Photochemical Reactions of *N*-Alkyl-α-oxoamides

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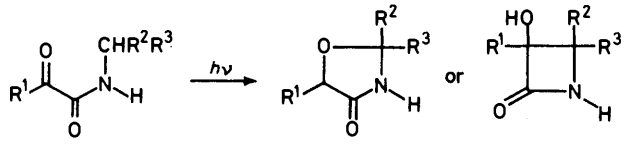
Photolysis of *N*-alkyl-α-oxoamides gave oxazolidin-4-ones or β-lactams as major products as in the case of *NN*-dialkyl-α-oxoamides. The formation of cyclohexanone in the photolysis of *N*-cyclohexylbenzoylformamide in an aqueous acidic medium was most reasonably explained by hydrolysis of an intermediate, *N*-cyclohexylidenemandelamide.

PHOTOCHEMICAL reactions of α-oxoamides are of interest from the synthetic viewpoint.[1] Recently, we reported photochemical reactions of *NN*-dialkyl-α-oxoamides which gave β-lactams (type II cyclisation products) or oxazolidin-4-ones as the main products,[2] in yields which depended on the substituents and solvent. Type II elimination products were obtained as major products only in the case of *N*-alkyl-α-oxoanilides. Independently, Zehavi investigated the reactions of *N*-alkyl-α-oxoamides and reported that photolysis of *N*-cyclohexylbenzoylformamide (1a) in aqueous ethanol containing mineral acids gave cyclohexanone (77%).[3] He explained the formation of the ketone in terms of type II elimination of (1a) (path a, Scheme 2), which is surprising in view of the fact that type II elimination products are obtained only as minor products in the photolysis of *NN*-dialkyl-α-oxoamides.[2] He also reported that photolysis of (1a) in ethanol gave *N*-cyclohexylmandelamide (a photoreduction product) accompanied by two dimeric products whose structures were not completely determined. He isolated neither β-lactams nor oxazolidinones in the photolysis of (1a).



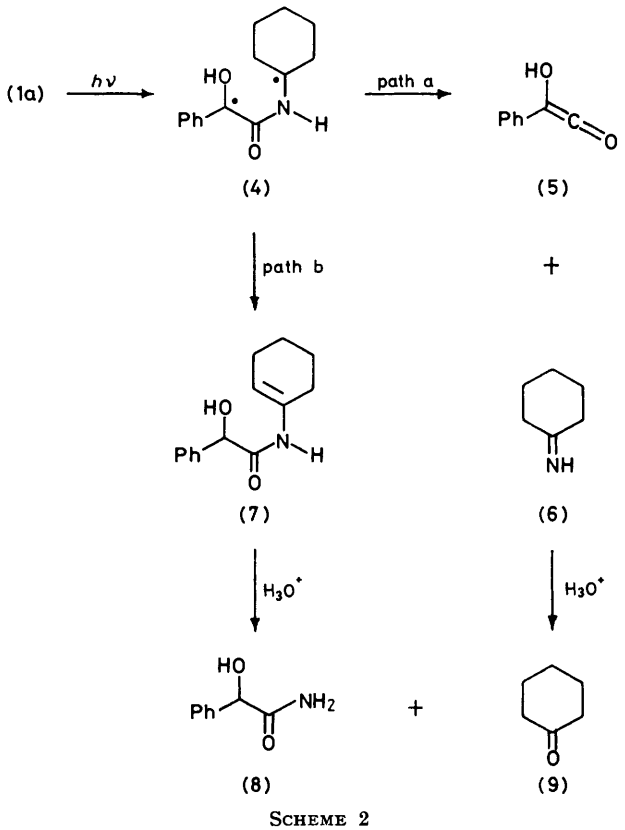
(1) (2) (3)

a; R^1 = Ph, R^2,R^3 = $[CH_2]_5$
b; R^1 = R^2 = R^3 = Me
c; R^1 = Me, R^2 = H, R^3 = Ph
d; R^1 = Ph, R^2 = R^3 = Me
e; R^1 = R^3 = Ph, R^2 = H

SCHEME 1

The different photochemical behaviour of the monosubstituted amide from that of the disubstituted amides prompted us to investigate the photolysis of some *N*-alkyl-α-oxoamides.

In general, photoreactions of *N*-alkyl-α-oxoamides are less clean than those of *NN*-dialkyl-α-oxoamides, and many unidentified by-products are formed in every case. In particular, irradiation of *N*-benzylpyruvamide (1c) in methanol or benzene afforded only an intractable mixture. Photolysis of the *N*-isopropyl-α-oxoamides (1b) and (1d) in methanol yielded the oxazolidinones (2b) and (2d) respectively (Scheme 1), while that of *N*-benzylbenzoylformamide (1e) gave the β-lactam (3e) in both methanol and benzene.† The substituent effects in these photoreactions are similar to those in the photolysis of the disubstituted oxoamides.[2] It is noteworthy that photolysis of (1d) and (1e) in methanol did not give methyl mandelate. This indicates that the hydroxyketen (5) (a type II elimination product) is not formed in these reactions, since it is known that the



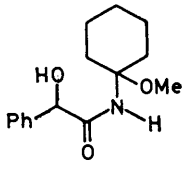
SCHEME 2

keten reacts with alcohols to yield the corresponding mandelic acid esters.[5] The fact that the benzoylformamides (1d) and (1e) do not undergo type II elimination is inconsistent with the efficient type II cleavage

† The photocyclisation of *N*-benzylamides has recently been reported,[4] but the results of our study [2a] appear to have been incorrectly interpreted. The formation of the lactam (3e) in protic solvents is not surprising since *NN*-dibenzylbenzoylformamide gave the corresponding β-lactam on irradiation in both protic and aprotic solvents.

of *N*-cyclohexylbenzoylformamide (1a). Accordingly, the photolysis of (1a) was reinvestigated.

When (1a) was irradiated in ethanol–10% aqueous sulphuric acid (4 : 1) (Scheme 2), cyclohexanone (9) (69%, lit.,[3] 77%) was obtained as Zehavi described. However, a good yield of mandelamide (8) (80%) was also obtained, while neither ethyl mandelate nor mandelic acid was detected. Irradiation of (1a) in an acidic aqueous methanol gave a similar result. It is unlikely that mandelamide was formed by the reaction of the hydroxyketen (5) with ammonia produced by hydrolysis of cyclohexanone imine (6), because ammonia would be converted into ammonium ion in the strongly acidic medium and the ion cannot undergo nucleophilic addition. In confirmation of this, cyclohexyl benzoylformate which is known to produce the hydroxyketen (5) on irradiation [5] was photolysed in the acidic medium. When the ester was irradiated in methanol–aqueous sulphuric acid containing an excess of ammonium sulphate, mandelic acid (29%) and methyl mandelate (3%) were obtained but mandelamide was not detected. These facts clearly show that the hydroxyketen (5) is not formed in the photolysis of (1a) and lead to the conclusion that the contribution of path a (type II elimination) for the formation of cyclohexanone is negligible.

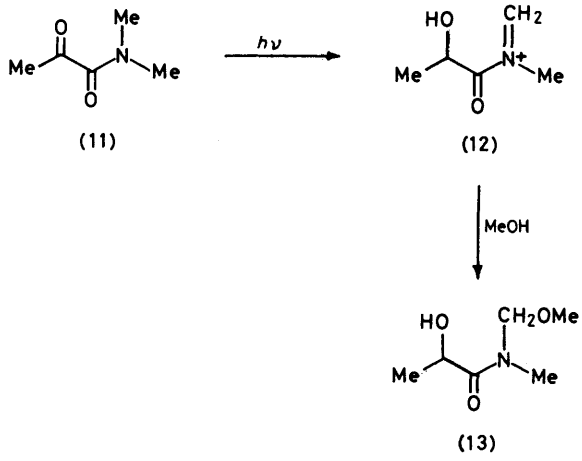


(10)

Another mechanism which involves intramolecular disproportionation of the biradical (4) and subsequent hydrolysis of the resulting enamide (7) (path b) is presumed to be improbable on the basis of the following experiments. Irradiation of (1a) in MeOD–D_2O–D_2SO_4 yielded mandelamide bearing a deuterium atom at the α-position while deuterium incorporation was not observed when mandelamide was set aside in the same medium. This indicates that the hydrogen at the α-position of the mandelamide formed in the photolysis of (1a) arises from the solvent and not from the cyclohexyl group.

When (1a) was irradiated in methanol, (2a) (14%) and the methanol adduct (10) (24%) were obtained in addition to the dimeric product which Zehavi obtained.[3] The observation that (2a) did not decompose when it was set aside in an aqueous acidic medium rules out the possibility that the photolysis products (8) and (9) arise from hydrolysis of (2a).

Recently, Shima *et al.* reported that photolysis of *NN*-dimethylpyruvamide (11) in methanol gave the methanol adduct (13), and the iminium ion (12) was presumed to be the intermediate (Scheme 3).[6] This fact and the formation of the methanol adduct (10) in the photolysis of (1a) strongly indicate the intermediacy of *N*-cyclohexylidenemandelamide (14). Although the mechanism for the formation of (12) or (14) is not clear at present, a possible mechanism is shown in Scheme 4, in which a zwitterion is formed from the biradical (4).* The deuterium incorporation at the α-position of mandel-

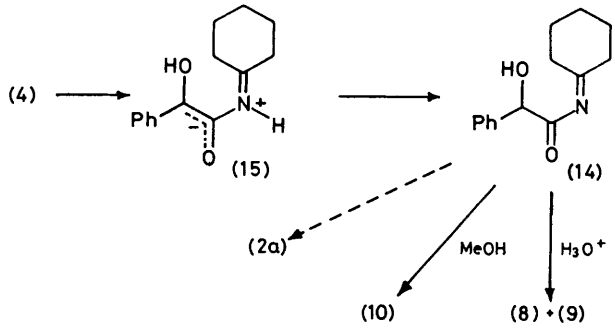


(11) (12) (13)

SCHEME 3

amide in the photolysis of (1a) in the deuteriated solvents (*vide supra*) is consistent with this mechanism. Since the photoreaction of (1a) in the acidic aqueous medium is much cleaner than that in methanol, (14) is presumed to decompose during irradiation in methanol, while it is presumably hydrolysed rapidly in the acidic aqueous medium to give the ketone and the amide in good yields.

Photolysis of a *NN*-dialkyl-α-oxoamides in acidic aqueous media was also studied in relation to that of (1a). Irradiation of *NN*-di-n-propylpyruvamide (16) (Scheme 5) in methanol does not give a methanol adduct but affords the corresponding oxazolidinone (18) quantitatively.[2a] On the other hand, irradiation of (16) in acidic aqueous methanol yielded *N*-n-propyllactamide (17) (41%) besides the oxazolidinone (32%)



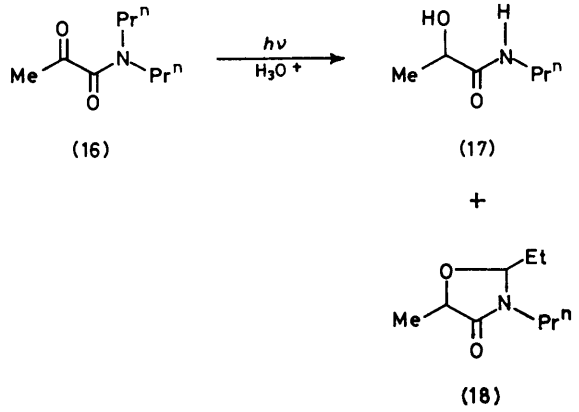
SCHEME 4

which did not decompose to (17) under the experimental conditions as in the case of (2a). The formation of the lactamide is most reasonably explained by hydrolysis of an iminium ion intermediate similar to (12), and this

* A similar biradical–zwitterion process has been reported.[7] A referee pointed out the possibility that the zwitterion (15) is produced directly from the excited state of (1a).

mechanism is quite analogous to that for the formation of (8).

Finally, it is worth noting that the oxazolidinone (2a) might be produced by cyclisation of the intermediate rather than *via* 1,4-hydrogen shift of the biradical (4) as we previously postulated.[2,8] The mechanism for the



(16) (17) + (18)

SCHEME 5

formation of oxazolidinones is being studied further by use of *NN*-disubstituted α-oxoamides and α-oxoanilides as substrates.

EXPERIMENTAL

Starting Materials.—The α-oxoamides were prepared according to previously described methods.[3,9] *N*-Cyclohexylbenzoylformamide (1a) had m.p. 111—112 °C (lit.,[3] 112 °C); N-*isopropylpyruvamide* (1b) had m.p. 39—41 °C; i.r. ($CHCl_3$) 3 380, 1 718, 1 673, and 1 510 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.20 (d, 6 H, $CHMe_2$) 2.42 (s, 3 H, COMe), 4.07 (m, 1 H, –CH), and 7.1 br (1 H, NH) (Found: C, 55.55; H, 8.5; N, 10.8. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.85%); N-*benzylpyruvamide* (1c) had b.p. 120—130 °C (bath temp.) at 2 Torr (Kugelrohr distillation); i.r. ($CHCl_3$) 3 390, 1 718, 1 670, and 1 512 cm^{-1}; n.m.r. ($CDCl_3$) δ 2.38 (s, 3 H, Me), 4.40 (d, 2 H, CH_2), and 7.25 (s, 5 H, ArH) (Found: C, 67.45; H, 6.2; N, 8.15. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; N, 7.9%); N-*isopropylbenzoylformamide* (1d) had m.p. 86—87 °C; i.r. ($CHCl_3$) 3 380, 1 662, and 1 500 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.25 (d, 6 H, $CHMe_2$), 4.2 (m, 1 H, –CH), 7.3—7.7 (m, 3 H, ArH), and 8.3—8.5 (m, 2 H, ArH) (Found: C, 69.3; H, 6.85; N, 7.3. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.35%); N-*benzylbenzoylformamide* (1e) had m.p. 97—98 °C; i.r. ($CHCl_3$) 3 390, 1 663, and 1 508 cm^{-1}; n.m.r. ($CDCl_3$) δ 4.46 (d, 2 H, CH_2), 7.1—7.4 (m, 8 H, ArH), and 8.1—8.35 (m, 2 H, ArH) (Found: C, 75.35; H, 5.35; N, 6.05. $C_{15}H_{13}NO_2$ requires C, 75.3; H, 5.5; N, 5.85%).

General Procedure for Photochemical Reactions of N-*Alkyl-α-oxoamides.*—A solution of the amide (1) (200 mg) in 40 ml of solvent was irradiated in a Pyrex tube under argon with a 450 W high-pressure mercury lamp for 2—4 h. After removal of the solvent the residue was chromatographed on silica gel.

2,2,5-*Trimethyloxazolidin*-4-*one* (2b) was obtained from the photolysis of (1b) in methanol (38% yield), m.p. 102—105 °C; i.r. ($CHCl_3$) 3 430, 3 200, and 1 700 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.41 (d, 3 H, 5-Me), 1.46 (s, 6 H, 2-Me_2), 4.42 (q, 1 H, 5-H), and 8.6 br (1 H, NH) (Found: C, 56.0; H, 8.65; N, 10.75. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.85%).

2,2-*Dimethyl*-5-*phenyloxazolidin*-4-*one* (2d) was obtained from the photolysis of (1d) in methanol (38% yield), m.p. 122—123 °C; i.r. (KBr) 3 180 and 1 698 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.50 (s, 6 H, 2-Me_2), 5.28 (s, 1 H, 5-H), 7.41 (s, 5 H, ArH), and 8.8 br (1 H, NH) (Found: C, 68.85; H, 6.8; N, 7.35. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%).

3-Hydroxy-3,4-diphenylazetidin-2-one (3e) was obtained from the photolysis of (1e) in methanol (18% yield), and benzene (32%), m.p. 198—199 °C (lit.,[4] 193—196 °C).

5′-*Phenylcyclohexanespiro*-2′-*oxazolidin*-4′-*one* (2a) had m.p. 165—167 °C; i.r. ($CHCl_3$) 3 430, 3 180, and 1 705 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.0—2.1 (m, 10 H, 5 × CH_2), 5.25 (s, 1 H, 5′-H), 7.1—7.7 (m, 5 H, ArH), and 8.95 br (1 H, NH) (Found: C, 72.7; H, 7.45; N, 6.15. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.05%).

N-(1-*Methoxycyclohexyl*)*mandelamide* (10) had m.p. 102—104.5 °C; i.r. ($CHCl_3$) 3 600, 3 390, 1 685, and 1 512 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.1—2.1 (m, 10 H, 5 × CH_2), 3.06 (s, 3 H, OMe), 4.4 and 6.4 br (each 1 H, NH and OH), 4.94 (s, 1 H, –CH), and 7.36 (s, 5 H, ArH) (Found: C, 68.0; H, 7.85; N, 5.5. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.05; N, 5.3%).

Irradiation of (1a) *in the Presence of Sulphuric Acid.*—The amide (1a) was irradiated in methanol–10% aqueous sulphuric acid (4 : 1) as just described. Cyclohexanone was identified by direct comparison with an authentic sample, and analysed by g.l.c. Mandelamide was identified by its m.p. (132—134 °C; lit.,[10] 133—134 °C) and by comparison with a sample obtained by ammonolysis of ethyl mandelate. The amide (1a) was also irradiated in MeOD–D_2O–D_2SO_4, and the n.m.r. spectrum of the mandelamide (in CD_3SOCD_3) obtained in this experiment showed that the α-position was completely deuteriated (the signal of the α-hydrogen of the non-deuteriated amide appeared at δ 4.70).

Irradiation of (16) *in the Presence of Sulphuric Acid.*—The amide (16) was irradiated as just described. The oxazolidinone (18) [2a] and the lactamide (17) [11] produced were identified by direct comparison with authentic samples.

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