Photocyclization of NN-Disubstituted Benzoylacetamides and Acetoacetamides

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NN-Dialkyl-benzoylacetamides (1a-e and j-n) and -acetoacetamides (1f-i), and N-methylbenzoylacetanilide (10) undergo photocyclization involving δ -hydrogen abstraction by the ketone carbonyl group to give N-substituted 4-hydroxypyrrolidin-2-ones (2a--o) in high yields.

Although the photochemistry of β -diketones ¹⁻⁵ and β -oxo-esters 5-7 has been studied extensively, that of β -oxo-amides has been paid little attention.⁸⁻¹⁰ Photocyclization involving intramolecular hydrogen abstraction by excited carbonyl oxygen is a well known reaction of carbonyl compounds; 11 however, much less is known about the cyclization of β-dicarbonyl compounds.¹² We report here the photocyclization of β -oxo-amides involving hydrogen abstraction by ketone carbonyl.

Irradiation of a solution of NN-dimethylbenzoylacetamide (1a) in a Pyrex vessel under nitrogen with a highpressure mercury lamp gave 4-hydroxy-1-methyl-4phenylpyrrolidin-2-one (2a) in 88% yield. Similarly,

† The absolute configuration of the substituents is not still elucidated.

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² P. De Mayo, H. Takeshita, and A. B. M. A. Sattar, Proc. Chem. Soc., 1962, 119.

 ³ G. Kornis and P. De Mayo, Canad. J. Chem., 1964, 42, 2822.
⁴ R. B. LaCount and C. E. Griffin, Tetrahedron Letters, 1965, 1549.

⁵ D. Veierov, T. Bercovici, E. Fisher, Y. Mazur, and A. Yogev, J. Amer. Chem. Soc., 1973, 95, 8173.

irradiation of the β -oxo-amides (1b-k) gave the corresponding 4-hydroxypyrrolidin-2-ones (2b-k') in high yields. In the cases of the oxo-amides (li, j, and k) stereoisomers (2i and i'; j and j'; k and k') were formed, whereas only one isomer was produced from the oxoamides (1b-c, e, and g). The structures of the pyrrolidin-2-ones (2a-k') were elucidated by i.r., n.m.r., and mass spectra, and by elemental analyses. The i.r. spectra showed characteristic hydroxy (ca. 3 300 cm⁻¹) and five-membered lactam carbonyl absorptions (ca. $1 660 - 1 680 \text{ cm}^{-1}$).

The configurations of the substituents in the pyrrolidin-2-ones were elucidated on the basis of the n.m.r. spectra.[†] The n.m.r. spectrum of (2d) showed peaks at

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7 S. P. Singh and J. Kagan, Chem. Comm., 1969, 1121.

⁸ J. Reisch and D. Niemeyer, Tetrahedron Letters, 1968, 3247.

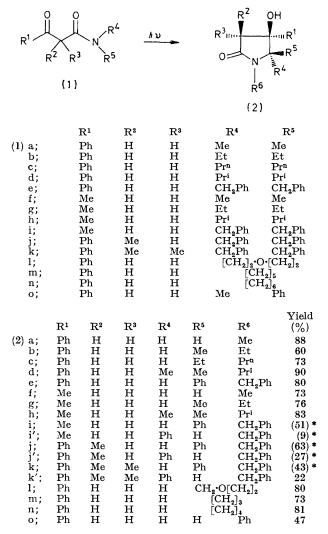
J. Reisch and D. H. Niemeyer, Tetrahedron, 1971, 27, 4637. ¹⁰ W. R. Oliver and L. R. Hamilton, Tetrahedron Letters, 1971, 1837.

¹¹ A. A. Lamola and N. J. Turro, 'Energy Transfer and Organic Photochemistry,' Interscience, New York, 1969. ¹² T. Hasegawa and H. Aoyama, J.C.S. Chem. Comm., 1974,

743.

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 δ 0.77 and 1.36, attributable to the C-5 methyl groups. The signal at δ 0.77 can be assigned to methyl protons *cis* to the C-4 phenyl group.[†] Only one signal was observed for the C-5 methyl group in (2b), at δ 1.19, suggesting that one stereoisomer was produced exclusively and that the methyl group is *trans* to the C-4 phenyl



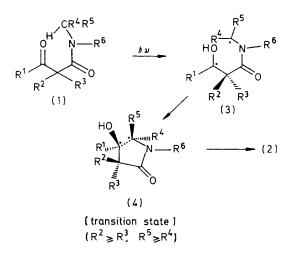
* Isomers were not isolated. Yields were determined on the basis of n.m.r. spectra.

group. This configuration would be expected to be the more thermally stable.

In the n.m.r. spectrum of the 4-methylpyrrolidin-2one (2h), methyl signals were observed at δ 1.25, 1.33, and 1.45, whereas the C-4 and C-5 methyl signals of (2g) appeared as a singlet at δ 1.39 and a doublet at δ 1.27, respectively. These results indicate that one stereoisomer was formed exclusively in the photolysis of (1g), and that the methyl groups in (2g) are *trans* to each other. In this case also the thermally stable isomer was formed exclusively.

The n.m.r. spectrum of (2i') showed a peak at δ 0.92, which can be assigned to the C-4 methyl protons *cis* to the C-5 phenyl group and shielded by the anisotropic effect of the latter. On the other hand, the n.m.r. signal of the C-4 methyl protons in (2i) was observed at δ 1.28, indicating their location *trans* to the C-5 phenyl group. In this case also the thermally stable isomer was produced predominantly. The predominant formation of the thermally stable isomers would be expected in the photolyses of (1j and k). More bulky substituents at C-3 or C-5 will appear *trans* to a C-4 phenyl or methyl group.

Formation of the pyrrolidin-2-ones from the β -oxoamides can be explained in terms of photocyclization involving δ -hydrogen transfer to ketone carbonyl oxygen.¹³ The favoured *trans*-configurations can be explained in terms of relief of steric compression between substituents in the reorganization step [1,5-diradical intermediate (3) to pyrrolidin-2-one (2)].



Irradiation of the β -oxo-amides (11—n) and the β -oxo-anilide (10) gave the corresponding bicyclic pyrrolidin-2-ones (21—n) or 1-phenylpyrrolidin-2-one (20), respectively, identified on the basis of i.r. and n.m.r, spectra and elemental analyses.

EXPERIMENTAL

I.r. spectra were recorded with a Hitachi EPI-2 spectrometer, n.m.r. spectra with a Hitachi R-20 spectrometer (tetramethylsilane as internal standard), and mass spectra with a Shimazu LKB-9000 spectrometer. A Ushio 450 W high-pressure mercury lamp was used as radiation source.

¹³ Further details of this reaction mechanism will be published soon, together with results of a mechanistic study.

 $[\]dagger$ A shift reagent study was attempted in order to assign methyl group *cis* or *trans* to the C-4 phenyl group in (2d). After addition of Eu(dpm)₃, however, only small changes in the chemical shifts of both methyl groups were observed. The shift reagent did not bond to the hydroxy but to the carbonyl oxygen.

The β -oxo-amides and β -oxo-anilide were prepared according to previously described methods.14-19

General Procedure for Photoreactions of β -Oxo-amides. A solution of the β -oxo-amide (1) in benzene was irradiated in a Pyrex vessel under nitrogen with a high-pressure mercury lamp for 1-50 (la-e and j-o) or 160-200 h (1f-i). The solvent was removed and the residue chromatographed on silica gel. Elution with benzene-ethyl acetate afforded the pyrrolidin-2-one (2).

(i) 4-Hydroxy-4-phenylpyrrolidin-2-one (2a) had m.p. 139—140 °C; $v_{max.}$ (KBr) 3 275 and 1 660 cm⁻¹; δ (CDCl₃) 2.80 (2 H, ABq, J 17.3 Hz, 3-H₂), 2.87 (3 H, s, NCH₃), 3.53 (2 H, ABq, J 10.5 Hz, 5-H₂), 3.77br (1 H, s, OH, D_2O -exchangeable), and 7.2-7.5 (5 H, m, aromatic) (Found: C, 69.3; H, 6.8; N, 7.1. C₁₁H₁₃NO₂ requires C, 69.1; H, 6.85; N, 7.35%).

(ii) 1-Ethyl-4-hydroxy-5-methyl-4-phenylpyrrolidin-2-one (2b) had m.p. 148—149 °C; ν_{max} . (KBr) 3 220 and 1 670 cm⁻¹; δ (CDCl₃) 1.00 (3 H, t, J 7.2 Hz, CH₂·CH₃), 1.11 (3 H, d, J 5.8 Hz, 5-CH₃), 2.74 (2 H, ABq, J 18.0 Hz, 3-H₂), 3.05 (1 H, q, J 5.8 Hz, 5-H), 3.65 (2 H, q, J 7.2 Hz, NCH₂·CH₃), 3.80 (1 H, s, OH), and 7.1-7.6 (5 H, m, aromatic) (Found: C, 71.15; H, 7.8; N, 6.2. C₁₃H₁₇NO₂ requires C, 71.2; H, 7.8; N, 6.4%).

(iii) 5-Ethyl-4-hydroxy-4-phenyl-1-n-propylpyrrolidin-2-one (2c) had m.p. 91—91.5 °C; ν_{max} (KBr) 3 350 and 1 680 cm⁻¹; δ (CDCl₃) 0.78 (3 H, t, J 6.5 Hz, CH₂·CH₂·CH₃), 0.89 (3 H, t, J 6.5 Hz, $CH_2 \cdot CH_3$), 1.2–2.0 (4 H, m, $CH_2 \cdot CH_2 \cdot CH_3$ and CH₂·CH₃), 2.80 (2 H, ABq, J 17.1 Hz, 3-H₂), 2.91 (1 H, t, J 6.8 Hz, 5-H), 3.13br (1 H, s, OH), 3.72 (2 H, t, J 6.9 Hz, NCH₂), and 7.2-7.6 (5 H, m, aromatic) (Found: C, 72.8; H, 8.4; N, 5.5. C₁₅H₂₁NO₂ requires C, 72.85; H, 8.55; N, 5.65%).

(iv)4-Hydroxy-1-isopropyl-5,5-dimethyl-4-phenylpyrrolidin-2-one (2d) had m.p. 193-194 °C; v_{max.}(KBr) 3 200 and 1 675 cm⁻¹; δ (CDCl₃) 0.77 (3 H, s, 5-CH₃ cis to 4-Ph), 1.36 (3 H, s, 5-CH₃ trans to 4-Ph), 1.42 (6H, d, J 7.5 Hz, CHMe₂), 2.83 (2 H, ABq, J 15.1 Hz, 3-H₂), 3.05br (1 H, s, OH, D₂O-exchangeable), 3.36 (1 H, septet, J 7.5 Hz, CHMe₂), and 7.2-7.6 (5 H, m, aromatic) (Found: C, 73.0; H, 8.75; N, 5.65. C₁₅H₂₁NO₂ requires C, 72.85; H, 8.55; N, 5.65%). (v) 1-Benzyl-4-hydroxy-4,5-diphenylpyrrolidin-2-one (2e) had m.p. 137–138 °C; ν_{max} (KBr) 3 300 and 1 675 cm⁻¹; δ(CDCl₃) 3.00 (2 H, ABq, J 15.6 Hz, 3-H₂), 3.08br (1 H, s, OH, D₂O-exchangeable), 3.57 (1 H, d, J 15.0 Hz, NCH₂-Ph), 4.53 (1 H, s, 5-H), 5.24 (1 H, d, J 15.0 Hz, NCH₂Ph), and 6.5–7.25 (15 H, m, aromatic); m/e 343 (M^+) (Found: C, 80.35; H, 6.15; N, 4.05. $C_{23}H_{21}NO_2$ requires C, 80.45 H, 6.15; N, 4.1%).

(vi) 4-Hydroxy-1,4-dimethylpyrrolidin-2-one (2f) had b.p. 125 °C at 2 mmHg; $\nu_{max.}$ (film) 3 400 and 1 670 cm⁻¹; δ (CDCl₃) 1.42 (3H, s, 4-CH₃), 2.44 (2 H, s, 3-H₂), 2.81 (3 H, s, NCH₃), 3.33 (2 H, s, 5-H₂), and 3.65 (1 H, s, OH, D₂Oexchangeable); m/e 129 (M⁺) (Found: C, 55.3; H, 8.5; N, 10.65. C₆H₁₁NO₂ requires C, 55.8; H, 8.6; N, 10.85%).† (vii) 1-Ethyl-4-hydroxy-4,5-dimethylpyrrolidin-2-one (2g)

had b.p. 155 °C at 4 mmHg; $\nu_{max.}({\rm film})$ 3 350 and 1 670

† The analyses are poor because these pyrrolidin-2-ones are so hygroscopic and volatile.

¹⁵ H. Bredereck, R. Gompper, K. Klem, and B. Föhlish, Chem. Ber., 1961, 94, 3119. ¹⁶ G. E. Utzinger, Helv. Chim. Acta, 1952, 35, 1359.

cm⁻¹; δ (CDCl₃) 1.17 (3 H, t, J 5.9 Hz, CH₂·CH₃), 1.27 (3 H, d, J 7.5 Hz, 5-CH₃), 1.39 (3 H, s, 4-CH₃), 2.46 (2 H, s, 3-H₂), 2.64 (1 H, s, OH, D₂O-exchangeable), 2.96 (1 H, q, J 7.5 Hz, 5-H), and 3.57 (2 H, q, J 5.9 Hz, NCH₂·CH₃) (Found: C, 60.45; H, 9.4; N, 8.7. C₈H₁₅NO₂ requires C, 61.1; H, 9.6; N, 8.9%).†

4-Hydroxy-1-isopropyl-4,5,5-trimethylpyrrolidin-2-(viii) one (2h) had m.p. 72.5–73 °C; ν_{max} (KBr) 3 300 and 1 665 cm⁻¹; δ (CDCl₃) 1.17 (6 H, d, J 6.4 Hz, CHMe₂), 1.25 (3 H, s, 5-CH₃), 1.33 (3 H, s, 4-CH₃), 1.45 (3 H, s, 5-CH₃), 2.37 (2 H, s, 3-H₂), 3.45 (1 H, septet, J 6.4 Hz, CHMe₂), and 3.49 (1 H, s, OH, D₂O-exchangeable) (Found: C, 65.1; H, 10.2; N, 7.45. C₁₀H₁₉NO₂ requires C, 64.85; H, 10.35; N, 7.6%).

(ix) The 1-benzyl-4-hydroxy-4-methyl-5-phenylpyrrolidin-2-ones (2i and i') could not be separated because of difficulties in crystallization and distillation. The 6:1 mixture had v_{max} (film) 3 375 and 1 670 cm⁻¹. The isomer (2i) showed $\delta(CDCl_3)$ 1.28 (3 H, s, 4-CH₃), 2.1br (1 H, s, OH), 2.54 (2 H, ABq, J 16.2 Hz, 3-H₂), 3.50 (1 H, d, J 15.0 Hz, NCH₂Ph), 4.14 (1 H, s, 5-H), 5.16 (1 H, d, J 15.0 Hz, NCH_2Ph), and 6.9-7.5 (10 H, m, aromatic); the isomer (2i') showed $\delta(\text{CDCl}_3)$ 0.92 (3 H, s, 4-CH₃), 2.1br (1 H, s, OH), 2.54 (2 H, ABq, J 16.2 Hz, 3-H₂), 3.50 (1 H, d, J 15.0 Hz, NCH₂Ph), 4.31 (1 H, s, 5-H), 5.16 (1 H, d, J 15.0 Hz, NCH, Ph), and 6.9-7.5 (10 H, m, aromatic).

(x) The 1-benzyl-4-hydroxy-3-methyl-4,5-diphenylpyrrolidin-2-ones (2j and j') could not be separated. The 7:3 mixture had m.p. 135—151 °C; ν_{max} (KBr) 3 330 and 1 670 cm⁻¹. The isomer (2j) showed δ (CDCl₃) 1.21 (3 H, d, J 7.0 Hz, 3-CH₃), 2.43 (1 H, s, OH, D₂O-exchangeable), 3.35 (1 H, q, J 7.0 Hz, 3-H), 3.62 (1 H, d, J 14.0 Hz, NCH₂-Ph), 4.45 (1 H, s, 5-H), 5.28 (1 H, d, J 14.0 Hz, NCH₂Ph), and 6.6-7.4 (15 H, m, aromatic). The isomer (2j') showed δ(CDCl₃) 1.17 (3 H, d, J 7.0 Hz, 3-CH₃), 2.43 (1 H, s, OH, D_2O -exchangeable), 3,35 (1 H, q, J 7.0 Hz, 3-H), 3.65 (1 H, d, J 14.0 Hz, NCH₂Ph), 4.65 (1 H, s, 5-H), 5.25 (1 H, d, J 14.0 Hz, NCH₂Ph), and 6.6-7.4 (15 H, m, aromatic). [Found (for mixture): C, 80.25; H, 6.5; N, 3.75. Calc. for C₂₄H₂₃NO₂: C, 80.65; H, 6.5; N, 3.9%].

(xi) The 1-benzyl-4-hydroxy-3,3-dimethyl-4,5-diphenylpyrrolidin-2-ones (2k and k') were obtained in 65% yield (ratio 2:1). The pyrrolidin-2-one (2k') was isolated by fractional recrystallization, but complete purification of (2k) was not achieved; the latter showed $\delta({\rm CDCl}_{s})$ 0.73 (3H, s, 3-CH₃ cis to 4-Ph), 1.27 (3 H, s, 3-CH₃ trans to 4-Ph), 1.7br (1 H, s, OH), 3.62 (1 H, d, J 14.1 Hz, NCH₂Ph), 5.10 (1 H, s, 5-H), 5.35 (1 H, d, J 14.1 Hz, NCH_2Ph), and 6.8-7.5 (15 H, m, aromatic). The isomer (2k') had m.p. 176-177 °C; ν_{max} (KBr) 3 450 and 1 665 cm⁻¹; δ (CDCl₃) 1.11 (3 H, s, 3-CH₃ cis to 4-Ph), 1.23 (3 H, s, 3-CH₃ trans to 4-Ph), 2.5br (1 H, s, OH), 3.67 (1 H, d, J 14.1 Hz, NCH₂Ph), 4.50 (1 H, s, 5-H), 5.32 (1 H, d, J 14.1 Hz, NCH₂Ph), and 6.6-7.3 (15 H, m, aromatic) (Found: C, 81.05; H, 6.85; N, 3.75. C₂₅H₂₅NO₂ requires C, 80.85; H, 6.8; N, 3.75%).

(xii) 7-Hydroxy-7-phenyl-4-oxa-1-azabicyclo[4.3.0]nonan-9-one (21) had m.p. 165-166 °C; v_{max} (KBr) 3 250 and 1 680 cm⁻¹; δ(CDCl₃) 2.80 (2 H, ABq, J 17.3 Hz, CO·CH₂), 3.4 (1 H, m, methine), 3.79 (5 H, m, $CH_2 \cdot CH_2 + NCH_2$), 4.0

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¹⁷ J. R. Treffer, U.S.P. 3,105,079/1963 (Chem. Abs., 1964, 60, 2913d).

¹⁸ C. F. Koelsch and J. W. Britain, J. Org. Chem., 1959, 24, 1551.

¹⁹ A. L. Searles and D. Ressler, J. Amer. Chem. Soc., 1958, 80, 3656,

(2 H, m, NCH₂ + OH; one D₂O-exchangeable), and 7.2—7.6 (5 H, m, aromatic) (Found: C, 66.4; H, 6.4; N, 5.7. $C_{13}H_{15}NO_3$ requires C, 66.95; H, 6.5; N, 6.0%).

(xiii) 4-Hydroxy-4-phenyl-1-azabicyclo[3.3.0]octan-2-one (2m) had m.p. 175—176 °C; v_{max} (KBr) 3 300 and 1 670 cm⁻¹; δ (CDCl₃) 2.0 (4 H, m, CH₂·CH₂), 2.8 (2 H, m, methine + OH; one D₂O-exchangeable), 3.02 (2 H, ABq, J 16.2 Hz, CO·CH₂), 3.6 (1 H, m, NCH₂), 4.22 (1 H, m, NCH₂), and 7.2—7.55 (5 H, m, aromatic) (Found: C, 71.75; H, 6.9; N, 6.15. C₁₃H₁₅NO₂ requires C, 71.85; H, 6.95; N, 6.45%).

(xiv) 4-Hydroxy-4-phenyl-1-azabicyclo[4.3.0]nonan-2-one (2n) had m.p. 157—158 °C; ν_{max} (KBr) 3 400 and 1 680 cm⁻¹;

$$\begin{split} &\delta(\text{CDCl}_3) \ 1.5 \ (6\text{H}, \ \text{m}, \ \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2), \ 2.7 \ (1 \ \text{H}, \ \text{m}, \ \text{methine}), \\ &2.80 \ (2 \ \text{H}, \ \text{ABq}, \ J \ 16.2 \ \text{Hz}, \ \text{CO} \cdot \text{CH}_2), \ 3.4 \ (1 \ \text{H}, \ \text{m}, \ \text{NCH}_2), \\ &3.68 \ (1 \ \text{H}, \ \text{s}, \ \text{OH}, \ \text{D}_2 \text{O} \cdot \text{exchangeable}), \ 4.1 \ (1 \ \text{H}, \ \text{m}, \ \text{NCH}_2), \\ &\text{and} \ 7.1 - 7.5 \ (5 \ \text{H}, \ \text{m}, \ \text{aromatic}) \ (\text{Found}: \ \text{C}, \ 72.45; \ \text{H}, \ 7.35; \\ &\text{N}, \ 5.9. \ \ C_{14} \text{H}_{17} \text{NO}_2 \ \text{requires} \ \text{C}, \ 72.7; \ \text{H}, \ 7.4; \ \text{N}, \ 6.05\%). \end{split}$$

(xv) 4-Hydroxy-1,4-diphenylpyrrolidin-2-one (20) had m.p. 178—179 °C; ν_{max} (KBr) 3 300 and 1 670 cm⁻¹; δ [(CD₃)₂SO] 2.96 (2 H, ABq, J 17 Hz, 5-H₂), 4.08 (2 H, ABq, J 9.5 Hz, 3-H₂), 5.93 (1 H, s, OH, D₂O-exchangeable), and 7.1—7.9 (10 H, m, aromatic) (Found: C, 75.5; H, 5.95; N, 5.3. C₁₆H₁₅NO₂ requires C, 75.85; H, 5.95; N, 5.55%).

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