Experiments towards the Synthesis of the Ergot Alkaloids and Related Structures. Part 6.[1] *N*-Acyl-*N*-(1,2,3,4-tetrahydro-1-oxo-2-naphthyl)glycines and a New Aromatisation Reaction

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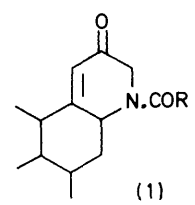
Three methods are reported for the preparation of *N*-(1,2,3,4-tetrahydro-1-oxo-2-naphthyl)glycine (4; R = H) hydrochloride from which the title compounds may be prepared. In the first, hydrolysis of the oxazolinone ester (3; R = CH_2CO_2Me, n = 1) with concentrated hydrochloric acid in acetic acid furnished a mixture (*ca.* 4:1) of the hydrochlorides of the required amino-keto-acid (4; R = H) and β-naphthylglycine (5; R^1 = R^2 = H) which were easily separable. In the second, a similar hydrolysis of the homologous oxazinedione (3; R = CH_2CO_2Me, n = 2) furnished it as the sole product in quantitative yield. In the third, 2-aminotetralone hydrochloride (7) was treated in formic acid solution with glyoxylic acid (*ca.* 3 mol equiv.) in the presence of base to give the *N*-formyl-keto-acid (10 = 4; R = CHO) in a crude yield of 85% and from which the hydrochloride of (4; R = H) was obtained by hydrolysis. Benzylamine reacted similarly to give *N*-formyl-*N*-benzylglycine but secondary amines do not appear to undergo this novel condensation-reduction reaction. Uncatalysed formolysis of the oxazolinone ester (3; R = CH_2CO_2Me, n = 1) furnished, in essentially quantitative yield, methyl *N*-formyl-2-naphthylglycinate (5; R^1 = CHO, R^2 = Me)—a new aromatisation reaction which may well be of general utility since the parent oxazolinone and its *N*-methyl derivative behaved similarly.

With the failure of model experiments in the '*endo*-amide' approach[2] to the construction of ring D in lysergic acid, attention was returned to possible alternative methods for its construction in the '*exo*'-form as in (1).

A recurrent starting point in such considerations was that represented by the general structure (2) where X was a group such as CO_2R or CHO, capable at a later stage of either reduction to methyl or removal to give the parent NH compound; here we report experiments on the synthesis of such compounds in the readily accessible α-tetralone series.



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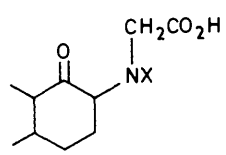

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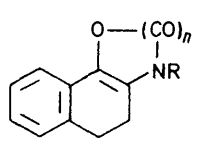

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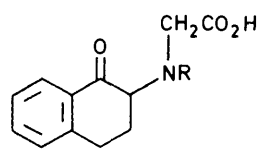

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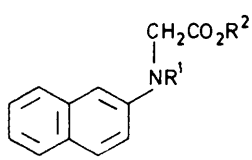

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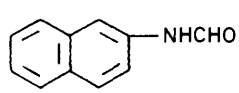

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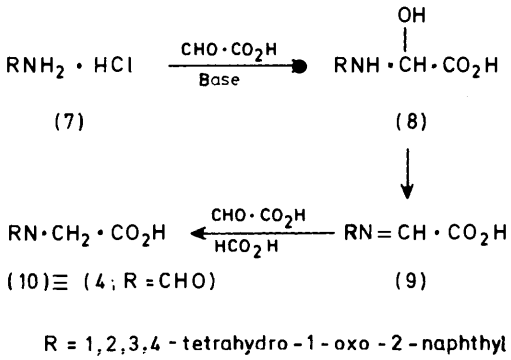
Results and Discussion

Following our general synthesis reported in Part 2,[3] the sodio-oxazoline (3; R = Na, n = 1) was treated with methyl chloroacetate to give the ester (3; R = CH_2CO_2Me, n = 1) in excellent yield. Hydrolysis of the latter with a mixture of hydrochloric and acetic acids furnished in high yield a colourless solid which was subsequently found to be a mixture (*ca.* 4:1) of the hydrochlorides of the required amino-keto-acid (4; R = H) and β-naphthylglycine (5; R^1 = R^2 = H) readily separable on account of the sparing solubility of the latter in dilute hydrochloric acid; acylation of the former then gave the title compounds (4; R = Acyl). The structure of β-naphthylglycine and some *N*-acyl derivatives were confirmed by synthesis from 2-formamidonaphthalene[4] (6) by standard procedures.

These results raised the possibility that the concomitant formation of the fully aromatic amine was a general feature of the acidic hydrolysis of *N*-substituted oxazolinones and had escaped our notice when this procedure was developed.[3] A purified sample of the *N*-methyloxazolinone (3; R = Me, n = 1) was submitted to the standard hydrolysis procedure to give crude 2-*N*-methylaminotetralone hydrochloride in 94% yield. Samples of the crude salt, a once recrystallised specimen, and 2-methylaminonaphthalene hydrochloride[5] were kindly examined by an independent worker, Mr. K. J. Caldicott (Warner-Lambert/Parke-Davis Research Division, U.K.). He reported that the presence of latter in the crude salt could be easily detected qualitatively by t.l.c., less readily from i.r. and u.v. spectra, and quantitatively (potentiometric titration) to be *ca.* 8%; the once recrystallised material was, however, free (t.l.c.) of the fully aromatic contaminant. The homologous oxazinediones,[3] however, would appear not to undergo this aromatisation reaction. Thus the ester (3; R = CH_2CO_2Me, n = 2) on hydrolysis with acetic–hydrochloric acids furnished the required amino-keto-acid (4; R = H) hydrochloride (100%) in an essentially pure condition and free of aromatic contaminant.

The foregoing oxazolinone and oxazinedione routes to the oxo-glycines (2) would appear to be of fairly general application but both failed in the vital 1,2,3,4-tetrahydrobenz-[*cd*]indol-4-one series on account of the resistance of the tetracyclic enol-esters to acidic hydrolysis;[2] alternative approaches had therefore to be considered. A one-stage



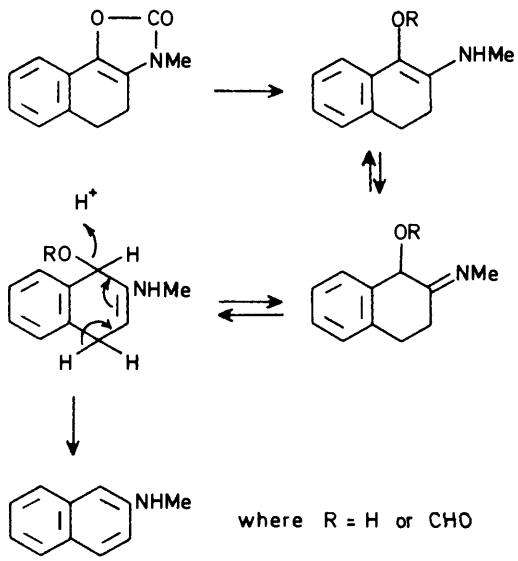
Leuckart-Wallach reaction [*e.g.* (7) ⟶ (10)] involving glyoxylic acid which is commercially available and relatively inexpensive, appeared an attractive alternative.

In the first experiment, glyoxylic acid (1 mol equiv.) was added to a mixture of 2-aminotetralone hydrochloride (7) in formic acid solution containing sodium formate at room temperature whereupon a slightly exothermic reaction set in accompanied by a vigorous evolution of carbon dioxide which ceased within 10 min. The mixture was then heated to complete *N*-formylation and diluted with water when the expected formamido-keto-acid (10) separated in *ca.* 45% yield. Classical Leuckart-Wallach reactions involving formic acid as reducing agent, do not usually take place at room temperatures but require temperatures of 100—250 °C depending on the nature of the carbonyl constituent.[6] It occurred to us that glyoxylic acid which is a powerful reducing agent,[7] was functioning in our reaction as both reactant and reducing agent and that the main function of the formic acid was to effect *N*-formylation. When the reaction was effected with *ca.* 3 mol equiv. of glyoxylic acid under the same conditions, the *N*-formyl acid (10) was obtained in a crude yield of 85%; hydrolysis then furnished the pure amino-keto-acid (4; R = H) hydrochloride in 86% yield. Such hydrolyses usually furnish the salts in yields of at least 94% thus suggesting that the crude starting acid (10) contained *ca.* 9% of a coloured impurity which was fortunately converted into an easily removable, black insoluble tar during the acidic hydrolysis.

Another primary amine, benzylamine, underwent this reaction to yield *N*-benzyl-*N*-formylglycine; secondary amines such as pyrollidine and dibenzylamine failed to react in this manner and it is for this reason that we postulate that reduction occurs at the Schiff base (9) rather than the carbinolamine (8) stages. The reaction appears to be restricted to glyoxylic acid only since it failed with pyruvic acid, thus distinguishing it from the remarkable reaction discovered by Erlenmeyer and Kunlin [8] in which glyoxylic and α-keto-acids react with ammonia to give α-acylamido acids and in which the three consecutive stages of condensation, reduction, and acylation are effected by the same α-carbonyl acid.

In a final set of experiments, the oxazolinone ester was subjected to formolysis using formic acid at 95 °C for 6 h and in the absence of catalyst. The product of this reaction, obtained in essentially quantitative yield, was *N*-formyl-*N*-β-naphthylglycine methyl ester (5; R^1 = CHO, R^2 = Me). This new aromatisation reaction could be of general application since the parent oxazolinone and its *N*-methyl derivative (3; R = H and Me respectively, *n* = 1) were converted under the same conditions into the corresponding formamidonaphthalenes.

A brief outline of this work was presented at a meeting of the Society at Bath in April 1980 when Professor A. H. Jackson suggested from the floor, the following mechanism for this aromatisation reaction:



Experimental

General procedures were as set out in Part 4; [2] i.r. and ^{1}H n.m.r. (90 MHz) spectra were run in Nujol mulls or in $CDCl_3$ solutions respectively unless otherwise stated. T.l.c. was effected on silica with solvent systems A (BuOH–AcOH–H_2O, 6 : 3 : 1) and B (MeOH–EtAc, 1 : 1). Potentiometric titrations were carried out in 50% aqueous methanol.

N-*Acylations.*—(a) *Formylation.* Formic acid (24 ml; 98—100%) was added to acetic anhydride (12 ml) and the mixture heated at 50 °C for 15 min, whereupon sodium formate (3 g) was added followed by the hydrochloride (10 g). The mixture was stirred at 50 °C for 15 min, diluted with water (50 ml), and the resulting solution cooled to 25 °C when the product crystallised.

(b) *Methoxycarbonylation.* Methyl chloroformate (6 ml) was added to a part-solution of the hydrochloride (15 g) in water (300 ml) with vigorous stirring followed by sodium hydrogencarbonate (24 g) in portions. Within 5 min a clear solution resulted and after 1 h the mixture was acidified and the product isolated with chloroform.

Oxazolinone and Oxazinedione Routes.—Methyl (2,3,4,5-*tetrahydro-2-oxonaphth*[2,1-d]*oxazol-3-yl*)*acetate* (3; R = CH_2CO_2Me, n = 1). (a) A solution of methyl *N*-(1,2,3,4-tetrahydro-1-oxo-2-naphthyl)carbamate [3] (21.9 g, 0.1 mol) in dimethylformamide (250 ml) was added during 25 min to a stirred suspension of sodium hydride (50%; 9.6 g, 0.2 mol) in the same solvent (500 ml) under nitrogen at 45—50 °C. The reaction mixture was kept at the same temperature for 1 h when methyl chloroacetate (29 ml, 0.3 mol) was added in three portions during 5 min. The stirred mixture was kept at 50 °C until neutral when most of the solvent was removed under reduced pressure. Addition of water (100 ml) to the viscous residue gave a sticky solid which was obtained by filtration, washed with water (100 ml), and the residue sucked at the pump for 15 min; the moist cake was then triturated with methanol (2 × 20 ml) and then ether (20 ml) to give after drying, crude ester (22.3 g, 86%) with m.p. 151—154 °C. Crystallisation from toluene (70 ml) furnished good quality

ester of m.p. 154—157 °C with 90% recovery. A further crystallisation from toluene gave the pure *ester*, m.p. 157 °C, $\nu_{max.}$ 1 755 (cyclic lactam) and 1 740 cm^{-1} (ester C=O) (Found: C, 64.9; H, 5.1; N, 5.4. $C_{14}H_{13}NO_4$ requires C, 64.9; H, 5.05; N, 5.4%).

(b) A mixture of the parent oxazolinone[3] (3.74 g), methyl chloroacetate (7 ml), anhydrous potassium carbonate (7 g) and acetone (75 ml) was refluxed with stirring for 8 h. Filtration and evaporation furnished an oil which was dissolved in ether (50 ml) whereupon the ester (4.82 g, 93%), m.p. 154—156 °C, rapidly crystallised.

Hydrolysis of the *oxazoline ester* (3; R = CH_2CO_2Me, n = 1). (i) A mixture of the preceding ester (m.p. 154—156 °C, 15 g), concentrated hydrochloric acid (30 ml), and acetic acid (70 ml) was heated on a steam-bath when dissolution occurred rapidly as the temperature of the mixture reached 50 °C. The solution was heated (internal temperature, 84 °C) for 2.5 h, treated with charcoal and evaporated to dryness under reduced pressure. Toluene (30 ml) was then added and the mixture again evaporated to dryness whereupon boiling acetone (200 ml) was added in portions to the hot residue with vigorous swirling to obtain as much dissolution as possible before crystallisation set in. The mixture was cooled to 8 °C, filtered, washed with acetone (100 ml), and finally ether (100 ml). The product (13.6 g), a mixture [R_F (A) 0.4 and 0.95, (B) 0.00 and 0.63] of the *anhydrous* * α-tetralone- and β-naphthyl-glycines hydrochlorides, had m.p. 184—187 °C with previous softening at 174 °C and $\nu_{max.}$ 2 720, 2 620, and 2 520 (NH_2^+), 1 750 (CO_2H), and 1 680 cm^{-1} (C=O). Crystallisation from boiling propan-2-ol containing a few drops of 2M-hydrochloric acid, yielded N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthyl*)*glycine* (4; R = H) *hydrochloride monohydrate* as prisms, m.p. 193—194 °C, R_F (A) and (B) 0.4 and 0.0 respectively; $\nu_{max.}$ 3 560 and 3 405 (OH), 2 720, 2 525, and 2 460 (NH_2^+), 1 720 (CO_2H) and 1 680 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 2.3—3.35 (4 H, m, 3, 4-H_2), 4.0 (2 H, s, CH_2CO_2H), 7.25—7.6 (3 H, m, 5, 6, 7-H) and 7.65—8.15 (3 H, m, 8-H and H_2O; 2 H interchangeable with D_2O) (Found: C, 52.9; H, 5.9; N, 5.1. $C_{12}H_{14}ClNO_3 \cdot H_2O$ requires C, 52.7; N, 5.9; N, 5.1%). The N-*formyl-derivative* (4; R = CHO) formed small prisms (from acetonitrile), m.p. 161—162 °C, $\nu_{max.}$ 1 745 (CO_2H), 1 690 (C=O), and 1 645 cm^{-1} (amide I); δ [$(CD_3)_2SO$] 2.2—2.6 and 2.8—3.35 (4 H, m, 3, 4-H_2), 3.6—4.26 (2 H, m, CH_2CO_2H), 4.7—5.0 (1 H, m, 2-H), 7.2—7.7 (3 H, m, 5, 6, 7-H), 7.85—8.0 (1 H, m, 8-H), and 8.2 (1 H, s, CHO) (Found: C, 63.05; H, 5.3; N, 5.65. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.3; N, 5.7%) and N-*methoxycarbonyl-derivative* (4; R = CO_2Me) as prisms (from benzene), m.p. 143—144 °C, $\nu_{max.}$ 1 730 (CO_2H) and 1 680 cm^{-1} (C=O); δ 2.2—2.45 and 3.0—3.3 (4 H, m, 3, 4-H_2) 3.7 (3 H, s, OMe), 3.8—4.4 (2 H, m, CH_2CO_2H), 4.6—5.0 (1 H, m, 2-H), 7.2—7.6 (3 H, m, 5, 6, 7-HO, 7.95—8.15 (1 H, m, 8-H), and 10.65br (1 H, CO_2H) (Found: C, 60.8; H, 5.55; N, 5.0. $C_{14}H_{15}NO_5$ requires C, 60.6; H, 5.45; N, 5.05%).

(ii) The solution obtained after hydrolysis, was evaporated to dryness and the residual gum freed from acetic acid by dissolution in hot water (50 ml) and re-evaporation. The resulting solid was then dissolved in boiling water (100 ml) and the resulting solution cooled rapidly to 25 °C; filtration yielded essentially pure N-2-*naphthylglycine* (5; $R^1 = R^2$ = H) *hydrochloride* (2.2 g, 19%),[9] needles (from propan-2-ol), m.p. 181—182 °C, R_F (A) and (B) 0.95 and 0.63 respectively; $\nu_{max.}$ 2 720, 2 560 and 2 380 (NH_2^+) and 1 750 (CO_2H) cm^{-1}; δ [$(CD_3)_2SO$] 3.95 (2 H, s, CH_2CO_2H), 6.95—8.2 (7 H, m, ArH), and 10.0br (3 H, NH_2^+ and CO_2H, all interchangeable with D_2O) (Found: C, 60.6; H, 5.2; Cl, 15.0; N, 5.8. $C_{12}H_{12}ClNO_2$ requires C, 60.6; H, 5.1; Cl, 15.0; N, 5.9%). It gave an N-*formyl-derivative* (5; R^1 = CHO, R^2 = H) as prisms (from acetonitrile), m.p. 182 °C, $\nu_{max.}$ 1 730 (CO_2H), 1 648 (amide I), 1 630 and 1 600 cm^{-1}; δ [$(CD_3)_2SO$] 4.6 (2 H, s, CH_2CO_2H), 7.45—8.03 (7 H, m, ArH), and 8.8 (1 H, s, CHO) (Found: C, 68.0; H, 4.9; N, 6.1. $C_{13}H_{11}NO_3$ requires C, 68.1; H, 4.8; N, 6.1%) and a N-*methoxycarbonyl derivative* (5; $R^1 = CO_2Me$, R^2 = H) as spherules (from acetonitrile), m.p. 152—153 °C, $\nu_{max.}$ 1 738 (CO_2H), 1 702 (CO_2Me), 1 625w, and 1 595 cm^{-1}; δ [$(CD_3)_2SO$] 3.65 (3 H, s, OMe), 4.4 (2 H, s, CH_2CO_2Me), and 7.35—7.95 (7 H, m, ArH) (Found: C, 64.7; H, 5.0; N, 5.4. $C_{14}H_{13}NO_4$ requires C, 64.9; H, 5.05; N, 5.4%).

Direct synthesis of N-2-*naphthylglycine hydrochloride and derivatives*. Sodium hydride (50%; 3.84 g, 80 mmol) was added in two portions to a solution of 2-formamidonaphthalene[4] (13.7 g, 80 mmol) in dimethylformamide (300 ml) with stirring under nitrogen. Reaction was slow at room temperature but at 40 °C complete within 15 min when methyl chloroacetate (10.5 ml, 120 mmol) was added. Neutrality was realised in 2 min whereupon the solvent was removed under reduced pressure. Isolation with benzene and crystallisation from ether (60 ml) yielded *methyl* N-*formyl*-N-2-*naphthylglycinate* (5; R^1 = CHO, R^2 = Me) (16 g, 84%), m.p. 86—88 °C. A sample crystallised from carbon tetrachloride as plates, m.p. 88 °C, $\nu_{max.}$ 1 751 and 1 742 (ester C=O), 1 685 (amide I), 1 632, and 1 600 cm^{-1}; δ 3.72 (3 H, s, OMe), 4.65 (2 H, s, CH_2CO_2Me), 7.2—7.9 (7 H, m, ArH), and 8.55 (1 H, s, CHO) (Found: C, 68.9; H, 5.3; N, 6.0. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.4; N, 5.8%).

Hydrolysis with ethanolic potassium hydroxide and acidification yielded the formamido-acid (5; R^1 = CHO, R^2 = H), m.p. 182 °C and i.r. spectrum identical with that of the earlier material. Hydrolysis of the latter or its methyl ester (1 g) with concentrated hydrochloric acid (2 ml) in acetic acid (5 ml) as before furnished the amino-acid (5; $R^1 = R^2$ = H) hydrochloride identical with the previous material.

Hydrolysis experiments on N-*methyloxazolinone* (3; R = Me, n = 1). (a) Conc. HCl–Propan-2-ol. A mixture of the oxazolinone (2.0 g),[3] hydrochloric acid (10 ml), and propan-2-ol (20 ml) was heated on a steam-bath for 1.5 h and the resulting solution evaporated to dryness. The residual solid was digested with propan-2-ol (10 ml) and re-evaporated. This process was repeated, the residue digested with hot acetone (10 ml), and the mixture cooled to 3 °C. Filtration yielded crude 1,2,3,4-tetrahydro-2-*N*-methylaminonaphthalen-1-one hydrochloride (2.0 g, 94%), m.p. 211—213 °C, R_F (B) 0.0 and 0.61, $\nu_{max.}$ 2 680, 2 460, and 2 430 ($MeNH_2^+$), 1 680 (C=O) and *inter alia* 860, 820, and 805 cm^{-1} (all w); it contained 8% of *N*-methylnaphthalene-2-amine hydrochloride (potentiometric titration).

A sample (900 mg) was crystallised[3] from propan-2-ol (10 ml) containing 2M-hydrochloric acid (1 ml) to give pure aminoketone hydrochloride (605 mg), m.p. 213—215 °C, pK_a 7.9, R_F (B) 0.0, $\lambda_{max.}$ 210, 251, and 294 nm (log ε 4.24, 4.12, and 3.27) and $\nu_{max.}$ 2 680, 2 460, 2 420, and *inter alia*, 820vw, cm^{-1}.

(b) Conc. HCl–AcOH. A mixture of the oxazolinone (1 g, hydrochloric acid (5 ml) and acetic acid (10 ml) was treated exactly as in (a) except that digestion was carried out with toluene in order to assist removal of residual acetic acid. Removal of traces of the latter from the product proved

* Absence of i.r. peaks at 3 560 and 3 405 cm^{-1}. Noteworthy is the peak at 1 750 (CO_2H) which changes to 1 720 cm^{-1} on hydration; this interpretation was later confirmed when the anhydrous salt was obtained in a pure state from hydrolysis of the oxazinedione analogue.

difficult; after 2 h at 50 °C *in vacuo*, the material (910 mg) still had traces of acid, m.p. 207—211 °C, R_F (B) 0.0 and 0.61; it contained 12% of the naphthylamine (potentiometric titration).

In summary, visual inspection of i.r. spectra relative peak intensifies at 2 460 and 2 420 and presence of peaks at 860 and 810 cm^{-1}, and t.l.c. provided reliable procedures for establishment of purity; in addition it was noted that solutions (5%) of the impure hydrochlorides in water or wet propan-2-ol turned yellow after 2 h exposure to daylight whilst those of the pure salt remained colourless.

N-*Methyl*-2-*naphthylamine Hydrochloride*.—A mixture of the *N*-formyl derivative of the title compound (see later) (800 mg), concentrated hydrochloric acid (1 ml), and propan-2-ol (3 ml) was heated in a steam-bath for 1 h; when the mixture cooled the *salt* (450 mg) separated as nacreous plates, m.p. 181—183 °C (lit.,[5] m.p. 182—183 °C), pK_a 4.0, R_F (B) 0.61, $\lambda_{max.}$ 242 and 282 nm (log ε 4.46 and 3.81); $\nu_{max.}$ 2 680, 2 620, 2 460, and 2 430 ($MeNH_2^+$) and *inter alia*, 860, 820, and 810 (all ms) cm^{-1}.

Methyl 2,3,5,6-*Tetrahydro*-2,3-*dioxo*-4H-*naphth*[1,2-b][1,4]-*oxazin*-4-*ylacetate* (3; R = CH_2CO_2Me, n = 2).—Reaction of the sodio-derivative (NaH procedure) of the parent dione with methyl chloroacetate was effected exactly as described in Part 2 [3] to give the *ester* as bright yellow prismatic needles (from toluene), m.p. 176—177 °C, $\nu_{max.}$ 1 768 (enol-lactone), 1 747 (ester C=O), 1 695 (C=C), and 1 652 cm^{-1} (amide I) (Found: C, 62.9; H, 4.6; N, 4.8. $C_{15}H_{13}NO_5$ requires C, 62.7; H, 4.6; N, 4.9%).

Hydrolysis of the Oxazine-ester (3; R = CH_2CO_2Me, n = 2).—A mixture of the ester (2.0 g), concentrated hydrochloric acid (6 ml), and acetic acid (14 ml) was heated on a steam-bath for 2.25 h and the resulting solution evaporated to dryness under reduced pressure. Re-evaporation with toluene (10 ml) furnished a solid which was treated with boiling acetone (12 ml). The mixture was cooled to 3 °C and filtered to give the *anhydrous amino-keto-acid* (4; R = H) *hydrochloride* (1.8 g, 100%), m.p. 192—193 °C, $\nu_{max.}$ 1 750 (CO_2H) and 1 680 (C=O) cm^{-1}; δ [$(CD_3)_2SO$] 2.2—3.4 (4 H, m, 3, 4-H_2), 3.95 (2 H, s, CH_2CO_2H), 7.3—7.7 (3 H, m, 5, 6, 7-H) and 7.75—7.95 (1 H, m, 8-H) (Found: C, 56.3; H, 5.5; N, 5.3. $C_{12}H_{14}ClNO_3$ requires C, 56.4; H, 5.5; N, 5.5%); the material did not contain any detectable amount [t.l.c. (B)] of β-naphthylglycine hydrochloride.

Glyoxylic Acid Route

N-*Formyl*-N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthyl*)*glycine* (10 ≡ 4; R = CHO).—Glyoxylic acid, *x*-hydrate (Aldrich; 20 g, *ca.* 200 mmol) was added under nitrogen to a stirred mixture of 2-amino-1,2,3,4-tetrahydronaphthalen-1-one hydrochloride, monohydrate [10] (15 g; 69 mmol) in formic acid (45 ml of 98—100%). Triethylamine (10.0 ml, 71 mmol) was then added in 2 portions during 15 min whereupon within 2 min a vigorous evolution of carbon dioxide took place and the temperature of the reaction mixture rose to 30 °C. After a further 10 min, and when gas evolution had practically ceased, the temperature was raised to 90 °C during 15 min (bath) and kept there for an additional 15 min. The cooled, red solution was then diluted with ice–water (100 ml), the mixture left in the refrigerator at 3 °C for 48 h and then filtered to give, after a small water wash and drying *in vacuo* at 80 °C, the crude *N*-formyl-acid (14 g, 85%) as a pink solid of m.p. 146—148 °C.

If the same reaction was carried out at room temperature for 2.5 and 24 h, the yield of almost colourless acid was 8 g of m.p. 157—160 °C and 10.1 g of m.p. 152—157 °C (48.6 and 61% respectively); when the reaction mixture was kept at room temperature for 0.5 h and at 50 °C for 0.5 h, the yield of acid was 10.2 g of m.p. 147—156 °C (62%).

N-(1,2,3,4-*Tetrahydro*-1-*oxo*-2-*naphthyl*)*glycine* (4; R = H) *Hydrochloride Monohydrate*.—The product from the previous reaction in the form of a moist cake, was boiled with a mixture of concentrated hydrochloric acid (30 ml) and water (100 ml) for 1 h, dissolution occurring as the mixture began to reflux. The reddish solution containing some black insoluble tar was charcoaled and worked up as previously to give the hydrochloride [12 g, 73% overall on (7) or 86% on (10)], identical with that obtained by the two alternative routes.

N-*Benzyl*-N-*formylglycine*.—The reaction was effected in exactly the same manner as that for (7) using benzylamine (11 ml) and glyoxylic acid (21 g) in formic acid (30 ml of 98—100%) and furnished the product (10 g, 54%) with m.p. 123—125 °C. The pure *formamido-acid* crystallised from acetonitrile, as small cubes, m.p. 128 °C, $\nu_{max.}$ 1 740 (CO_2H) and 1 640 (amide I) cm^{-1}; δ (CF_3CO_2H) 4.20 (2 H, s, CH_2CO_2H), 4.52 and 4.62 (2 H, 2s, $PhCH_2N$), 7.2—7.5 (5 H, m, ArH), and 8.4 and 8.5 (1 H, 2s, CHO) (Found: C, 62.3; H, 5.8; N, 7.4. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%).

Formolysis of Oxazolinones (3; n = 1, R = H, Me, *and* CH_2CO_2Me).—The oxazolinones (1 g) were boiled under reflux with formic acid (20 ml of 98—100%) for 6 h after which the mixture was evaporated to dryness under reduced pressure; any remaining acid was then removed by re-evaporation with toluene (2 × 10 ml) and the residue triturated with the minimum of cold ether to give respectively: 2-formamidonaphthalene (830 mg, 91%), m.p. 126—128 °C, 2-N-*methylformamidonaphthalene* (730 mg, 80%), m.p. 84—85 °C with softening at 82 °C; it formed laths (from light petroleum), m.p. 89.5—90 °C, $\nu_{max.}$ 1 668 (amide I), 1 625w, 1 595, and 1 575w cm^{-1}; δ 3.42 (3 H, s, NMe), 7.25—7.60 (4 H, m, ArH), 7.75—7.95 (3 H, m, ArH), and 8.6 (1 H, s, NCHO) (Found: C, 77.7; H, 6.0; N, 7.7. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%) and methyl *N*-formyl-*N*-2-naphthylglycinate (5; R^1 = CHO, R^2 = Me) (895 mg, 94.5%), m.p. 85 °C with softening at 81 °C. Both the first and third materials had i.r. spectra virtually identical with that of the pure materials.

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References

1 Part 5, R. E. Bowman, *Synth. Commun.*, 1983, in the press.
2 R. E. Bowman, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1897.
3 R. E. Bowman, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2126.
4 H. R. Hirst and J. B. Cohen, *J. Chem. Soc.*, 1895, **67**, 829.
5 R. Pschorr and W. Karo, *Ber.*, 1906, **39**, 3141.
6 M. L. Moore, *Org. React.*, 1949, **4**, 301.

7 For a recent example; P. Kolsaker, E. Bernatek, R. Johanson, and R. Hytta, *Acta Chem. Scand.*, 1973, **27**, 1526.
8 E. Erlenmeyer, jun., and J. Kunlin, *Liebigs Ann. Chem.*, 1899, **307**, 146; *idem.*, *Ber.*, 1902, **35**, 2438; M. A. W. K. De Jong, *Recl. Trav. Chim. Pays Bas*, 1900, **19**, 259.
9 Y. Watanabe, S. C. Shim, T. Mitsudo, M. Yamashita, and Y. Takegami (*Chem. Lett.*, 1975, **7**, 699) mention this compound without analyses or physical constants.
10 F. W. Neber, A. Burgard, and W. Their, *Annalen*, 1936, **526**, 277.

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