14**. This difference in the reaction of the 2-methyl- and 2-ethyl-pyridine is not likely to be due to an electronic effect and may be due to a steric compression through which the bulky methyl group (compared with hydrogen atom) causes

Scheme 1



the reactive sites to approach more closely than is the case in **15** and **16**. Demethylation of **19** by ethanethiolate [17] was unsatisfactory. However, satisfactory demethylation was achieved by the use of hydrobromic acid to give the unstable phenol **24**. The ^{1}H nmr of **24** did not show a peak for OCH_3 at 3.77 ppm and because of its instability, full characterization was not attempted. The compound **24** was quickly converted to the aminoethyl ether **25**.

The three compounds tested **21**, **23** and **25** for binding to estrogen showed poor relative affinity when compared with tamoxifen. This is different from the benzofuran [10] and indoles [12], though the substitution patterns are different and the bicyclic system in our compounds does not contain a benzene nucleus.

EXPERIMENTAL

The general experimental procedures and apparatus are as previously described [18].

1-Benzyl-2-methylpyridinium chloride (**10**) was prepared by the method reported [15].

General Procedure for the Preparation of 2-Alkyl-1-arylpyridinium Chlorides **9** and **11**.

A mixture of the 2-alkylpyridine and the appropriate benzyl chloride (1.1 molar equivalents) was heated on a steam-bath for 6 hours. The viscous oil was dissolved in water and washed with chloroform. Evaporation of the water *in vacuo* left a gum.

1-(4-Methoxybenzyl)-2-methylpyridinium Chloride (**9**).

This compound was obtained in 75% yield; ^{1}H nmr (deuteriochloroform): δ 2.87 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 6.03 (s, 2H, CH_2), 6.73-6.87 (dd, 2H, 3- and 5-H of C_6H_4, J = 2, 9 Hz), 7.18-7.29 (dd, 2H, 2- and 6-H of C_6H_4, J = 2, 7 H), 7.82-7.98 (m, 3H, 3-, 4- and 5-H), 9.45 (dd, 1H, 6-H, J = 2, 7 Hz); ms: m/z 156 (18%), 121 (100), 93 (35).

2-Ethyl-1-(4-methoxyphenyl)pyridinium Chloride (**11**).

This compound was isolated in 72% yield; ^{1}H nmr (deuterium oxide): δ 1.35 (t, 3H, CH_3, J = 7 Hz), 3.17 (q, 2H, CH_2, J = 7 Hz), 3.85 (s, 3H, OCH_3), 5.79 (s, 2H, CH_2), 6.97-7.23 (m, 4H, C_6H_4), 7.83-8.78 (m, 4H, C_5H_4N); ms: m/z 227 (9), 121 (100), 106 (39).

General Procedure for the Preparation of **15**, **16** and **19**.

To a vigorously stirred solution of the appropriate pyridinium chloride (27 mmoles) in water (24 ml) and dichloromethane (50 ml) under a nitrogen atmosphere was added the appropriate aroyl chloride (50 mmoles). Sodium hydroxide solution (25%, 36 ml) was added over 5 minutes and the stirring continued for a further 30 minutes. The organic solvent was evaporated and the dark residue was dissolved in dilute hydrochloric acid, boiled with decolorizing charcoal, filtered, the filtrate neutralized with sodium bicarbonate, and the precipitate filtered.

2-Benzoylmethylene-1,2-dihydro-1-(4-methoxybenzyl)pyridine (**15**).

The solid was crystallized from aqueous methanol to give **15** (70%), mp 144-146° (lit [14] mp 142-143°).

1-Benzyl-1,2-dihydro-2-(4-methoxybenzoylmethylene)pyridine (**16**).

The product (60%) was an unstable solid, mp 168-169.5°; ir: ν CO 1650 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.76 (s, 3H, OCH_3), 4.97 (s, 2H, CH_2), 5.53 (s, 1H, CH), 6.24 (m, 1H, 4-H), 6.69-7.62 (m, 11H, C_6H_5, C_6H_4, 3- and 5-H), 9.12 (dd, 1H, 6-H, J = 2, 10 Hz); ms: m/z 317 (M^+, 28), 300 (81), 182 (82), 91 (100).

3-(4-Methoxyphenyl)-1-methyl-2-phenylindolizine (**19**).

The solid was crystallized from aqueous methanol to give **19** (30%), mp 104-105°; ^{1}H nmr (deuteriochloroform): δ 2.34 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.30-7.26 (m, 12H, C_6H_5, C_6H_4, 6-, 7- and 8-H), 7.88 (dd, 1H, 5-H, J = 1, 8 Hz); ms: m/z 313 (M^+, 25%), 149 (100).

Anal. Calcd. for $C_{22}H_{19}NO \cdot 1/4H_2O$: C, 83.14; H, 6.14; N, 4.09. Found: C, 83.43; H, 6.03; N, 4.38.

1-Acetyl-3-(4-methoxyphenyl)-2-phenylindolizine (**17**).

This compound was prepared (20% yield) as described [14] and had mp 173-174° (lit [14] mp 173-174°); ^{1}H nmr (deuteriochloroform): δ 1.96 (s, 3H, $COCH_3$), 3.77 (s, 3H, OCH_3), 6.60-7.23 (m, 11H, C_6H_5, C_6H_4, 6- and 7-H), 7.92 (d, 1H, 8-H, J = 7 Hz), 8.53 (d, 1H, 5-H, J = 8 Hz); ms: m/z 341 (M^+, 95), 326 (100).

1-Acetyl-2-(4-methoxyphenyl)-3-phenylindolizine (**18**).

A mixture of **16** (1 g, 3.2 mmoles) and acetic anhydride (20 ml) was boiled under reflux for 1.5 hours. Water (100 ml) was added and the mixture stirred vigorously for 10 minutes. The precipitate was filtered and crystallized from ethanol to give **18** (0.54 g, 50%), mp 180-182°; ir: ν CO 1650 cm^{-1}; ^{1}H nmr (hexadeuteriodimethyl sulfoxide): δ 1.87 (s, 3H, $COCH_3$), 3.74 (s, 3H, OCH_3), 6.85-7.43 (m, 11H, C_6H_5, C_6H_4, 6- and 7-H), 8.03 (d, 1H, 8-H, J = 6 Hz), 8.41 (d, 1H, 5-H, J = 10 Hz); ms: m/z 341 (M^+, 47), 234 (100).

Anal. Calcd. for $C_{23}H_{19}NO_2 \cdot 1/8H_2O$: C, 80.40; H, 5.61; N, 4.07. Found: C, 80.43; H, 5.61; N, 4.08.

General Procedure for the Demethylation to Give **20** and **22**.

Ethanethiol (9.7 mmoles) was added dropwise to a slurry of sodium hydride (prepared from a mineral oil dispersion (60%, 0.4 g, 17 mmoles) washed with dry tetrahydrofuran) in dry dimethylformamide (DMF) (18 ml) cooled to 10°, and the mixture stirred for 10 minutes after the addition was complete. The appropriate methoxyphenylindolizine (0.4 g, 2 mmoles) in dry DMF (5 ml) was added in one portion and the mixture refluxed for 6-18 hours. On completion of the reaction (tlc), the product was poured into dilute hydrochloric acid and extracted with chloroform. The extract was washed with dilute hydrochloric acid and saturated brine, and then dried (sodium sulfate). Evaporation of the solvent gave a residue which was purified by column chromatography (petroleum ether-ethyl acetate, 19:1).

1-Acetyl-3-(4-hydroxyphenyl)-2-phenylindolizine (**20**).

Crystallization of the major component from aqueous methanol gave **20** (60%), mp 239.5-241.5°; ir: ν OH 3120, CO 1620 cm^{-1}; ^{1}H nmr (hexadeuteriodimethyl sulfoxide): δ 2.06 (s, 3H, $COCH_3$), 6.73-7.64 (m, 11H, C_6H_5, C_6H_4, 6- and 7-H), 8.01 (m, 1H, 8-H), 8.39 (dd, 1H, 5-H, J = 2, 9 Hz), 9.65 (s, 1H, OH, deuterium oxide exchangeable); ms: m/z 327 (M^+, 100), 312 (84).

Anal. Calcd. for $C_{22}H_{17}NO_2 \cdot 1/4H_2O$: C, 79.63; H, 5.27; N, 4.22. Found: C, 79.78; H, 5.18; N, 4.08.

1-Acetyl-2-(4-hydroxyphenyl)-3-phenylindolizine (**22**).

This compound was obtained (40%) by crystallization (aqueous ethanol) of the major component, mp 197-199°; ir: ν OH 3400-3200, CO 1645 cm^{-1}; ^{1}H nmr (hexadeuteriodimethyl sulfoxide): δ 1.88 (s, 3H, $COCH_3$), 6.68-7.59 (m, 11H, C_6H_5, C_6H_4, 6- and 7-H), 8.04 (m, 1H, 8-H), 8.41 (d, 1H, 5-H, J = 9 Hz), 9.30 (s, 1H, OH, deuterium oxide exchangeable); ms: m/z 327 (M^+, 100), 312 (95).

Anal. Calcd. for $C_{22}H_{17}NO_2 \cdot 1/8H_2O$: C, 80.18; H, 5.24; N, 4.25. Found: C, 80.14; H, 5.19; N, 4.23.

General Procedure for the Preparation of the Ethers **21** and **23**.

A vigorously stirred mixture of 1-chloro-2-dimethylaminoethane hydrochloride (29 molar equivalents), the hydroxyphenylindolizine (0.16 g, 0.49 mmole), anhydrous potassium carbonate (2 g) and dry acetone (20 ml) was refluxed for 4 hours. After pouring the mixture into ice-water, it was extracted with chloroform, dried, the solvent removed and the residue distilled (bulb to bulb) under vacuum.

1-Acetyl-3-(4-[2-dimethylaminoethoxy]phenyl)-2-phenylindolizine (**21**).

The ether **21** (50%) had bp 202° at 1 mm Hg; ir (liquid): ν CO 1615 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.96 (s, 3H, OCH_3), 2.39 (d, 6H, NMe_2, J = 3 Hz), 2.76 (m, 2H, CH_2), 4.07 (m, 2H, OCH_2), 6.54-7.68 (m, 11H, C_6H_5, C_6H_4, 6- and 7-H), 7.92 (d, 1H, 8-H, J = 7 Hz), 8.53 (d, 1H, 5-H, J = 10 Hz); ms: m/z 398 (M^+, 5), 123 (11), 72 (100).

Anal. Calcd. for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.02; H, 6.56; N, 6.94.

1-Acetyl-2-(4-[2-dimethylaminoethoxy]phenyl)-3-phenylindolizine (**23**).

The ether **23** (50%) had bp 192° at 0.5 mm Hg; ir (liq.): ν CO 1620 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.00 (s, 3H, OCH_3), 2.34 (d, 6H, NMe_2, J = 2 Hz), 2.76 (m, 2H, CH_2), 4.12 (m, 2H, OCH_2), 6.13-8.02 (m, C_6H_5, C_6H_4, 6-, 7- and 8-H), 8.53 (d, 1H, 5-H, J = 9 Hz); ms: m/z 398 (M^+, 100).

Anal. Calcd. for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.13; H, 6.59; N, 6.95.

3-(4-Methoxyphenyl)-1-methyl-2-phenylindolizine (**24**) and 1-Methyl-3-(4-[2-dimethylaminoethoxy]phenyl)-2-phenylindolizine (**25**).

A mixture of **19** (1 g, 3.2 mmoles) and hydrobromic acid (48%, 17 ml) was refluxed under a nitrogen atmosphere for 1 hour, and then the mixture was poured into ice-water, neutralized with sodium bicarbonate and extracted with ether. Evaporation of the solvent gave the demethylated compound **24**; ir (liquid): ν OH 3200 cm^{-1}; ms: m/z 299 (M^+, 100).

The phenol **24** was treated immediately with 1-chloro-2-dimethylaminoethane hydrochloride (1.5 g, 10 mmoles), dry acetone (30 ml) and anhydrous potassium carbonate (5 g), and boiled under reflux for 5 hours. The mixture was poured into water, extracted with chloroform, the organic layer evaporated, and the residue purified by preparative thin layer chromatography (ethyl acetate-methanol, 7:3) to give **25** as an oil (32%), bp 219° at 0.7 mm Hg; ^{1}H nmr (deuteriochloroform): δ 2.32 (s, 6H, NMe_2), 2.35 (s, 3H, CH_3), 2.71 (m, 2H, CH_2), 4.04 (m, 2H, OCH_2), 6.30-7.31 (m, 11H, C_6H_5, C_6H_4, 6- and 7-H), 7.34 (d, 1H, 8-H, J = 9 Hz), 7.93 (d, 1H, 5-H, J = 8 Hz); ms: m/z 370 (M^+, 50), 299 (10), 149 (12), 72 (100).

Anal. Calcd. for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 80.80; H, 7.01; N, 7.29.

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