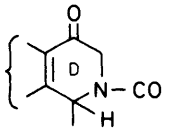
Experiments Towards the Synthesis of the Ergot Alkaloids and Related Structures. Part 4.[1] Lysergic Acid—An Attempted 'Endo-amide' Approach

By **Ralph E. Bowman**, Welsh School of Pharmacy, University of Wales Institute of Science and Technology, King Edward VII Avenue, Cardiff CF1 3NU

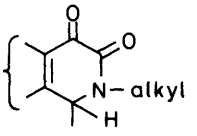
Two attempts to synthesise the tricyclic α-keto-amide (6) are described. In the first, 1,2,3,4-tetradihydro-2-methylaminonaphthalen-1-one hydrochloride (3) was allowed to react with pyridine–hydroxymaleic anhydride at −20 °C and then at room temperature to give a complex mixture from which the naphth[1,2-*b*]-1,4-oxazinone (14), 2-pyruvamido-1-tetralone (16; R = Ac) contaminated with the oxazinone (14) and the phenolic acid (13c) were isolated. A tetracyclic oxazinone was also obtained from the appropriate methylaminotetrahydroacenaphthenone but not from the corresponding benz[*cd*]indolone (7; R = NHMe.HCl). In the second, the *N*-methyldione (10) was converted in three stages into the tricyclic acid (13c) which proved unexpectedly stable. However, its triethylamine salt lost carbon dioxide at 140 °C to give not the required keto-amide (6) but the isomeric hydroxybenz-[*f*]quinolone (13d). Both the oxazinone (14) and the impure pyruvamido-ketone (16; R = Ac) were converted within seconds by treatment with 2M-sodium hydroxide into the sparingly soluble sodium salt of the phenol (13d) as was the pure pyruvamido ketone whose synthesis is described.

OUR continued approach to the synthesis of lysergic acid and analogues has been, in contrast to that of previous workers in the field,[2-5] to retain a neutral (*i.e.* amido) function in ring D up to as late a stage as possible in the synthesis in order to facilitate subsequent manipulations.

As was pointed out in Part 2,[6] the amido-group in ring D can take either the '*exo*' or '*endo*' form as in (1) or (2) respectively, although there was the obvious danger that the latter might take up the isomeric hydroxyquinolone structure which would probably be useless for our purposes.



(1)



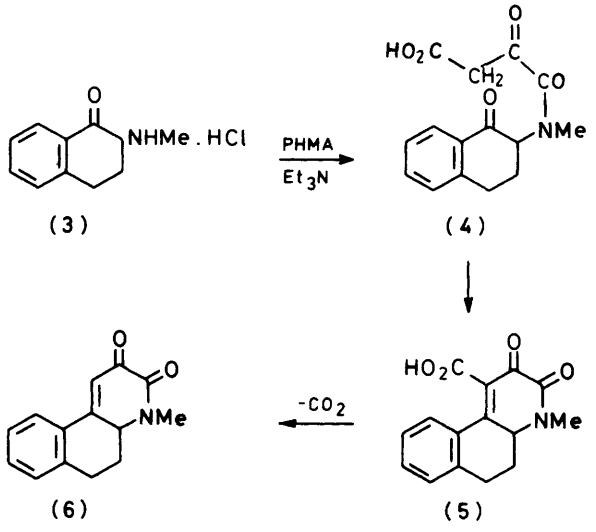
(2)

In this paper we report experiments on the '*endo*-amide' approach starting, in the first instance, with 2-methylaminotetralone hydrochloride (3) which is readily accessible through our oxazolinone synthesis.[6]

RESULTS AND DISCUSSION

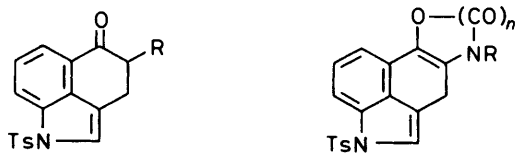
Wohl,[7] as far back as 1907, had shown that hydroxymaleic anhydride in the form of its pyridine salt (PHMA) reacted with aniline at −12 °C to give the relatively stable oxaloacetic-1-anilide. It was hoped that application of this reaction to (3) would lead directly to the required tricyclic keto-amide (6) in the manner shown in Scheme 1.

The reaction was carried out in acetone in the presence of an excess of triethylamine at −20 °C and then at room temperature for 16 h, followed by heating under reflux for a short time. The products were a neutral crystalline solid (A), a neutral oil (B), and a small quantity of a solid carboxylic acid (C). The solid (A) gave a satisfactory elemental analysis for the expected tricyclic keto-amide (6) containing one mole of water of crystallisation, which appeared to be tightly held since the compound crystallised unchanged from boiling acetic anhydride; the structure was also supported by the i.r. spectrum of the compound which had peaks at 3 260 (OH), 1 675 (C=C–C=O), and 1 640 cm^{-1} (amide I). A similar tetracyclic product was obtained in the tetrahydroacenaphthene series.

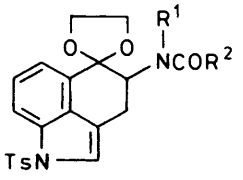


SCHEME 1

In view of this apparent success, attention was now turned to the preparation of the requisite starting amine (7; R = NHMe.HCl) in Uhle's ketone series using methodology previously successful in the tetralone and tetrahydroacenaphthenone series.[6] Thus, the oxazolinone (8; R = Me, n = 1) and later, the oxazinedione (8; R = Me, n = 2) were prepared but unlike members of the other series, both resisted hydrolysis. The *N*-trifluoroacetamido ketone (7; R = $HNCOCF_3$) was also prepared; however, although it appeared to form a sodio-derivative, all attempts to bring about methylation failed, starting material being recovered.



(7) (8)



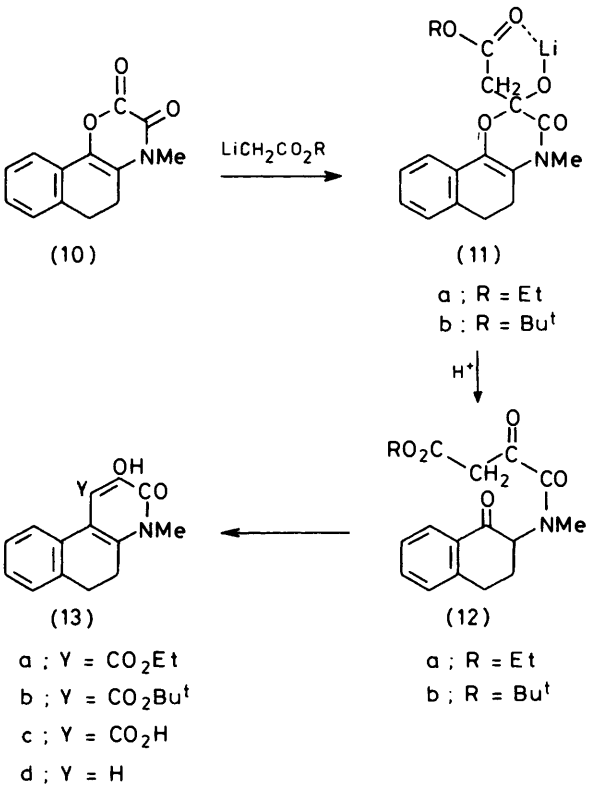
(9)

a ; $R^1 = R^2 = H$
b ; $R^1 = H$, $R^2 = Me$
c ; $R^1 = Me$, $R^2 = H$
d ; $R^1 = R^2 = Me$

In another approach, the *N*-formyl- and *N*-acetyl-acetals (9a and b) were converted into their *N*-methyl derivatives (9c and d), albeit relatively slowly, *via* their sodio-derivatives. All attempts to hydrolyse the *N*-acetyl-*N*-methyl-acetal proved abortive, but at room temperature the *N*-formyl-*N*-methyl derivative (9c) was converted by concentrated hydrochloric acid into the required *N*-methylamino-ketone hydrochloride (7; R = NHMe.HCl). Reaction of this salt with PHMA, under the same conditions as described previously, failed to provide any crystalline products.

At a later date, when our oxazinedione work had been completed and the high reactivity of these compounds to nucleophiles had been demonstrated,[6] a further approach became apparent (Scheme 2). Thus, in principle, reaction of the *N*-methyldione (10) with t-butyl lithioacetate [8] would furnish a complex (11b) [9] which would be converted by protonation into the diketo-ester (12b). Base-induced cyclisation of the latter should yield the tricyclic ester (13b) which would be converted by trifluoroacetic acid into the corresponding keto-acid (13c); this would be expected, following the PHMA route, to lose carbon dioxide spontaneously to give the tricyclic keto-amide (6) already obtained. The attraction of this new approach lay in the fact that the starting *N*-methyldione (8; R = Me, $n = 2$), derived from Uhle's ketone, had already been prepared.

In a trial run, the sparingly soluble dione (10) reacted rapidly with ethyl lithioacetate [10] in tetrahydrofuran at −70 °C to give a product which, on decomposition with dilute mineral acid, furnished an oil; this appeared to be a mixture of the expected diketo-ester (12a) and its enolic counterpart. Treatment of the oil with a catalytic amount of pyrrolidine in boiling ether rapidly furnished the crystalline enolic tricyclic ester (13a) in high yield. In a similar manner, t-butyl lithioacetate yielded an oily diketo-ester (12b) from which the enolic form could be separated in a crystalline condition. Treatment of the mixed esters with pyrrolidine in boiling benzene furnished the tricyclic ester (13b) converted by trifluoracetic acid, rapidly at room temperature and in essentially quantitative yield, into the enolic-acid (13c) which, far from decomposing spontaneously at room temperature, melted



(10) (11)

a ; R = Et
b ; R = Bu^t

(13) (12)

a ; Y = CO_2Et
b ; Y = CO_2Bu^t
c ; Y = CO_2H
d ; Y = H

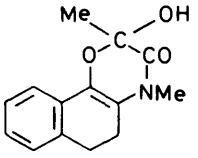
a ; R = Et
b ; R = Bu^t

SCHEME 2

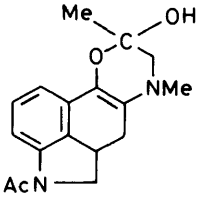
at 210 °C with decomposition, and could be crystallised unchanged from boiling diglyme (164 °C). The acid formed a crystalline triethylammonium salt which lost carbon dioxide in boiling xylene to yield, again in quantitative yield, the hydroxybenz[*f*]quinolone (13d). Regretfully the latter quinolone failed to show ketonic properties; for example, it was recovered unchanged from treatment with an excess of hydroxylamine or methylenetriphenylphosphorane, but it did form a crystalline sodium salt which was sparingly soluble even in boiling water.

The phenolic structure of (13d) necessitated a re-examination of the tricyclic product (A) obtained from the PHMA route. The original experiments were carried out several years ago when n.m.r. spectral determinations were not readily available to us and we were satisfied with its i.r. spectrum which was in accord with our expectations—a cautionary tale indeed! The ^1H n.m.r. spectrum showed clearly the presence of a methyl and hydroxy-group accommodated by the oxazinone structure (14) and resulting, presumably, from enolisation of the hydroaromatic carbonyl at an early stage in the synthesis. A related structure (15) has been proposed for a substance obtained by the Harvard-

Lilly groups during their original synthesis of lysergic acid.[2] Attempts to prepare an *O*-acetyl derivative of (14) by treatment with acetic anhydride in the presence of pyridine or triethylamine–4-dimethylaminopyridine [11] were unsuccessful; however, oximation furnished, in relatively low yield, a dioxime presumably derived from the ' open ' keto-pyruvamide (16; R = Ac).

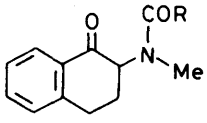


(14)



(15)

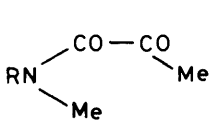
It was this last finding that prompted attempts to prepare the latter amide. Reaction of α-methoxyacrylic acid (improved preparation) with the methylamino ketone hydrochloride (3) by the mixed carbonic methyl ester–anhydride route furnished the nicely crystalline amide [16; R = C(OMe)=CH_2].



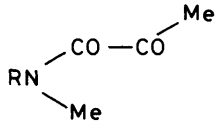
(16)

Hydrolysis at room temperature with 70% trifluoroacetic acid furnished an oily keto-amide which, initially, resisted determined attempts to effect crystallisation. However, to our surprise, treatment with 2M-sodium hydroxide gave, within seconds, a high yield of the sparingly soluble sodium salt of the phenol (13d). Crystallisation of the mixture was later achieved to give the oxazinone (14) and the pyruvamide (16; R = Ac), neither in a pure condition. The latter amide was subsequently obtained in a pure state by direct acylation using pyruvic acid itself in the presence of dicyclohexylcarbodiimide.[12] Its ^{1}H n.m.r. spectrum proved more complex than expected, signals due to Ac and NMe each being present as two singlets * and the 2'-H as a triplet and quartet, presumably due to the presence of *cis*- and *trans*-forms [(17) and (18), respectively] and possibly others involving 2'-H, in solution at room temperature.† As now to be expected, on being treated with 2M-sodium hydroxide, the amide (16) underwent rapid cyclisation to give the sodium salt of (13d) in high yield as also did the oxazinone (14), presumably as the result of initial ring opening followed by recyclisation.

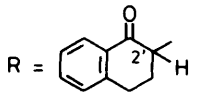
Finally we returned to a re-examination of products (B) and (C). The former, on treatment with 2M-sodium hydroxide, gave the same sodium salt and presumably



(17)



(18)



consisted mainly of the pyruvamide (16; R = Ac), a supposition readily demonstrated by low-temperature crystallisation from ether in the presence of seed that was now available; a small amount of the phenol (13d) also appeared to be present. The solid (C) was readily purified to give, in very small overall yield, the hydroxy-(oxo)benzo[*f*]quinoline-1-carboxylic acid (13c).

EXPERIMENTAL

General procedures were as described in Part 2.[6] The expression ' isolated with ' refers, when applied to neutral substances, to an overall process whereby the product was extracted with solvent and the organic extract washed sequentially with dilute hydrochloric acid, water, and dilute sodium hydrogencarbonate; it was then dried over anhydrous sodium sulphate with subsequent addition of charcoal where necessary, filtered, and evaporated using a rotary evaporator under reduced pressure. I.r. and ^{1}H n.m.r. (90 MHz) spectra were run in Nujol mulls and $CDCl_3$ solutions respectively, unless stated otherwise. Throughout, ether refers to diethyl ether. The light petroleum used was of boiling range 60—80 °C.

Reaction of 1,2,3,4-*Tetrahydro*-2-*methylaminonaphthalen*-1-*one Hydrochloride* (3) *with Pyridine–Hydroxymaleic Anhydride*.—Triethylamine (11.2 ml, 80 mmol) was added to a stirred suspension of the anhydride [14] (7.8 g, 40 mmol), in dry acetone (40 ml) under nitrogen at −20 °C (inner temp.); to the resulting solution was added in one portion, the hydrochloride [6] (3) (4.2 g, 20 mmol). The mixture was kept at −20 °C for 0.75 h, then at −10 °C for 0.5 h, when the cooling bath was removed. After 16 h, triethylamine hydrochloride (2.65 g) was filtered off; the filtrate was then refluxed for 0.2 h, after which it was evaporated to a small bulk on the steam-bath. The residue was cooled and treated with 0.1M-sodium hydrogencarbonate; the neutral products were then isolated with ethyl acetate as a sticky solid (4.3 g) which, on trituration with ether (25 ml), furnished the crude oxazinone (A) (2.1 g), m.p. 147—152 °C. 2,3,5,6-*Tetrahydro*-2-*hydroxy*-2,4-*dimethyl*-4H-*naphth*[1,2-b]-1,4-*oxazin*-3-*one* (14) formed prisms [from methanol (7 vol)], m.p. 156—158 °C, $\nu_{max.}$ 3 260 (OH), 1 675br (C=C), and 1 640 cm^{-1} (amide I); δ 1.72 (4 H, s, Me and OH interchangeable with D_2O), 2.5—3.0 (4 H, m, 5- and 6-H_2), 3.18 (3 H, s, NMe), 7.05—7.22 (3 H, m, 7-, 8-, and 9-H), and 7.4—7.5 (1 H, m, 10-H) (Found: C, 68.5; H, 6.2; N, 5.6. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.2; N, 5.7%).

Oximation of (14) in the usual manner (1 h, 80 °C) and isolation with ethyl acetate, furnished a gum which crystallised on treatment with ether to give [N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthyl*)-N-*methyl*]-2-*oxopropanamide*, *dioxime*, as prisms (from ethanol–water 1 : 1), m.p. 202 °C,

* The author originally reported each two singlets as doublets and is most grateful to a referee who queried these assignments.

† A more simple example is that of *NN*-dimethylformamide where NMe signals are present at δ 2.88 and 2.97 due to the existence of *cis*- and *trans*-forms.[13]

$\nu_{max.}$ 1 640w, 1 609, and 1 585 cm^{-1} (Found: C, 61.2; H, 6.2; N, 15.0. $C_{14}H_{17}N_3O_3$ requires C, 61.1; H, 6.2; N, 15.2%).

The ethereal filtrate obtained from the isolation of the crude oxazinone (A), furnished, on evaporation, an oil (B) (2.0 g) which on trituration with 2M-sodium hydroxide (15 ml) gave, with evolution of heat, a transient solution from which the hydrated, sparingly soluble sodium salt of the phenol (13d) separated rapidly; after being washed with water, acetone and ether, it weighed 1.4 g and had an i.r. spectrum identical with that of the authentic material.

On a later occasion, the ethereal solution was allowed to evaporate to a small bulk and was then cooled to −15 °C, when on seeding there separated the pyruvamide (16; R = Ac) (865 mg), m.p. 71—73 °C undepressed by admixture with authentic material and presumably almost pure, since its i.r. spectrum was virtually superimposable on that of the pure amide.

The sodium hydrogencarbonate extract of the original reaction products furnished, on acidification, a red-tinged solid (650 mg) which, on trituration with ether and methanol, gave the hydroxybenzoquinolone acid (13c) (250 mg, 4.4%).

4,5,5a,6,8,9-*Hexahydro*-9-*hydroxy*-7,9-*dimethyl*-7H-*acenaphthylen*[5,4-b][1,4]*oxazin*-8-*one*.—2a,3,4,5-Tetrahydro-4-methylaminoacenaphthen-5-one hydrochloride[6] was allowed to react with PHMA as in the previous example to give the *oxazinone* as prisms (from benzene), m.p. 166—167 °C; $\nu_{max.}$ 3 350br and 3 200br (OH), 1 687 and 1 657 (C=C), and 1 640 cm^{-1} (amide I); δ 1.2—3.0 (7 H, m, 5a-H and 4-, 5-, and 6-H_2), 1.7 (4 H, d, Me and OH, reduced to a singlet on treatment with D_2O), 3.15 (3 H, d, *J* 3 Hz, NMe), and 7.0—7.3 (3 H, m, 1-, 2-, and 3-H) (Found: C, 70.9; H, 6.3; N, 5.1. $C_{16}H_{17}NO_3$ requires C, 70.8; N, 6.3; N, 5.2%).

4,6,7,8-*Tetrahydro*-4-(p-*tolylsulphonyl*)*indolo*[3,4-fg]*benzoxazol*-8-*ones* (8; n = 1).—Sodium hydride (300 mg of 80% dispersion in oil, 10 mmol) was added in one portion to a solution of methyl *N*-{1,3,4,5-tetrahydro-5-oxo-1-(*p*-tolylsulphonyl)benz[*cd*]indol-4-yl}carbamate [15a] (2.0 g, 5 mmol) in dry dimethylformamide (30 ml) at 40 °C whereupon a gas was evolved. After 25 min, a clear solution of the sodio-derivative (8; R = Na, *n* = 1) resulted.

(a) The above solution was poured into an excess of dilute hydrochloric acid and the solid filtered off. The *parent oxazolinone* (8; R = H, *n* = 1) formed yellow prismatic needles [from 2-methoxyethanol–DMF (3 : 1)], m.p. 283 °C, $\nu_{max.}$ 3 220—3 020 (bonded NH), 1 755 (oxazolinone) and 1 648 cm^{-1} (C=C) (Found: C, 62.5; H, 3.8; N, 7.7. $C_{19}H_{14}N_2O_4S$ requires C, 62.3; H, 3.85; N, 7.65%).

(b) Alkyl halide (15 mmol) was added to the solution of sodio-derivative and the mixture kept at 50—60 °C until it became neutral after which most of the solvent was removed under reduced pressure; isolation as in (a) furnished the following compounds: the N-*methyloxazolinone* (8; R = Me, *n* = 1), as off-white needles (from the same solvent mixture), m.p. 258 °C, $\nu_{max.}$ 1 760 and 1 640 cm^{-1} (Found: C, 63.2; H, 4.4; N, 7.5. $C_{20}H_{16}N_2O_4S$ requires C, 63.15; H, 4.2; N, 7.4%); the N-*prop*-2-*ynyloxazolinone* (8; R = $CH_2{\cdot}C{\equiv}CH$, *n* = 1), as pale yellow needles (from 2-methoxyethanol), m.p. 257 °C; $\nu_{max.}$ 3 240 (C≡CH), 2 120 (C≡C), 1 770, and 1 640 cm^{-1} (Found: C, 65.1; H, 4.0; N, 7.1. $C_{22}H_{16}N_2O_4S$ requires C, 65.3; H, 4.0; N, 6.9%); and the *oxazolinone-ester* (8; R = CH_2CO_2Me, *n* = 1) (70%) as needles (from 2-methoxyethanol), m.p. 252 °C; $\nu_{max.}$ 1 775, 1 735 (ester), and 1 642 cm^{-1} (Found: C, 60.3; H, 4.1; N, 6.5. $C_{22}H_{18}N_2O_6S$ requires C, 60.3; H, 4.1; N, 6.4%).

4,6,8,9-*Tetrahydro*-7-*methyl*-4-(p-*tolylsulphonyl*)*indolo*-[3,4-gh][1,4]*benzoxazine*-8,9-*dione* (8; R = Me, n = 2).—Ethyl oxalyl chloride (2.0 ml) was added under nitrogen at 3 °C to a stirred mixture of 4-amino-1,3,4,5-tetrahydro-1-(*p*-tolylsulphonyl)benz[*cd*]indol-5-one hydrochloride [15a] (4.2 g) in dichloromethane (100 ml) followed by triethylamine (4 ml). The mixture was stirred at 3 °C for 0.5 h, and then decomposed with 2M-hydrochloric acid; the oxamidic-ester was isolated with chloroform as a red glass (4.2 g). The latter was dissolved in tetrahydrofuran (100 ml) and potassium t-butoxide (1.3 g) was added. The solution was stirred for 1.5 h after which methyl iodide (2 ml) was added; the mixture was then kept at 20 °C for 1 h and finally at 60 °C until neutral (0.25 h). Isolation with chloroform yielded a crystalline mass which on trituration with ether gave the crude product (2.0 g). The pure *dione* formed yellow prismatic needles (from diethylene glycol–dimethyl ether), m.p. 228 °C; $\nu_{max.}$ 1 778 (enol-lactam), 1 688 (C=C), 1 638 (amide I), 1 612, and 1 605 cm^{-1} (Found: C, 61.8; H, 4.0; N, 6.7. $C_{21}H_{16}N_2O_5S$ requires C, 61.8; H, 4.0; N, 6.9%).

4-*Trifluoroacetamido*-1,3,4,5-*tetrahydro*-1-(p-*tolylsulphonyl*)*benz*[cd]*indol*-5-*one* (7; R = $NHCOCF_3$).—Trifluoroacetic anhydride (2.3 ml) was added at 15 °C under nitrogen to a stirred suspension of the parent amino-ketone hydrochloride [15a] (2.3 g) in dichloromethane (70 ml) whereupon dissolution occurred rapidly. The solution was stirred for 0.3 h and then evaporated to dryness under reduced pressure. The resulting gum was dissolved in boiling carbon tetrachloride (27 ml) and the solution cooled to give the amide (1.7 g), double m.p. *ca.* 120 and 145 °C. The pure *amide* formed yellow needles (from propan-2-ol), m.p. 119 °C with partial melting, solidification, and remelting sharply at 146 °C, $\nu_{max.}$ 3 380br (NH), 1 720 (amide I), 1 690 (C=O), and 1 535br cm^{-1} (amide II) (Found: C, 55.1; H, 3.9; N, 6.5. $C_{20}H_{15}F_3N_2O_4S$ requires C, 55.05; H, 3.7; N, 6.4%).

5-*Ethylenedioxy*-4-*formamido*-1,3,4,5-*tetrahydro*-1-(p-*tolylsulphonyl*)*benz*[cd]*indole* (9a).—Dry pyridine (10 ml) was added to a solution of the parent amine [15b] (3.0 g) in chloroform at 3 °C with stirring followed by acetic–formic anhydride [16] [*ex.* formic acid (4 ml)–acetic anhydride (5 ml)] during 5 min. The mixture was stirred at this temperature for a further 0.3 h, treated with ethanol (5 ml), and poured into water. Isolation with chloroform yielded a gum which solidified under ether (2.3 g, m.p. 161—163 °C). The pure *amide* formed prisms (from ethyl acetate), m.p. 163 °C, $\nu_{max.}$ 3 410 (NH), 1 665 (amide I), and 1 525br cm^{-1} (amide II) (Found: C, 61.0; H, 4.9; N, 6.7. $C_{21}H_{20}N_2O_5S$ requires C, 61.2; H, 4.9; N, 6.7%).

5-*Ethylenedioxy*-4-N-*methylamido*-1,3,4,5-*tetrahydro*-1-(p-*tolylsulphonyl*)*benz*[cd]*indoles* (9c and d).—(*a*) Sodium hydride (375 mg of 80%, 12.5 mmol) was added with stirring under nitrogen to a solution of the preceding amide (5.15 g, 12.5 mmol) in dimethylformamide (75 ml) at 35 °C; formation of the sodio-derivative was relatively slow but complete after 50 min. Methyl iodide (2.5 ml) was then added, and the reaction mixture was heated to 80 °C during 1 h, after which the solvent was removed under reduced pressure. Addition of water furnished the N-*methylformamide* (9c) as a solid which crystallised on boiling with methanol (10 ml) (4.2 g), m.p. 186 °C, $\nu_{max.}$ 1 665 cm^{-1} (amide I) (Found: C, 61.8; H, 5.2; N, 6.6. $C_{22}H_{22}N_2O_5S$ requires C, 62.0; H, 5.2; N, 6.6%).

(*b*) The corresponding N-*methylacetamide* (9d) was similarly obtained (reaction time, 2 h at 60 °C) as plates (from methanol), m.p. 208 °C, $\nu_{max.}$ 1 647 cm^{-1} (amide I) (Found: C, 62.5; H, 5.4; N, 6.3. $C_{23}H_{24}N_2O_5S$ requires C, 62.7; H, 5.5; N, 6.4%).

1,3,4,5-*Tetrahydro*-4-*methylamino*-1-(p-*tolylsulphonyl*)-*benz*[cd]*indol*-5-*one Hydrochloride* (7; R = NHMe.HCl).—Concentrated hydrochloric acid (2 ml) was added to a solution of the *N*-methylamide (9c) (3.0 g) in acetic acid (30 ml) and the solution kept at room temperature under nitrogen for 5 d. Evaporation and re-evaporation with toluene (10 ml) furnished a dark glass which, on treatment with boiling acetone (15 ml), gave slowly the impure *salt* as a yellowish-red solid (700 mg), m.p. *ca.* 190 °C, $\nu_{max.}$ 2 650, 2 460, and 2 440 ($\overset{+}{N}H_2Me$), and 1 690 cm^{-1} (C=O) (Found: C, 57.7; H, 4.9; N, 6.7. $C_{19}H_{19}ClN_2O_3S$ requires C, 58.4; H, 4.9; N, 7.2%). Attempts to purify this salt by crystallisation were not successful.

Alkyl 3,4,5,6-*Tetrahydro*-2-*hydroxy*-4-*methyl*-3-*oxobenzo*[f]-*quinoline*-1-*carboxylates*.—(a) *Ethyl ester* (13a). n-Butyllithium (1.6M in hexane; 3.1 ml, 5 mmol) was added with stirring under nitrogen to a solution of hexamethyldisilazane (1.06 ml, 5 mmol) at −20 °C; the mixture was cooled to −70 °C and ethyl acetate (0.59 ml, 6 mmol) was added during 10 min. The solution was then stirred for a further 45 min at −70 °C after which the oxazinedione (10) [6] (920 mg, 4 mmol) was added in one portion. Dissolution occurred within 2 min and after a further 45 min the cooling bath was removed; the mixture was allowed to warm to room temperature and then poured into an excess of 2M-hydrochloric acid. Isolation with chloroform yielded an oil (1.4 g) (deep red $FeCl_3$ test) comprising of the β-keto-ester (12a) and its enolic counterpart; $\nu_{max.}$ 3 400br (OH), 1 740 (ester C=O), 1 720 (CH_2C=O), 1 690 (ring C=O), 1 655sh (amide I), and 1 635 cm^{-1} (C=C).

The oily ester was then dissolved in ether (15 ml) containing pyrrolidine (0.1 ml) and the solution was refluxed; after 5 min, crystalline material separated. Some 15 min later, the cooled solution was filtered to give the *tricyclic ethyl ester* (13a) (1.05 g, 88%), m.p. 177—180 °C, which gave a deep green colour with ferric chloride and appeared to be somewhat unstable to light inasmuch as the crystals developed a grey tinge on storage. A sample formed cubes (from methanol or ethyl acetate), m.p. 179—180 °C, $\nu_{max.}$ 3 380—3 120 with a peak at 3 260 (bonded OH), 1 725 and 1 720sh (ester), 1 640 (amide I), 1 608, 1 595vs, and 1 537 cm^{-1}; δ 1.25 (3 H, t, CH_2CH_3), 2.8 (4 H, s, 5-, and 6-H_2), 3.65 (3 H, s, NMe), 4.33 (2 H, q, CH_2CH_3), 6.8—7.25 (4 H, m, 7-, 8-, 9-, and 10-H) and 7.25—7.6 (1 H, m, OH exchangeable with D_2O) (Found: C, 68.4; H, 5.7; N, 4.6. $C_{17}H_{17}NO_4$ requires C, 68.2; H, 5.7; N, 4.7%).

(b) *t-Butyl ester* (13b). The procedure followed exactly that of (a) and was carried out on ten times the scale employing t-butyl acetate and isolation with benzene. On one occasion the crude β-keto-ester mixture partially crystallised and a portion was removed and treated with ether to give *t-butyl* 3{[N-(1′,2′,3′,4′-*tetrahydro*-1′-*oxo*-2′-*naphthyl*)-N-*methylamino*]*carbonyl*}-3-*hydroxypropenoate*, as pale yellow tetrahedra (from methanol) (deep red $FeCl_3$ test), m.p. 135—136 °C, $\nu_{max.}$ 3 360 (OH), 1 730 (ester), 1 680 (C=O), and 1 640 cm^{-1} (amide I); δ 1.52 (9 H, s, Bu^t), 2.5—3.0 (5 H, m, 2′-H and 3′- and 4′-H_2), 3.15 (3 H, s, NMe), 3.44 (1 H, d, *J* 8 Hz, 2-H), 6.18 (1 H, s, OH exchangeable with D_2O), and 7.05—7.4 (4 H, m, 5′-, 6′-, 7′-, and 8′-H) (Found: C, 65.9; H, 6.65; N, 4.0. $C_{19}H_{23}NO_5$ requires C, 66.1; H, 6.7; N, 4.1%).

The total crude ester dissolved in benzene (75 ml) containing pyrrolidine (0.5 ml) was refluxed with a Dean and Stark phase separator until no further water (0.65 ml) separated (1.25 h) and then for a further 0.75 h. Evaporation to dryness furnished a dark viscous gum which was dissolved in hot methanol (25 ml); cooling and seeding resulted in immediate crystallisation with evolution of heat to give the *tricyclic t-butyl ester hemihydrate* (9.8 g, 76%), m.p. 177—180 °C. A sample formed prisms (from methanol) (deep green $FeCl_3$ test), m.p. 180 °C, $\nu_{max.}$ 3 360br and 3 180 (OH), 1 720 and 1 710 (ester), 1 640 (amide I), 1 597vs, and 1 538 cm^{-1}; δ (CCl_4) 1.52 (9 H, s, Bu^t), 2.76 (4 H, s, 5- and 6-H_2), 3.1 (1 H, s, 0.5H_2O), 3.58 (3 H, s, NMe), 7.1—7.4 (4 H, m, 7-, 8-, 9-, and 10-H), and 7.3—7.5 [1 H, m, OH (both signals at 3.1 and 7.3—7.5 were interchangeable with D_2O)] (Found: C, 67.5; H, 6.5; N, 4.1. $C_{19}H_{21}NO_4$,-0.5H_2O requires C, 67.8; H, 6.6; N, 4.2%); drying *in vacuo* at 60 °C gave the *anhydrous ester* (Found: C, 69.6; H, 6.6; N, 4.3. $C_{19}H_{21}NO_4$ requires C, 69.7; H, 6.5; N, 4.3%).

3,4,5,6-*Tetrahydro*-2-*hydroxy*-4-*methyl*-3-*oxobenz*[f]*quinoline*-1-*carboxylic Acid* (13c).—Trifluoroacetic acid (25 ml) was added to a suspension of the preceding t-butyl ester (16 g) in toluene (60 ml) and the resulting deep green solution was kept at room temperature for 0.5 h. Evaporation under reduced pressure furnished a solid which was triturated with ether to give the *acid* (13 g, 97%), m.p. 210 °C with vigorous evolution of gas. A sample formed small prisms (from 2-methoxyethanol) (deep green $FeCl_3$ test), m.p. unchanged; $\nu_{max.}$ 3 250br (bonded OH), 1 690 (C=C–CO_2H), 1 625 (amide I), 1 560, and 1 515 cm^{-1} (Found: C, 66.3; H, 4.9; N, 5.3. $C_{15}H_{13}NO_4$ requires C, 66.4; H, 4.8; N, 5.2%).

A suspension of the acid (12 g) in ethanol (50 ml) was treated with triethylamine (8 ml) and the resulting solution evaporated to dryness to give a viscous gum which crystallised on boiling with acetone (100 ml) to give the *triethylammonium salt* (8.0 g), m.p. 136—137 °C with evolution of gas, then solidification and remelting at 206 °C, $\nu_{max.}$ 3 260br (OH), 1 635 (amide I), 1 585vs (CO_2^-), 1 570sh, and 1 535 cm^{-1} (Found: C, 67.5; H, 7.7; N, 7.5. $C_{21}H_{28}N_2O_4$ requires C, 67.7; H, 7.6; N, 7.5%). The filtrate, on standing, deposited a further crop (2.6 g).

3,4,5,6-*Tetrahydro*-2-*hydroxy*-4-*methylbenzo*[f]*quinolin*-3-*one* (13d).—A suspension of the preceding salt (8 g) in xylene (70 ml) was brought rapidly to the boil whereupon the salt melted to a viscous oil from which a gas was vigorously evolved. Within 2 min, decarboxylation was complete and the resulting solution, on being cooled to room temperature, deposited the *phenol* (4.8 g, 98%) as plates (deep green $FeCl_3$ test), m.p. 207 °C; $\nu_{max.}$ 3 260br (bonded OH), 1 650 (amide I) and 1 610 cm^{-1} (C=C), δ 2.8—3.0 (4 H, m, 5- and 6-H_2), 3.66 (3 H, s, NMe) and 7.15—7.45 (6 H, m, 1-, 7-, 8-, 9-, and 10-H and OH interchangeable with D_2O) (Found: C, 74.2; H, 5.9; N, 6.1. $C_{14}H_{13}NO_2$ requires C, 74.0; H, 5.8; N, 6.2%).

When 2M-sodium hydroxide (2 ml) was added to a partial solution of the phenol (454 mg) in boiling methanol (10 ml) and the mixture cooled, its *sodium salt, dihydrate* was obtained. On crystallisation from boiling water (80 parts) it formed lustrous plates, m.p. >325 °C, $\nu_{max.}$ 3 510 and 3 460 (OH), 1 640w (amide I), 1 602, 1 585, 1 555, and 1 520 cm^{-1} (Found: C, 59.2; H, 5.7; N, 4.9. $C_{14}H_{12}NNaO_2.2H_2O$ requires C, 58.9; H, 5.7; N, 4.9%).

Reactions of (13d) *with Ketonic Reagents.*—(*a*) *Hydroxylamine.* A mixture of compound (13d) (480 mg), hydroxylamine hydrochloride (700 mg), sodium acetate trihydrate (1.5 g), water (4 ml), and ethanol (10 ml) was heated on a steam-bath and the resulting solution kept at reflux temperature for 3 h. Removal of ethanol was accompanied by separation of the starting material (470 mg).

(*b*) *Methylenetriphenylphosphorane.* n-Butyl-lithium (1.6M; 1.23 ml, 2 mmol) was added to a suspension of methyltriphenylphosphonium bromide (714 mg, 2 mmol) in tetrahydrofuran (20 ml) at 3 °C and compound (13d) (400 mg, 1.75 mmol) was added. The mixture was stirred for 20 h and poured into an excess of 2M-hydrochloric acid. Isolation with chloroform furnished a solid which on trituration with ether yielded starting material (378 mg).

Methyl 2,2-Dimethoxypropionate.—Concentrated sulphuric acid (0.5 ml) was added to a solution of pyruvic acid (100 ml) in methanol (120 ml) followed by trimethyl orthoformate (220 ml) in four equal portions during 1 h with occasional cooling. The mixture was kept at room temperature for 3 d, and then neutralised by the addition, with swirling, of anhydrous potassium carbonate (2 g). The solution was then freed from most of the inorganic sediment by decantation and distilled at normal pressure through a Fenske column (30 cm in length) fitted with a variable take-off head until *ca.* 220 ml of methyl formate and methanol had been collected. Distillation at 13 mmHg then yielded the ester, b.p. 58—60 °C, $\nu_{max.}$ 2 840 (OMe) and 1 750br cm^{-1} (ester C=O). (Yield dependent on quality of starting acid but usually not less than 75%.)

2-Methoxypropenoic Acid.—The preceding ester (125 g) containing toluene-4-sulphonic acid monohydrate (1 g) [17] was distilled slowly through the Fenske column until 31 ml of methanol had been collected; the residue was then distilled at 13 mmHg to give methyl 2-methoxypropenoate (83 g), b.p. 76—78 °C, $\nu_{max.}$ 2 850 (OMe), 1 740br (ester C=O), and 1 625 cm^{-1} (C=C).

(*a*) Hydrolysis and isolation with ether [18] yielded the crude acid as a solid.

(*b*) The ester (83 g) was added in portions (very exothermic) to a solution of potassium hydroxide (46 g of 85%) in propan-2-ol (200 ml) and water (40 ml) when a solid separated. The mixture was refluxed for 0.5 h and evaporated to dryness under reduced pressure; re-evaporation with propan-2-ol (2 × 200 ml) followed by cooling and filtration yielded the potassium salt which was washed with a little methanol and ether; after drying at 80 °C *in vacuo*, the salt weighed 88 g. A suspension of the salt (20 g) and Amberlite 120 (H^+) ion exchange resin (100 ml) in ethyl acetate (280 ml) was stirred until the salt had disappeared (*ca.* 0.25 h). Filtration followed by evaporation yielded the crude crystalline acid (11 g).

Both the potassium salt and the acid could be stored at −18 °C for at least 6 and 4 months, respectively, without apparent deterioration.

N-(1′,2′,3′,4′-Tetrahydro-1′-oxo-2′-naphthyl)-N-methyl-2-methoxypropenamide [16; R = C(OMe)=CH_2].—Triethylamine (5.6 ml, 40 mmol) followed by methyl chloroformate (1.9 ml, 25 mmol) were added with stirring under nitrogen to an ice-cooled solution of the crude methoxy-acid (4.1 g, 40 mmol) in dichloromethane (100 ml). The mixture was stirred for 10 min after which the *N*-methylamino-ketone hydrochloride [6] (3) (4.24 g, 20 mmol) was added followed by triethylamine (2.9 ml, 20 mmol). After 5 min, the cooling bath was removed and the mixture allowed to warm to room temperature after which it was warmed to 30 °C for 5 min. Addition of water and isolation with chloroform furnished the solid crude *product* (4.2 g) which was sufficiently pure for subsequent reactions. The pure *amide* formed long prisms (from light petroleum–benzene), m.p. 92—93 °C, $\nu_{max.}$ 1 690 (C=O), 1 640sh (amide I), and 1 630 cm^{-1} (C=C); δ 2.3—3.6 (4 H, m, 3′- and 4′-H_2), 3.0 (3 H, s, OMe), 3.55 (3 H, s, NMe), 4.25—4.7 (2 H, m, C=CH_2), 5.1—5.5 (1 H, m, 2′-H), 7.25—7.5 (3 H, m, 5′-, 6′-, and 7′-H), and 8.05 (1 H, d, *J* 9 Hz, 8′-H) (Found: C, 69.6; H, 6.6; N, 5.3. $C_{15}H_{17}NO_3$ requires C, 69.6; H, 6.6; N, 5.4%).

N-(1′,2′,3′,4′-Tetrahydro-1′-oxo-2′-naphthyl)-N-methyl-2-oxopropanamide (16; R = Ac).—(*a*) *Hydrolysis of the enol-ether.* The preceding amide (1.7 g) was added to a mixture of trifluoroacetic acid (6 ml) and water (3 ml); after 10 min dissolution had occurred. The solution was kept at room temperature for 16 h after which it was poured carefully into an excess of aqueous 1M-sodium hydrogencarbonate; the product was then isolated with benzene as a gum (1.6 g); $\nu_{max.}$ 3 300br, 1 710, 1 685br, 1 640br, and 1 615sh cm^{-1}. The latter was dissolved in warm ether (10 ml) and the solution cooled to 3 °C when crystallisation occurred. The product melted mainly between 70—73 °C but not completely until 120 °C. Trituration with ether (20 ml) gave impure oxazinone (14) (55 mg), m.p. 135—145 °C, $\nu_{max.}$ 3 260, 1 675, and 1 640 cm^{-1}.

The latter ethereal mother-liquors on evaporation, furnished a gum which was extracted with benzene–light petroleum (1 : 9; 2 × 20 ml); after being cooled, the extract yielded the amide (16; R = Ac) as plates, m.p. 72—73 °C, which still contained a small amount of the oxazinone (14). The i.r. and n.m.r. spectra of the amide were virtually identical with those of the pure amide [see (b)] except for $\nu_{max.}$ 3 200br, w and δ 1.7 (s, Me and OH) due to the presence of the oxazinone (14). The residue, a sticky solid, gave an intense green ferric chloride test presumably due to the presence of the phenol (13d).

(*b*) *Direct acylation.* Triethylamine (1.54 ml, 11 mmol) was added to a stirred mixture of 1 2,3,4-tetrahydro-2-methylaminonaphthalen-1(2*H*)-one hydrochloride [6] (2.12 g, 10 mmol) suspended in dichloromethane (50 ml) containing redistilled pyruvic acid (0.77 ml, 11 mmol) followed by dicyclohexylcarbodi-imide (2.06 g, 10 mmol) in toluene (20 ml). Some heat was evolved and after 1 h, insoluble material was filtered off and the filtrate washed successively with dilute hydrochloric acid, water, and aqueous 0.1M-sodium hydrogencarbonate. After being dried, the organic extract was evaporated to give an oil containing a small amount of dicyclohexylurea, which was removed by addition of ether (20 ml) and filtration. Evaporation yielded the crude amide (1.8 g) which was dissolved in fresh ether (10 ml) and the solution cooled to 0 °C when the product (650 mg), m.p. 75—76 °C, separated. The pure *amide* formed slender needles (benzene–light petroleum; 1 : 9), m.p. 77.5—78.0 °C, $\nu_{max.}$ 1 710 (MeC=O), 1 685 (C=O), and 1 635 cm^{-1} (amide I); δ 2.1—3.4 (4 H, m, 3′- and 4′-H), 2.42 and 2.48 (3 H, 2s, COMe), 2.91 and 2.96 (3 H, 2s, NMe), 4.75 and 5.25 (1 H, t and q, 2′-H), 7.15—7.6 (3 H, m, 5′-, 6′-, 7′-H), and 8.05 (1 H, d, *J* 9 Hz, 8′-H) (Found: C, 68.65; H, 6.2; N, 5.7. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.2; N, 5.7%).

Reaction of Pyruvamide (16; R = Ac) *and Oxazinone* (14) *with Aqueous* NaOH.—2M-Sodium hydroxide (2 ml, 4 mmol) was added to a solution of the reactants (490 mg, 2 mmol) in methanol (4 ml) whereupon heat was evolved and shortly,

a solid was deposited. Filtration, followed by washing with water (1 ml), acetone (5 ml), and ether yielded the hydrated sodium salt of the phenol (13d) (91%) with m.p. >325 °C and an i.r. spectrum identical with that of authentic material.

This work was carried out during 1974—1977 under an Allen and Hanbury Research Fellowship (see ref. 6 for full acknowledgements) and subsequently under a Boots Senior Research Fellowship. The author thanks the Directors of the latter Company for the grant and Drs. J. R. Housley and J. S. Nicholson for continued interest and a gift of 2-aminotetralone hydrochloride. N.m.r. spectra were measured by Mr. P. C. Martin and microanalyses were carried out by Mr. G. Crouch and his staff, School of Pharmacy, University of London.

[1/1717 *Received*, 5*th November*, 1981]

REFERENCES

[1] Part 3. R. E. Bowman, *J. Heterocycl. Chem.*, 1982 in the press.

[2] E. C. Kornfeld, E. S. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R B. Woodward, *J. Am. Chem. Soc.*, 1956, **78**, 3087 and references therein.

[3] (*a*) M. Julia, F. Le Goffic, J. Ingolen, and M. Baillage, *Tetrahedron Lett.*, 1969, 1569; (*b*) V. W. Armstrong, S. Coulton, and R. Ramage, *ibid.*, 1976, 4311; *Tetrahedron*, 1981, **37**, Supplement No. 1, 157; (*c*) W. Oppolzer, E. Francotti, and K. Battig, *Helv. Chim. Acta*, 1981, **64**, 478.

[4] J. C. Craig, D. M. Temple, and B. Moore, *Aust. J. Chem.*, 1961, **14**, 84.

[5] J. C. Craig and S. D. Hurt, *J. Org. Chem.*, 1979, **44**, 1108 and 1113.

[6] R. E. Bowman, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2126.

[7] A. Wohl, *Ber.*, 1907, **40**, 2286; A. Wohl and C. H. Lips, *ibid.*, p. 2294.

[8] M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, 1973, **95**, 3050.

[9] *Cf.* A. J. Duggan, M. A. Adams, R. J. Byrnes, and J. Meinwald, *Tetrahedron Lett.*, 1978, 4323.

[10] M. W. Rathke, *J. Am. Chem. Soc.*, 1970, **92**, 3222.

[11] W. Steglich and G. Hofle, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 98.

[12] B. W. Bycroft and G. R. Lee, *J. Chem Soc., Chem. Commun.*, 1975, 988.

[13] W. Kemp, ' Organic Spectroscopy,' Macmillan, London, 1975, p. 96.

[14] D. A. van Dorp and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1948, **67**, 459.

[15] (*a*) R. E. Bowman, D. D. Evans, J. Guyett, H. Nagy, J. Weale, and D. S. Weyell, *J. Chem. Soc., Perkin Trans. 1*, 1973, 438; (*b*) R. E. Bowman, D. D. Evans, J. Guyett, J. Weale, and A. C. White, *ibid.*, 1973, 760.

[16] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, vol. 1, p. 4.

[17] C. G. Wermuth and H. Marx, *Bull. Soc. Chim. Fr.*, 1964, 732.

[18] L. N. Owen and H. M. B. Somade, *J. Chem. Soc.*, 1947, 1030.