Selective Hydrogenation of 4,5-Dihydro-1,3-oxazin-6-ones to Carbaldehyde Derivatives; Chemical Differentiation between Acylazetidin-2-ones and the Corresponding Isomeric Oxazin-6-ones [1]

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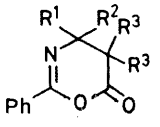
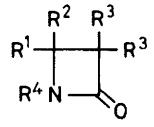
Catalytic hydrogenation of optically active and non-active dihydro-oxazin-6-ones unexpectedly led to preferential reduction of the carbonyl group with ring-opening yielding carbaldehyde derivatives. This reaction resolved a structural problem by leading to the positive characterisation of an isomeric acylazetidin-2-one and the corresponding dihydro-oxazin-6-one.

CYCLISATION of substituted 3-benzoylaminopropionic acids may in principle give rise to isomeric compounds, namely 6-membered-ring dihydro-oxazin-6-ones (1) or the 4-membered-ring *N*-acylazetidin-2-ones, represented by (2; R^4 = PhCO). Synthesis of a dihydro-oxazin-2-one (1a) was first achieved by cyclisation of 3-benzoylamino-3-methylbutanoic acid (3a) using acetic anhydride; [2] more recently Ivanov and Dobrev reported that analogous reactions utilising 3,3-diaryl-3-benzoylaminopropanoic acid derivatives yielded *N*-benzoylazetidin-2-ones.[3] Structures were assigned solely on the basis of their i.r. spectra. Preparation (by alternative methods) of isomeric pairs of compounds of the general structure (1) and (2) led to the suggestion that cycloelimination of 3-acylaminopropionic acids yields dihydro-oxazin-6-ones exclusively.[4] Once more structures were designated by comparison of i.r. spectra, but in conjunction with n.m.r. spectra. There was also other evidence that i.r. assignments and chemical precedence did not provide substantial criteria for the assignation of structures.[5]



(1)

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



(2)

a; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = PhCO$
b; $R^1 = R^2 = Me$, $R^3 = R^4 = H$

As it has been reported that dihydro-oxazin-6-ones are useful intermediates for the preparation of hindered β-peptides,[6] it became increasingly important to resolve the ambiguity. Todd and his co-workers [7] undertook a careful examination of compounds representative of structures (1) and (2) and demonstrated that mass-spectral studies provide an unequivocal physical method for establishing their identity. Simultaneously, in our study, the oxazinone [2] (1a) and azetidinone [8] (2a) were compared. Differences were noted in their m.p.s; t.l.c. behaviour and spectroscopic data also demonstrated clear but minor dissimilarities. It seemed reasonable that isomeric derivatives of (1) and (2) should have different chemical properties and that examination of the products of reaction would provide unambiguous structural information. This paper describes chemical methods which confirm the conclusions reached in the mass spectral study,[7] and in addition, a new and high-yield route for the preparation of 3-benzoylaminopropionals.

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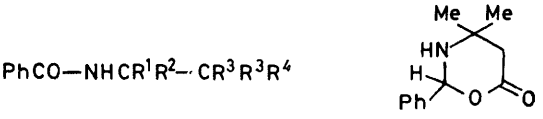
RESULTS AND DISCUSSION

Initially, attempts were made to selectively remove the benzoyl group from the azetidionine [8] (2a) by electrolysis,[9] after optimum conditions for the cleavage were ascertained in preliminary reactions. Subsequently, the free lactam [10] (2b) was recovered in 20% yield accompanied by poly-β-aminoisovaleric acid and methyl benzoylaminoisovalerate (3b). Clearly the polymer had arisen from the free lactam (2b) as precursor, whilst the ester (3b) may have formed through reaction of the starting material [8] (2a) with the solvent, methanol.



(3) (4)

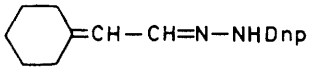
a; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = CO_2H$
b; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = CO_2Me$
c; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = CHO$
d; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = CH{=}N{-}NHDnp$
e; $R^1 = R^2 = [CH_2]_5$, $R^3 = H$, $R^4 = CHO$
f; $R^1 = R^2 = [CH_2]_5$, $R^3 = H$, $R^4 = CH{=}N{-}NHDnp$
g; $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = CHO$
h; $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = CH{=}N{-}NHDnp$
i; $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = CHO$
j; $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = CH{=}N{-}NHDnp$

Under identical conditions the oxazinone [2] (1a) suffered complete degradation; products were not isolated. This reaction was therefore able to differentiate between the two compounds (1a) [2] and (2a).[7] Alternative reactions were considered, for example catalytic hydrogenation of oxazinone [2] (1a) should occur with the uptake of one equivalent of hydrogen affording a saturated derivative (4), whilst the azetidinone [8] (2a) should not undergo hydrogenation. Treatment of (2a) [8] with hydrogen, over palladium–charcoal or platinum oxide,

confirmed the latter suggestion. On the other hand, the oxazinone [2] (1a) quickly absorbed hydrogen over palladium–charcoal and afforded a low-melting crystalline substance of two mass units (M^+ 205) higher than the starting material (1a). This was consistent with structure (4). However, hydrolysis of the latter did not give benzaldehyde in accordance with the expected structure. The unknown substance gave positive Schiff's and Tollen's tests, and the spectrum displayed a triplet at low field consistent with that of an aldehyde as in structure (3c). Treatment of the hydrogenated product with 2,4-dinitrophenylhydrazine provided two derivatives, consistent with the proposed structure (3c). The unsaturated derivative (5) may arise through β-elimination from the parent hydrazone (3d) or alternatively from (3c) followed by derivatisation to give (5); both pathways were found experimentally. The reaction, therefore, clearly differentiated between structure (1a) [2] and (2a),[8] and confirmed that the former was the expected dihydro-oxazin-6-one.

$Me_2C{=}CH{-}CH{=}N{-}NHDnp$

(5)



(6)

Hydrogenation of other oxazinones (1b),[6] (1c),[7] and (1d) likewise proceeded readily, leading to the recovery of the corresponding aldehydes (3e), (3g), and (3i) in high yield. Structures of the aldehydes (3e), (3g), and (3i) were confirmed by n.m.r. spectra, qualitative tests, derivatisation, and elemental analysis. In the case of the aldehyde (3g) derivatisation gave one product only, as β-elimination is excluded. The aldehyde (3e) and its 2,4-dinitrophenylhydrazone derivative (3f) also underwent β-elimination yielding the unsaturated compound (6). A formal chemical analogy for the hydrogenation of oxazinones giving rise to acylaminopropionals may be made with respect to the reductive cleavage of 2-pyridinylbenzoates,[11] which occurs between the carbon–oxygen bond of the ester linkage.

The selective and reductive fission of 4,5-dihydro-1,3-oxazin-6-ones (1) provides a route for the conversion of the readily accessible 3-acylaminopropionic acids [12] into 3-acylaminopropionals, and *inter alia* differentiates between the isomeric structures of (1) and (2; R^4 = PhCO).

EXPERIMENTAL

M.p.s were recorded on a Gallenkamp apparatus. Solvents were purified by literature methods.[13] Petrol refers to the fraction of b.p. 60—80 °C. I.r. spectra were recorded on a Perkin-Elmer 137 or 457 spectrophotometer for Nujol mulls or liquid films, and ^1H n.m.r. spectra (60 MHz) were recorded on a Perkin-Elmer R12 B with tetramethylsilane as internal standard. Mass spectra were obtained with an A.E.I. MS-902. Optical rotations were measured on a Bellingham and Stanley polarimeter. Unless otherwise stated neutral products were isolated by washing in ethyl acetate with 1M hydrochloric acid (3 aliquots), 5% sodium hydrogencarbonate solution (3 aliquots), and then water to neutrality. Organic solutions were dried with either anhydrous magnesium sulphate or sodium sulphate and all evaporations were carried out under reduced pressure on a rotary evaporator. 10% Palladium–charcoal was used for all hydrogenations. 2,4-Dinitrophenylhydrazine reagent was prepared by dissolving the hydrazine (100 mg) in acidified methanol (5 ml). Silica gel (60—120 mesh) for column chromatography was washed with 6M hydrochloric acid and then with water and dried overnight at 100 °C. T.l.c. on Merck Kieselgel G (0.25 mm) employed the following solvent systems (v/v) : (A) ethyl acetate, (B) chloroform–ethyl acetate (24 : 1), (C) chloroform, (D) benzene, and (E) chloroform–cyclohexane–acetic acid (8 : 2 : 1).

Synthesis of 4,5-Dihydro-oxazin-6-ones.—Preparation of 4,5-dihydro-4,4-dimethyl-2-phenyl-1,3-oxazin-6-one (1a).[2] 3-Benzoylamino-3-methylbutanoic acid [12] (8 g, 36 mmol) was dehydrated to the oxazinone (5.7 g, 77%) by the method of Baker and Ollis.[2] On agitation, *the product* (1a) crystallised for the first time, m.p. 34.5—36.5 °C, R_{FC} 0.79, R_{FD} 0.30 (Found: C, 71.1; H, 6.5; N, 6.9%; $M^{+\bullet}$, 203; $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.5; N, 6.9%; $M^{+\bullet}$, 203); $\nu_{max.}$ (Nujol) 1 790 and 1670 cm^{-1}.

Preparation of N-benzoyl-L-3-aminobutanoic acid. Benzoyl chloride (8.9 g, 7.4 ml, 64 mmol) was added in three portions to a stirred and cooled (5 °C) solution of L-β-aminobutanoic acid [14] (6 g, 58 mmol) in sodium hydroxide (60 ml, 2N). The solution was stirred for 10 min at 5 °C, after addition of benzoyl chloride, and then for 6 h at room temperature. The reaction mixture was extracted with ether and the aqueous phase made acid to Congo Red. The precipitate was filtered off, dried, and recrystallised from ethyl acetate–petrol to yield the *benzoyl derivative* (8.6 g, 68.2%), m.p. 143—145 °C (raised to 144—146 °C on further recrystallisation); $[\alpha]_D^{20}$ +24.2 °C (*c* 3 in acetone), R_{FE} 0.40 (Found: C, 63.7; H, 6.3; N, 6.9. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.3; N, 6.8%).

Preparation of (+)-*4,5-dihydro-4-methyl-2-phenyl-1,3-oxazin-6-one* (1d). A solution of *N*-benzoyl-L-3-aminobutanoic acid (3 g, 14.55 mmol) and *N*-methylmorpholine (1.8 g, 17.4 mmol) in dichloromethane (60 ml) was added in three portions to a stirred and cooled (−15 to −10 °C) solution of isobutyl chloroformate (2.46 g, 2.36 ml, 18.0 mmol) in dichloromethane (10 ml). The reaction was stirred for 15 min at −15 to −10 °C and for another 15 min at room temperature. Dichloromethane was evaporated, the residue triturated with petrol (2 × 25 ml), and the insoluble hydrochloride (2.36 g, 98.7%) removed by filtration. The filtrate was evaporated to yield the oily *oxazinone derivative* (1d) (2.64 g, 97.8%), b.p. 80 °C at 0.15 mmHg; $[\alpha]_D^{20}$ +26.8 °C (*c* 1 in ether) (Found: C, 69.8; H, 5.75; N, 7.05%; $M^{+\bullet}$, 189. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%; $M^{+\bullet}$, 189); $\nu_{max.}$ (film) 1 795 and 1 675 cm^{-1}.

Reduction of (1a) [2] *and* (2a).—*Electrolytic reduction of 1-benzoyl-4,4-dimethylazetidin-2-one* (2a).[8] A solution of the benzoylazetidinone (2a) (1 g, 4.9 mmol) and tetramethylammonium chloride (4.1 g, 37 mmol) in methanol (50 ml) was electroysed [9] for 2 h between a mercury cathode and a

platinum anode, at 0.25 A and 9 V. The temperature was maintained at 10—15 °C by an ice–salt bath. The reaction solution was chromatographed over silica (100 g) and eluted with ethyl acetate. Fractions containing the product were combined and evaporated to yield an oil which was triturated with ethyl acetate, and insoluble polymeric material (120 mg), m.p. >240 °C, was filtered off. A further crop (40 mg) precipitated from the filtrate on standing; $\nu_{max.}$ (Nujol) 3 333, 2 857, 1 639, 1 550, and 1 459 cm^{-1}. The filtrate was evaporated to an oil (830 mg), R_{FC} 0.07 and 0.38. Passage of a portion over silica (30 g) with chloroform resulted in partial separation of the two components. Preparative t.l.c. (300 mg) over silica using ethyl acetate effected separation. The slow running material, R_{FC} 0.07, a mobile oil (40 mg) was identified as 4,4-dimethylazetidin-2-one [10] (2b) by comparison with an authentic sample. The faster running material, R_{FC} 0.38, obtained as a colourless oil (140 mg), was identified as methyl 3-benzoylamino-3-methylbutanoate by comparison with an authentic sample, m.p. 61—61.5 °C.[15]

Electrolytic reduction of 4,5-*dihydro*-4,4-*dimethyl*-2-*phenyl*-1,3-*oxazin*-6-*one* (1a). Treatment of the oxazinone [2] (1a) under the conditions detailed above for the benzoylazetidinone (2a) led to degradation. Starting material could not be detected by t.l.c., nor were any products isolated.

Hydrogenolysis of Dihydro-oxazinones (1a),[2] (1b), (1c), *and* (1d).—*Isolation of* 3-*benzoylaminoaldehydes* (3c), (3e), (3g), *and* (3i). The experimental details for these reactions are as described for the azetidinone (2a) above. Compound (1a) (300 mg, 1.5 mmol) gave (3c) (167 mg, 55%), m.p. 42—45 °C (ether–petrol) (Found: C, 69.8; H, 7.6; N, 7.0%. $M^{+\bullet}$, 205. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%, $M^{+\bullet}$ 205); τ ($CDCl_3$) 0.14, 0.18, and 0.21 (1 H, t, CH_2CHO); R_{FA} 0.85, R_{FB} 0.46.

Compound (1b) (500 mg, 2.1 mmol) [reaction carried out over 72 g in benzene (25 ml) with catalyst (250 mg)] gave (3e) (450 mg, 89%), an oil; $\nu_{max.}$ (film) 1 769 and 1 709 cm^{-1}; τ (CCl_4) 0.01, 0.04, and 0.07 (1 H, t, CH_2CHO); R_{FA} 0.88, R_{FC} 0.22.

Compound (1c) (500 mg, 2.5 mmol) [reaction carried out over 24 h in benzene (25 ml) with catalyst (250 mg)] gave (3g) (365 mg, 72%), as an oil; $\nu_{max.}$ (film) 3 225, 2 985, 2 857, 2 817, 1 769, 1 709, 1 639, and 1 562 cm^{-1}; τ ($CDCl_3$) 0.25 (1 H, s, CHO); R_{FA} 0.81, R_{FC} 0.19.

Compound (1d) (1.6 g, 8.47 mmol) [reaction time 7 h, solvent methylene chloride (40 ml)] gave (3i) (1.1 g, 67.9%), m.p. 46—47 °C (petrol); $[\alpha]_D^{19}$ +2.4° (*c* 1 in dichloromethane) (Found: C, 68.9; H, 6.8; N, 7.0. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%); $\nu_{max.}$ (film) 3 300, 2 950, 1 715, 1 625, and 1 520 cm^{-1}; τ (DMSO) 0.22 (1 H, s, CH_2CHO) and 7.2—7.5 (2 H, d, $CHCH_2CHO$); R_{FA} 0.78, R_{FC} 0.48.

Preparation of 2,4-*Dinitrophenylhydrazones of* (3c), (3e), (3g), *and* (3i). Generally the derivatives were prepared by heating an equal volume of 2,4-dinitrophenylhydrazine reagent with the aldehyde in methanol for 2 min. In those reactions accompanied by elimination [(3c) and (3e)], the products were isolated by chromatography over silica gel using benzene and ethyl acetate as the eluants. Compound (3c) (250 mg, 1.22 mmol) gave (3d) (90 mg, 19.3%), m.p. 168—169 °C (from methanol) (Found: C, 56.0; H, 5.1; N, 18.3. $C_{18}H_{19}N_5O_5$ requires C, 56.1; H, 5.0; N, 18.2%); R_{FC} 0.28, R_{FD} 0.04: and (5) (45 mg, 14.6%), m.p. 178—179.5 °C (methanol) (Found: C, 50.1; H, 4.8; N, 21.1. $C_{11}H_{12}N_4O_4$ requires C, 49.8; H, 4.9; N, 21.1%); R_{FC} 0.92, R_{FD} 0.52.

Compound (3e) (250 mg, 1.02 mmol) gave (3f) (106 mg, 32.1%), m.p. 156—157.5 °C (methanol) (Found: C, 59.2; H, 5.6; N, 16.8. $C_{21}H_{23}N_5O_5$ requires C, 59.3; H, 5.5; N, 16.5%); R_{FC} 0.43, R_{FD} 0.04; and (6) (10 mg, 4.1%), m.p. 195—197 °C (ethyl acetate–petrol) (Found: C, 55.3; H, 5.3; N, 18.2. $C_{14}H_{16}N_4O_4$ requires C, 55.3; H, 5.3; N, 18.4%); R_{FC} 0.93, R_{FD} 0.64.

Compound (3g) (240 mg, 1.22 mmol) gave (3h) (147 mg, 31.3%), m.p. 183.5—185.5 °C (methanol) (Found: C, 55.8; H, 5.0; N, 18.2. $C_{18}H_{18}N_5O_5$ requires C, 56.1; H, 5.0; N, 18.2%); R_{FC} 0.22.

Compound (3i) (500 mg, 2.65 mmol) gave (3j) (300 mg, 30.5%), m.p. 175—177 °C (ethanol–ether) (Found: C, 54.6; H, 4.6; N, 18.5. $C_{17}H_{17}N_5O_5$ requires C, 54.98; H, 4.6; N, 18.96%); R_{FC} 0.36, R_{FA} 0.73.

Elimination Reactions of Aldehydes (3c) *and* (3e).—In these reactions, the aldehydes were heated with sulphuric acid (2M, 5 ml) for 10 min and the oily suspension taken up in methanol (5 ml) to which was added an equal volume of hydrazine reagent. The hydrazones (5) and (6) were isolated in the usual manner: (3c) (250 mg, 1.22 mmol) gave (5) (140 mg, 45.3%), m.p. 174—175.5 °C; R_{FC} 0.92, R_{FD} 0.52. (3e) (250 mg, 1.02 mmol) gave (6) (33 mg, 11.8%), m.p. 195—197 °C; R_{FC} 0.93, R_{FD} 0.64.

Elimination Reactions of 2,4-*Dinitrophenylhydrazones* (3d) *and* (3f).—The hydrazones were dissolved in a small quantity of methanol to which was added a few drops of concentrated sulphuric acid. The solutions were gently boiled for 15 min and the unsaturated derivatives (5) and (6) recovered in the usual way. (3d) (8 mg, 0.021 mmol) gave (5) (3 mg, 57.0%), m.p. 174—175 °C; R_{FC} 0.92, R_{FD} 0.52. Compound (3f) (10 mg, 0.02 mmol) gave (6) (2 mg, 28%), m.p. 194—196 °C; R_{FC} 0.94, R_{FD} 0.64.

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