Photochemistry of Chloroacetanilide Derivatives: Rearrangement, Cyclization, and Solvolysis

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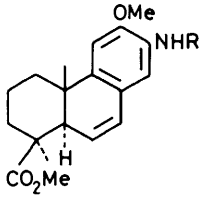
N-Chloroacetylamines on photolysis in methanol, rearrange to give *N*-substituted glycine esters and methyl esters. Conditions have been established for the formation of a five-membered lactam system by cyclization. A dual mechanism is shown to be operative in the photolysis of the chloroacetamide function in polar and non-polar solvents, giving solvolytic and hydrogen-abstracted products respectively.

Witkop and Yonemitsu *et al.*[1-6] have reported photolytic cyclizations of chloroacetyl derivatives of pharmacodynamic amines, amino acids, and other related compounds and reported the formation of seven- and ten-membered ring systems. We were interested in the cyclization of the chloroacetyl derivatives of estrogenic amines,[7] obtained from podocarpic acid, in order to obtain heterosteroidal systems.[8] This paper reports the details of the novel rearrangement,[9,10] formation of a five-membered lactam system by photocyclization, and mechanistic ideas about the solvolysis of the chloroacetamide function.

Results and Discussion

Photolysis of compound (**1a**) in various solvents (0.01M) was carried out for 1 h. Two compounds (**1b**) and (**1c**) were isolated in yields of 40—50 and 30% respectively, when the photolysis was carried out in methanol. Similar products (**1d**) and (**1e**) were also isolated when ethanol was used as the solvent. In tetrahydrofuran or dioxane, the product (**1f**) was obtained in 15% yield along with large amounts of unidentifiable polymeric material. The reaction was slower in dioxane and tetrahydrofuran (THF), since, for the same reaction time as that used for reactions in polar solvents, starting compound was also isolated.



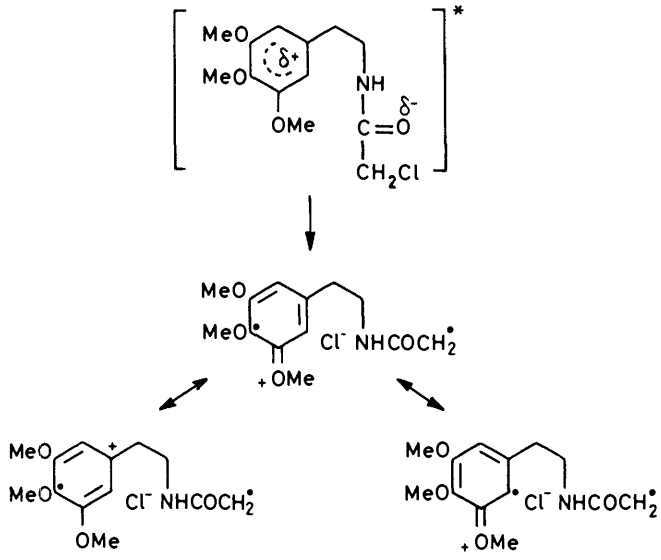
(1)

a; R = $COCH_2Cl$ **e**; R = CH_2CO_2Et
b; R = $COCH_2OMe$ **f**; R = COMe
c; R = CH_2CO_2Me **g**; R = $COCH_2CH_2Cl$

Compound (**1g**) failed to undergo photolysis in methanol, only starting material being isolated from the reaction mixture.

N-Chloroacetylcyclohexylamine (**2**) in aqueous methanol on irradiation gave *N*-cyclohexylglycine (**2a**), m.p. 231—232 °C (lit.,[11] m.p. 229 °C) in *ca.* 20% yield. The amino acid exists in the dipolar, *i.e.* zwitterionic form as evidenced by the appearance of bands in its i.r. (KBr) spectrum at 6.17 and 6.34 (CO_2^-) 3.15 and 3.28 μm ($\overset{+}{N}H_2$).[12] No cyclized product was isolated from work-up of the photolysed solution obtained in the various experiments described so far, using different solvents.

$$\underset{(2)}{C_6H_{11}NHCOCH_2Cl} \xrightarrow{h\nu} \underset{(2a)}{C_6H_{11}\overset{+}{N}H_2CH_2CO_2}$$

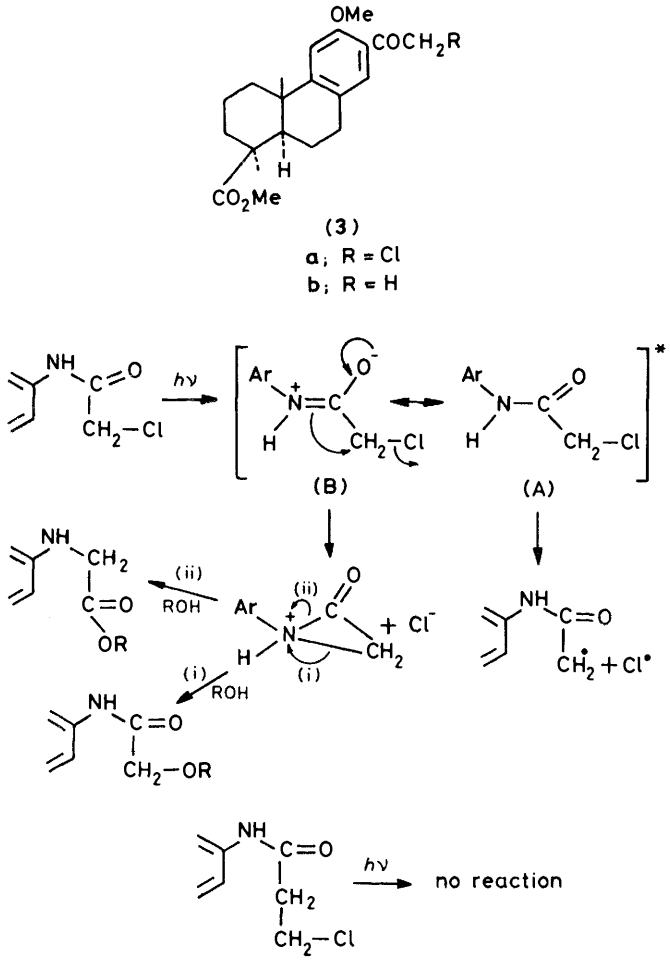


Scheme 1.

Witkop *et al.*[2], have proposed a π–π* excitation and induction of a partial electron transfer from the aromatic moiety to the chlorinated amide, in order to suggest an intramolecular exciplex which breaks into cage complexes as shown in Scheme 1. Two other groups[13,14] using a substituted naphthalene system suggest that photoexcitation of the aromatic moiety of the molecule to give a π–π* singlet state leads to increased electron density at C-8 and chloride ion displacement from the side-chain of the intermediate.

These considerations however appear irrelevant for our compounds since all of them have conjugated aromatic and amide chromophores, in contrast to Witkop's in which separated aromatic and amide chromophores were involved. Thus, the first excited state for the conjugated group involves the whole chromophore and it may not be correct to consider electron transfer between the aromatic and amide groups.

In another set of experiments, compound (**3a**) was irradiated separately under the same conditions in methanol as well as tetrahydrofuran. In both cases only compound (**3b**) (a product of hydrogen abstraction) was obtained in more than 65% yield, irrespective of the solvent used. It would thus appear that it is the NH grouping which is responsible for the dual behaviour of (**1a**), in polar and non-polar solvents. Earlier workers,[15-17] on the basis of u.v. studies, have shown the existence of a contributing state such as (B) in amides. Such structures are more important in the excited state Q, rather than in the ground state N, and accordingly would facilitate the N⟶Q or n⟶π* transition.



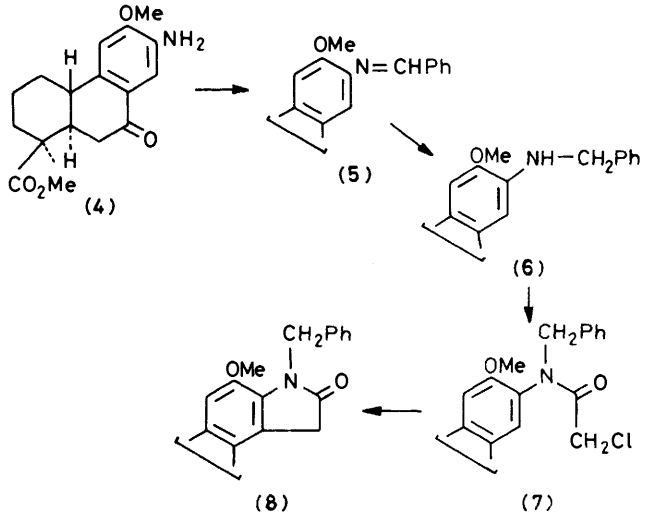
Scheme 2.

On the basis of our results it is suggested that the excited state is more polar than the ground state, and in a polar solvent it appears to undergo an intramolecular nucleophilic displacement reaction (see Scheme 2) to give an α-lactam intermediate. Entropy considerations make this favourable for chloroacetamides and less favourable for chloropropionamides, the latter not undergoing this reaction. The α-lactam could open in manner (i) or (ii) thus giving rise on photolysis of (**1a**) to compounds (**1b**) and (**1c**) in methanol or compounds (**1d**) and (**1e**) in ethanol.

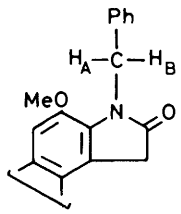
An alternative relaxation pathway for the excited state is by vibrational decay to the ground state, the vibrational energy then causing homolysis of the weakest bond. In this case, the carbon–chlorine bond is the weakest one, giving a stabilized carbon radical. In non-polar solvents the latter process predominates and leads to hydrogen abstraction by the carbon radical so formed.

There were no detectable amounts of other solvolytic products since alkoxide ion being a high-energy anion departs less readily than the chloride ion. Zimmerman[18] *et al.* have previously observed similar results in both polar and non-polar solvents in the photolytic solvolysis of substituted benzyl chlorides and benzyl acetates.

Photocyclization to a γ-Lactam.—Although secondary chloroacetamides have also been shown to undergo photorearrangement as discussed above tertiary chloroacetamides undergo photocyclization. Compound (**4**)[8,19] was converted into its Schiff's base (**5**) on reaction with benzaldehyde, which without purification was reduced with sodium borohydride to give the secondary amine (**6**). The amine (**6**) was converted into its chloroacetyl derivative (**7**) on treatment with the chloroacetyl chloride. The structures of most of these compounds were confirmed from their elemental analyses, and by n.m.r. and i.r. studies. The chloroacetyl derivative (**7**) was photolysed under the same conditions and work-up of the photolysis mixture provided the photoproduct (**8**), the elemental analysis of which



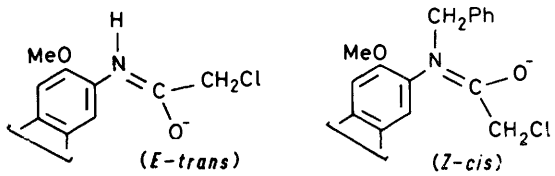
was in agreement with the molecular formula $C_{28}H_{31}NO_4$. The n.m.r. spectrum showed the presence of six aromatic protons instead of seven and, notably, the absence of an aromatic proton signal at δ 7.9 (1 H) observed in the n.m.r. spectrum of compound (**6**). Secondly, the benzylic methylene (1 H singlets at δ 4.16 and 4.32) shows non-equivalence of the two protons (H_A and H_B) because of its attachment to asymmetric nitrogen, thus providing different magnetic environments for the two protons at low inversion rate.[20–22] The methylene signal at δ 3.55 has



been assigned to the oxindole methylene, its low position being due to its benzylic nature and the deshielding effect of the carbonyl group. These facts support the cyclization and hence structure (8) was assigned to the photoproduct.

A similar photocyclization, using *meta*-anisidine as the parent amine followed by tertiary chloroacetamide formation have been described by Yonemitsu *et al.*[23]

Since *N*-monosubstituted amides in solution are present predominantly in their *trans*-form[24] (shown as the *E*-conformer) the chloromethyl group would not be close to the aromatic ring. Thus it seems likely that the introduction of a bulky substituent on the nitrogen leads to the amide group being fixed in the *cis*-configuration (shown as the *Z*-



conformer) and this results in cyclization taking place. This assumption seems to be true, since chloroacetylamine in amide with an unsubstituted nitrogen atom (*trans*-form) rearranges to *N*-substituted α-amino acids, while the corresponding *N*-substituted compound (*cis* form) undergoes cyclization to the oxindole system.

Experimental

M.p.s are uncorrected. I.r. and n.m.r. spectra have been recorded on IR-20 and Varian A-60 instruments respectively. Compound (**1**; R = H) was prepared in accordance with work already reported from our laboratory.[19]

Preparation and Photolysis of Compound (**1a**).—Compound (**1**; R = H) on treatment with chloroacetyl chloride, by a normal acetylation procedure gave compound (**1a**), m.p. 146—147 °C, $\lambda_{max.}$(KBR) 2.98, 5.81, 5.95, and 6.33 μm; δ($CDCl_3$) (all singlets) 0.83 (3 H), 1.15 (3 H), 3.65 (3 H), 3.87 (3 H), 4.12 (2 H), 6.38 (2 H), 6.72 (1 H), and 8.0 (1 H).

Compound (**1a**) (1.13 g) in methanol (220 ml) was irradiated with a 125 W Hg arc lamp using a quartz filter for 1 h. The photolysate was reduced in volume to 10 ml and with time and cooling precipitated (**1b**) (400 mg); this on recrystallization had m.p. 182—183 °C (Found: C, 68.0; H, 7.6; N, 3.4. Calc. for $C_{22}H_{29}NO_5$: C, 68.2; H, 7.5; N, 3.6%); δ($CDCl_3$) (all singlets) 0.9 (3 H), 3.5 (3 H), 3.68 (3 H), 3.85 (3 H), 4.10 (2 H), 6.45 (2 H), 6.8 (1 H), and 8.15 (1 H).

The filtrate left was evaporated to dryness and the resulting gummy mass chromatographed on alumina. Benzene–light petroleum (2 : 3) gave, on evaporation and crystallization from methanol, compound (**1c**), m.p. 162—163 °C; $\lambda_{max.}$ 1 695, 1 720, and 3 400 cm^{-1}; δ($CDCl_3$) (all singlets) 0.82 (3 H), 1.3 (3 H), 3.5 (3 H), 3.68 (3 H), 3.85 (3 H), 4.0 (1 H), 6.15 (1 H), 6.35 (2 H), 6.75 (1 H), and 8.0 (1 H) (Found: C, 68.2; H, 7.4; N, 3.5. Calc. for $C_{22}H_{29}NO_5$: C, 68.31; H, 7.49; N, 3.61%).

Compound (**1a**) when photolysed in ethanol under similar conditions to those employed for the photolysis in methanol gave compounds (**1d**), m.p. 129 °C, and (**1e**), m.p. 101 °C.

Compound (**1a**) was photolysed using dioxane as the solvent under similar conditions. The photolysate was evaporated to a small volume and left for several days when it deposited compound (**1f**) (150 mg), m.p. 149 °C. Some starting material (250 mg) was also recovered. The primary amine (**1**; R = H) on acetylation gave (**1f**), m.p. 148 °C.

Similar results were obtained using THF as the solvent, when again compound (**1f**) was isolated.

Preparation and Photolysis of Compound (**3a**).—Compound (**3a**) was prepared by chloroacetylation of methyl *O*-methylpodocarpate, using aluminium chloride as catalyst and carbon disulphide as the solvent. Upon work-up, the Friedel-Crafts reaction product (**3a**), m.p. 163 °C, was obtained (Found: C, 67.4; H, 6.25; Cl, 9.4. Calc. for $C_{21}H_{23}ClO_4$: C, 67.01; H, 6.39; C, 9.45%).

Compound (**3a**) on photolysis using the same conditions and methanol as the solvent gave compound (**3b**) (65%), m.p. 150—151 °C. The structural assignment was confirmed by the synthesis of (**3b**) using Friedel-Crafts acylation of methyl *O*-methylpodocarpate with aluminium chloride and acetyl chloride.

Preparation and Photolysis of Compound (**1g**).—Compound (**1g**) was prepared by treating the amine (**1**; R = H) with chloropropionyl chloride thus providing (**1g**), m.p. 171—172 °C.

Compound (**1g**) was photolysed in methanol as the solvent, under similar conditions to those employed for compound (**1a**). After irradiation for 1 h, the photolysed solution was evaporated, to give starting material (**1g**) in almost quantitative yield. An increase in the irradiation time had no effect on the result.

Photolysis of N-*Chloroacetylcyclohexylamine to* N-*Cyclohexylglycine*.—Compound (**2**) (1 g) was dissolved in methanol–H_2O (8:2) (220 ml) and the solution was irradiated under similar conditions to those described earlier. The photolysed solution was reduced in volume to 5 ml, cooled, and left overnight, when a creamy white crystalline product (**2a**) (200 mg), m.p. 231 °C (lit.,[11] m.p. 229 °C) was obtained in 20% yield; $\lambda_{max.}$(KBr) 6.17, 6.34, 3.15, and 3.28 μm.

Preparation of Compound (**6**).—Compound (**4**) (11 g) was dissolved in methanol (10 ml) and a solution of benzaldehyde (4.0 g) in methanol (5 ml) was added. The mixture was triturated, and compound (**5**) separated as a solid. This was crystallized from methanol and had m.p. 195 °C.

Compound (**5**) on reduction with sodium borohydride by the usual procedure gave on work-up compound (**6**), m.p. 114—115 °C (71%); δ($CDCl_3$) (all singlets) 0.84 (3 H), 1.2 (3 H), 3.73 (3 H), 4.02 (3 H), 4.3 (2 H), 6.68 (2 H), 7.0 (5.48, m), 7.52 (1 H), and 7.9 (1 H) (Found: C, 76.8; H, 7.2; N, 3.3. Calc. for $C_{25}H_{28}NO_3$: C, 76.93; H, 7.17; N, 3.58%).

Preparation of Compound (**7**) *and Its Photolysis*.—Compound (**7**), the *N*-chloroacetyl derivative of compound (**6**), was prepared in a similar manner as compound (**1a**).

Compound (**7**) (0.5 g) in methanol (220 ml) was irradiated under similar conditions to those described earlier for 30 min. After work-up as described earlier, compound (**8**) (170 mg), m.p. 175—176 °C, was obtained (34%), δ($CDCl_3$) (all singlets) 0.9 (3 H), 1.32 (3 H), 3.55 (3 H), 3.72 (3 H), 4.02 (2 H), 4.16 (1 H), 5.65 (2 H), 7.05 (5 H, br), and 7.6 (1 H) (Found: C, 75.1; H, 6.8; N, 3.1. Calc. for $C_{28}H_{31}NO_4$: C, 75.50; H, 6.96, N, 3.14%).

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