N-(2-Chloroethyl)-N'-[(3,17β-dihydroxyestra-1,3,5(10)-trien-17α-yl)methyl]-N-nitrosourea (5a). To a solution of the amine 4 (0.70 g, 2.3 mmol) in pyridine (15 mL) at 0 °C, (2-chloroethyl)nitrosocarbamoyl azide (0.42 g, 2.3 mmol) in ether (1.3 mL) was added dropwise with stirring. The mixture was stirred at 0 °C for 3 h and then ice water was added, followed by extraction with ether. The ether extract was washed (ice-cold 2 N HCl, 10% $NaHCO_3$, and brine successively), dried ($MgSO_4$), and evaporated to dryness. Crystallization from ether yielded the nitrosourea **5a** as a pale-yellow crystalline product (0.70 g, 70% yield): mp 116–119 °C dec; IR (CH_2Cl_2) 3560 (OH), 3410 (NH), 1720 (C=O), 1525 (CNH), 1490 cm^{-1} (NO); NMR (acetone-d_6) δ 1.00 (s, 3 H, C_{18}-H), 3.66, 4.28 (A_2B_2 system, 2 t, J = 7 Hz, 4 H, $-N(NO)CH_2CH_2Cl$), 3.70 (m, 2 H, 17α-CH_2N-), 6.60–7.20 (m, 3 H, Ar H); MS m/e 327 (M^+ – $HON{=}NCH_2CH_2Cl$). Anal. ($C_{22}H_{30}ClN_3O_4$) C, H, Cl, N.

N-Methyl-N'-[(3,17β-dihydroxyestra-1,3,5(10)-trien-17α-yl)methyl]-N-nitrosourea (5b). Following the general procedure described for the synthesis of **5a**, reaction of the amine **4** (1.4 g, 4.8 mmol) with methylnitrosocarbamoyl azide[14] (4.8 mmol) gave compound **5b** as a pale-yellow crystalline product after crystallization from CH_3OH–ether–hexane (1.1 g, 60% yield): mp 144–146 °C dec; NMR (acetone-d_6) δ 1.00 (s, 3 H, C_{18}-H), 3.22 (s, 3 H, $-N(NO)CH_3$), 3.40 (s, ~3 H, CH_3 of CH_3OH), 3.65 (m 2 H, 17α-CH_2N), 6.60–7.20 (m, 3 H, Ar H); MS m/e 327 (M^+ – $HON{=}NCH_3$). Anal. ($C_{21}H_{29}N_3O_4{\cdot}CH_3OH$) C, H, N.

N-(2-Chloroethyl)-N'-(3-hydroxyestra-1,3,5(10)-trien-17β-yl)-N-nitrosourea (6a). Following the general procedure described above, reaction of 17β-amino-3-hydroxyestra-1,3,5-(10)-triene[20] (2.5 g, 9.2 mmol) with (2-chloroethyl)nitrosocarbamoyl azide (9.2 mmol), after crystallization from CH_3OH, gave **6a** as a colorless crystal (1.6 g, 43% yield): mp 87–90 °C dec; NMR δ 0.86 (s, 3 H, C-18), 3.66, 4.26 (A_2B_2 system, 2 t, J = 7 Hz, 4 H, $-N(NO)CH_2CH_2Cl$), 4.00 (m, 1 H, C_{17}-H), 6.60–7.35 (m, 3 H, Ar H); MS m/e 405 (M^+), 297 (M^+ – $HON{=}NCH_2CH_2Cl$), 255 (M^+ – side chain). Anal. ($C_{21}H_{28}ClN_3O_3$) C, H, Cl, N.

N-Methyl-N'-(3-hydroxyestra-1,3,5(10)-trien-17β-yl)-N-nitrosourea (6b). Following the general procedure described above, reaction of 17β-amino-3-hydroxyestra-1,3,5(10)-triene (2.4 g, 8.9 mmol) and methylnitrosocarbamoyl azide (8.9 mmol) furnished **6b** (1.7 g, 54% yield): mp 140–142 °C dec; NMR δ 1.00 (s, 3 H, C_{18}-H), 3.24 (s, 3 H, $-N(NO)CH_3$), 4.20 (m, 1 H, C_{17}-H), 6.60–7.35 (m, 3 H, Ar H); MS m/e 357 (M^+), 297 (M^+ – $HON{=}NCH_3$), 255 (M^+ – side chain). Anal. ($C_{20}H_{27}N_3O_3$) C, H, N.

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Phototoxicity of Chlorpromazine

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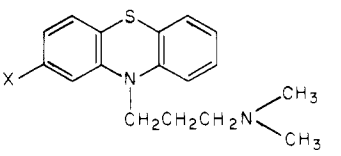
The constitution of chlorpromazine has been studied in the context of its phototoxicity. Electron transfer from the side chain to the aromatic nucleus of the drug contributes to its instability to light. Even without the side chain, however, chlorophenothiazines appear to be very photolabile, so that it is unlikely that nonphototoxic analogues of chlorpromazine can be prepared merely by altering the constitution of the side chain.

Phototoxicity has been noted as a side effect in chlorpromazine therapy for a number of years,[1] but only recently has the photochemical breakdown of the drug been studied. Grant[2] observed that chlorpromazine (**1**) was reduced to promazine (**2**) and also underwent substitution to the hydroxy compound **3** upon illumination in aqueous solution. Formation of **3** was deduced to be a photonucleophilic process, because other nucleophiles such as alcohols and amines could undergo analogous reactions. Reduction and substitution are known photoreactions of other aryl halides.[3]



1, X = Cl
2, X = H
3, X = OH

Photodechlorination of chloro aromatic compounds has been extensively studied in other systems.[3-6] Two reaction

pathways appear to operate. Direct homolysis (eq 1)

$$ArCl \xrightarrow{h\nu} Ar\cdot + Cl\cdot \xrightarrow{RH} ArH + HCl \quad (1)$$

affords radicals which abstract hydrogen atoms from the solvent. Alternatively, electron donors such as amines may donate an electron to the excited state of the aromatic compound,[7] whereupon chloride ion may be lost from the radical anion (eq 2 and 3). In either case, radicals Ar· are

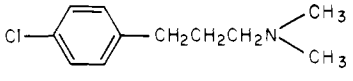
$$ArCl^* + D \rightarrow D^{+}\cdot + ArCl^{-}\cdot \quad (2)$$

$$ArCl^{-}\cdot \rightarrow Cl^{-} + Ar\cdot \xrightarrow{RH} ArH \quad (3)$$

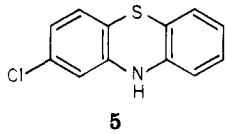
reaction intermediates, and these are widely believed to be responsible for photoallergic reactions.[8]

The structure of 1 is such that the molecule contains an aryl chloride unit with an intramolecular, but unconjugated, amino group. Electron transfer as represented by eq 2 should therefore be facile. However, experience with other aryl chlorides suggests that electron transfer does not always increase the efficiency of photodecomposition. 1-Chloronaphthalene, which is inherently rather light stable, has its reactivity increased in the presence of amines.[6] However, the reverse is true of the much more photolabile (in the UV region) chlorobenzene, toward which amines exert a stabilizing effect in nonpolar solvents.[9a] This last effect is exaggerated for compound 4 where the amino group is intramolecular but disappears in very polar media.[9b] This may be explained by the fact that in nonpolar solvents back electron transfer competes with diffusion apart of the radical ions in eq 2, whereas in polar media diffusion is more facile.

It seemed likely that intramolecular electron transfer could intervene in the photochemistry of 1 as it does in that of 4. The point was investigated by comparing the



4



5

photochemical behavior of 1 with 5, which lacks the aminopropyl side chain. The practical purpose behind these experiments was to determine whether electron transfer is the major reason for the photochemical instability of 1. The information might aid in the search for structural analogues of 1 that are not phototoxic.

Fluorescence. Quenching of the fluorescence of aromatic compounds by amines indicates electron transfer in the excited singlet state.[7] We measured the fluorescence of 5, 1, and a number of related phenothiazine drugs.[10] All exhibited a broad featureless emission with a maximum near 450 nm. Qualitatively, all emissions were of comparable intensity. The similarity of the emissions of 1 and 5 suggests that there is little interaction between the side chain and the nucleus of 1 in the excited singlet state. This view was strengthened by the results of attempted quenching of the fluorescence of 1 and of 5 by added triethylamine. The fluorescence of 1 was unaffected by triethylamine and that of 5 was quenched only slightly.

The efficiency of quenching was determined using the Stern–Volmer equation

$$I^{F}_{0}/I^{F}_{Q} = 1 + k_{Q}\tau[Q]$$

where I^{F}_{Q} and I^{F}_{0} are the fluorescence intensities in the presence and absence of quencher Q; k_Q is the bimolecular rate constant for quenching and τ is the lifetime of the excited state. The slope of the Stern–Volmer line, $k_Q\tau$, was 0.3 M^{-1} in isooctane and 0.1 M^{-1} in aqueous acetonitrile. The singlet lifetime τ was unavailable experimentally and was estimated for 5 at 2.5×10^{-8} s from the relationship[11] $\tau_{rad} \approx 10^{-4}/\epsilon_{max}$. Here ϵ_{max} is the extinction coefficient at the maximum of the absorption band (4×10^3 at 310 nm in this case). τ_{rad} is the radiative lifetime of the state; the actual lifetime τ is generally less than τ_{rad}. Therefore, our rate constants are estimated to be too small, to the extent that τ_{rad} is larger than τ in this case.

Thus, we estimate k_Q to be of the order of 10^7 L mol^{-1} s^{-1}, which is considerably less than the rate constant for diffusion. Intermolecular quenching is seen to be rather inefficient, and it would be supposed that the same is true intramolecularly. By contrast, the fluorescence of 5 is quenched much more efficiently by 1,4-dicyanobenzene (a good electron acceptor). Here $k_Q\tau = 11$ M^{-1} in benzene and so $k_Q \approx 4.4 \times 10^8$ M^{-1} s^{-1}, in line with the fact that the phenothiazine nucleus is more susceptible to oxidation than to reduction.

Table I. Quantum Yields (ϕ) for Photodecomposition of 1 and 5[a]

compd	ϕ degassed	ϕ aerated
1	0.46	0.29
5	0.20	0.21

[a] In CH_3CN–H_2O, 4:1, irradiated at 300 nm.

Table II. Effect of Added Amine on the Photodecomposition of 1 and 5[a]

compd, M	[Et_3N] =	% decomposition[b] 0.00 M	0.01 M	0.05 M	0.25 M
5,[c] 2.0×10^{-3}		15	80	95	95
1,[c] 2.1×10^{-3}		48	80	81	81
5,[d] 2.0×10^{-3}		16	24	34	42
1,[d] 2.0×10^{-3}		30	31	32	32

[a] In CH_3CN–H_2O, 4:1, irradiated at 300 nm. [b] Solutions of 1 and 5 at the same Et_3N concentration were illuminated in parallel to assure equal light absorption. [c] Degassed. [d] Aerated.

Photodecomposition. Quantum yields for the photodecomposition of chlorpromazine and the model compound 5 are given in Table I. Both degassed and aerated systems were studied, although the degassed situation more closely resembles that in vivo, where the free oxygen concentration is low. The solvent in all cases was CH_3CN–H_2O. We observed that chlorpromazine was more reactive than 5, and that externally added triethylamine increased the decomposition efficiency of 1 further still under degassed conditions (Table II). Correspondingly, added amine had a large promoting effect on the decomposition of 5. These results point to involvement of the aminopropyl side chain in the photochemistry of 1 and are significant also in view of the large number of biological nitrogen compounds with which 1 might interact in vivo.

In aerated solution, added amine did not enhance the decomposition of 1 and had a much smaller effect on 5 compared with the degassed system. We conclude that chlorpromazine reacts by way of the triplet excited state; not only is oxygen an effective triplet quencher, but the enhancement of decomposition by amine cannot involve the singlet state, otherwise we would have observed efficient fluorescence quenching by amine. Davies et al.[12] had previously concluded that 1 photodegrades by way of the triplet state in isopropyl alcohol solution. However, their mechanism for decomposition involves direct

homolysis (eq 1), whereas we implicate electron transfer (eq 2 and 3).

A rather different mechanism has been advanced by Iwaoka and Kondo.[13] In aqueous alcohol, dioxane, and glycerol, they find photoionization (from an upper triplet[13b]) to be a major process. However, photoionization is much less important in pure water or in aqueous acetonitrile,[13a] making the latter solvent much more suitable for the present investigation.

We conclude that the interaction of amines with photoexcited chlorophenothiazines **1** and **5** contributes to their photoreactivity. However, even in the absence of the side chain, **5** is still decomposed rather efficiently (ϕ = 0.2). This makes it relatively unlikely that a photostable drug of the chlorpromazine family can be synthesized merely by altering the constitution of the side chain of the drug. On photochemical grounds, substitution of the chlorine atom might be more fruitful.

Experimental Section

Fluorescence spectra were run in aerated solutions of aqueous acetonitrile and of isooctane at 23 °C using a Hitachi-Perkin-Elmer Model MPF-2A spectrophotofluorimeter. In the case of the drugs, supplied as salts, the free base was liberated from its salt with alkali. For the study in isooctane, the free base was then extracted into purified isooctane. Photolyses were carried out at 300 nm using a Rayonet Model RUL photoreactor. A "merry-go-round" was used to assure equal light absorption by samples irradiated in parallel. The samples were contained in Pyrex glass ampules, which were evacuated on a vacuum line where necessary using the freeze–pump–thaw technique. The progress of the reaction was followed by a potentiometric method (Orion Model 407A pIon meter and Orion Model 94-17A chloride-sensitive electrode). Because the solvent was CH_3CN–H_2O, it was necessary to make careful calibrations using solutions of known chloride concentration. Quantum yields of the reaction were made by comparison of the progress of the reaction with that of the ferrioxalate actinometer.[14]

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Aminotetralins as Narcotic Antagonists. Synthesis and Opiate-Related Activity of 1-Phenyl-2-aminotetralin Derivatives

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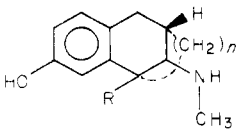
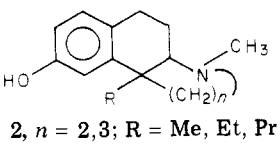
The synthesis and the opiate agonist and antagonist activities of three derivatives of *cis*-2-[methyl(cyclopropanemethyl)amino]-1-phenyltetralin are reported. The compounds were obtained by synthetic modification from 2-amino-1-tetralone. The 1-propionoxy derivative **4c** shows analgetic activity (ED_{50} = 17.8 mg/kg) one-half that of codeine, and the 1-methoxy derivative **4b** has weak antagonist activity (AD_{50} = 33.5 mg/kg). The compounds showed no other significant opiate-related activity.

Several reports on the 1-substituted 2-aminotetralin series with opiate activity have appeared. Freed et al.[1,2] have found the bridged aminotetralins of structure 1 to

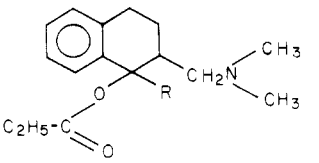


1, n = 4,5; R = Me, Et

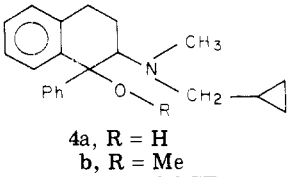


2, n = 2,3; R = Me, Et, Pr

be analgetic agonists and antagonists. In a similar series of compounds (**2**) synthesized by Takeda et al.,[3] analgetic activity in the range of codeine to morphine was found. Analgetic activities have also been reported for compounds of structure **3**.[4] Narcotic antagonist activity has not been



3, R = $CH_2C_6H_5$, $CH_2C_5H_4N$



4a, R = H
b, R = Me
c, R = OOCEt

reported for derivatives of **2** or **3**. Proper substitution of aminotetralin structures of this type could reasonably lead to compounds with mixed agonist–antagonist activity and possibly improved pharmacological properties over agents now available.

In the course of synthetic studies to prepare 1-substituted 3-aminotetralins,[5] several synthetic pathways were

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