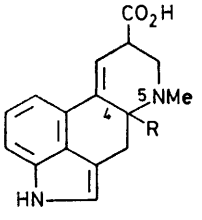
Experiments towards the Synthesis of the Ergot Alkaloids and Related Structures. Part 2.[1] New Alkylations on α-Carbon and Nitrogen in α-Amidoketones

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

The alkylation of a number of α-amidoketones in the 3,4-dihydro-naphthalen-1(2*H*)-one and -acenaphthen-5(2a*H*)-one series, involving treatment with sodium hydride (1 or 2 mol equiv.) in dimethylformamide solution and subsequent reaction with alkyl halides, has been examined. Whilst the acetamido-derivatives furnished good yields of the *C*-alkyl products (6 and 8; R^1 = Ac, R^2 = H, R^3 = alkyl), the formamido-ketones gave rise to a complex mixture on methylation, but with 2 mol equiv. of base, the *CN*-dimethylated ketones (6 and 8; R^1 = CHO, R^2 = R^3 = Me) were obtained in essentially quantitative yield. In contrast, the keto-urethanes (14) and homologous oxamic esters (17) yielded the *N*-alkyloxazolinones [(15) and (16)] and *N*-alkyloxazinediones (19), respectively. All three groups of alkyl-derivatives could be converted in high yield (>95%) by acidic hydrolysis to the corresponding *C*- or *N*-alkyl- or *CN*-dialkyl-aminoketones. In addition the oxazinediones were found to be particularly sensitive to nucleophilic attack, a property which would appear to have useful synthetic potential.

In Part 1 [1] we reported earlier work aimed at a rational synthesis of lysergic acid (1; R = H) in which the N-5 function was to be kept neutral, *e.g.* amidic, as late as possible in the synthesis to facilitate chemical manipulations. To this end we prepared the tricyclic diketo-amide (2) but were unable to effect ring-closure to the tetracyclic keto-amide (3).

An alternative approach would be to build up a structure in which the amidic function was to be part of ring D itself for which a precursor such as (4) would be required. For this purpose a general synthesis of *N*-alkylaminoketones (5; R^1 = H) was needed and our experiments in the readily accessible dihydro-naphthalenone (6) and -acenaphthenone (8) series towards



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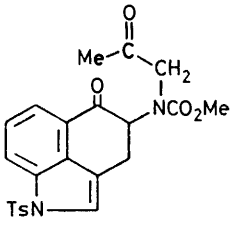

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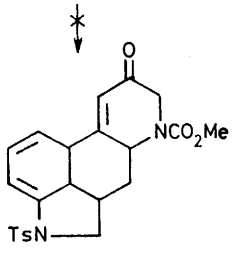
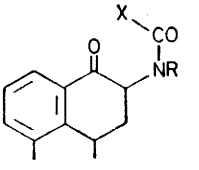


(3)

this objective form the major part of this communication; attempts to extend these procedures to the corresponding dihydrobenz[*cd*]indolone (7) series will be reported later.

A second important objective of the larger programme is the synthesis of the ' blocked ' 4-methyl-lysergic acid (1; R = Me) and to this end *C*-methylation leading to (5; R^1 = Me) has also been examined.



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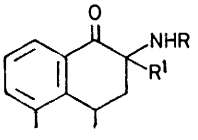

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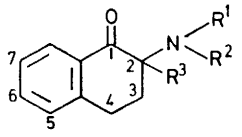
Some earlier work on the alkylation of α-amidoketones had already demonstrated the occurrence of both *N*- and *C*-alkylation. Thus, Thrift [2] had shown that treatment of the 6,7-dimethoxy-derivative of 2-acetamido-1-tetralone (6; R^1 = Ac, R^2 = R^3 = H)



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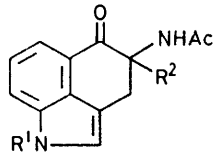

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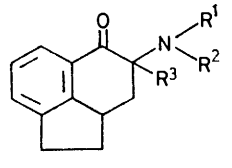


(8)

with sodium hydride (2 mol equiv.) followed by an excess of methyl iodide gave a single crystalline product in which both C-2 and N-2 methylation had occurred to give 6,7-dimethoxy-2-methyl-2-*N*-methylacetamido-1-tetralone. An identical reaction with the 4-acetamido-derivative of Uhle's ketone (7; R^1 = R^2 = H) gave a high yield of a dimethylated product (7; R^1 = R^2 = Me), in which both indolic-*N* and *C*-4 methylation had

taken place, suggesting that C-methylation may precede amido-methylation.[1]

RESULTS AND DISCUSSION

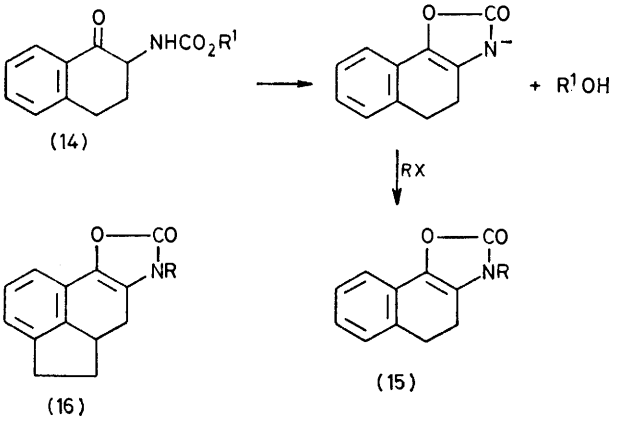
Our first experiment involved the reaction of 2-acetamido-1-tetralone (6; R^1 = Ac, R^2 = R^3 = H) with sodium hydride (1 mol equiv.) in dimethylformamide solution, and subsequent addition of methyl iodide to the resulting solution of the sodio-derivative when a rapid exothermic reaction took place; the sole crystalline product (isolated in 76% yield) proved to be the product of C-2 methylation, *i.e.* 2-acetamido-2-methyl-1-tetralone (6; R^1 = Ac, R^2 = H, R^3 = Me) which could be converted by boiling 5M-hydrochloric acid into 2-amino-2-methyl-1-tetralone (6; R^1 = R^2 = H, R^3 = Me) hydrochloride in virtually quantitative yield; the corresponding 2-prop-2-ynyl derivative was obtained similarly. C-Methylation also occurred when 4-acetamido-3,4-dihydro-acenaphthen-5(2a*H*)-one [3] was subjected to the same procedures yielding (8; R^1 = Ac, R^2 = H, R^3 = Me) which again could be hydrolysed to the corresponding 4-amino-4-methylketone (8; R^1 = R^2 = H, R^3 = Me) hydrochloride.

It seemed a reasonable assumption that the proportion of C- and N-alkylation in such systems, other factors such as steric hindrance apart, would depend on the relative acidities of the enolic and amidic groupings respectively and the latter, in turn, upon the strength of the acid from which it was derived. In support of this, the sodio-derivative of trifluoroacetamido-1-tetralone (6; R^1 = CF_3CO, R^2 = R^3 = H) reacted with methyl iodide, albeit relatively slowly due presumably to steric hindrance, to give an almost quantitative yield of the corresponding *N*-methyl derivative (6; R^1 = CF_3CO, R^2 = Me, R^3 = H) which furnished 2-(methylamino)-1-tetralone (6; R^1 = R^3 = H, R^2 = Me) on acidic hydrolysis. Attempts to extend this reaction to other halides such as prop-2-ynyl bromide and benzyl chloride failed, indicating that this procedure was of limited utility; a similar failure was also encountered in attempts to methylate 2-pivalamido-1-tetralone (6; R^1 = Me_3C–CO, R^2 = R^3 = H), due again presumably to steric hindrance.

It was expected that alkylation of sulphonamidoketones would take place solely at nitrogen, but it would appear that their sodio-derivatives are unstable in dimethylformamide solution since reaction of 2-methanesulphonamido-1-tetralone (6; R^1 = $MeSO_2$, R^2 = R^3 = H) with sodium hydride and then methyl iodide yielded only an evil-smelling gum.

Finally we turned our attention to α-formamidoketones, having in mind the fact that formic acid is some ten times stronger an acid than acetic acid. In the event, reaction of the sodio-derivative of 2-formamido-1-tetralone (6; R^1 = CHO, R^2 = R^3 = H) with methyl iodide gave a complex mixture from which the only isolated crystalline product was starting material in 25% yield. Such a result is consistent with a situation where, steric hindrance being minimal, the acidities of the enolic and formamido-groups were of a similar order giving rise to a mixture of starting amide, *C*- and *N*-monomethyl, and *CN*-dimethyl derivatives. In line with this suggestion was the experimental finding that treatment with sodium hydride (2 mol equiv.) followed by an excess of methyl iodide gave an essentially quantitative yield of the *CN*-dimethyl derivative (6; R^1 = CHO, R^2 = R^3 = Me), hydrolysed readily to 2-methyl-2-methylamino-1-tetralone (6; R^1 = H, R^2 = R^3 = Me); the corresponding dimethyldihydroacenaphthenone amide (8; R^1 = CHO, R^2 = R^3 = Me) and amine (8; R^1 = H, R^2 = R^3 = Me) could be obtained similarly.

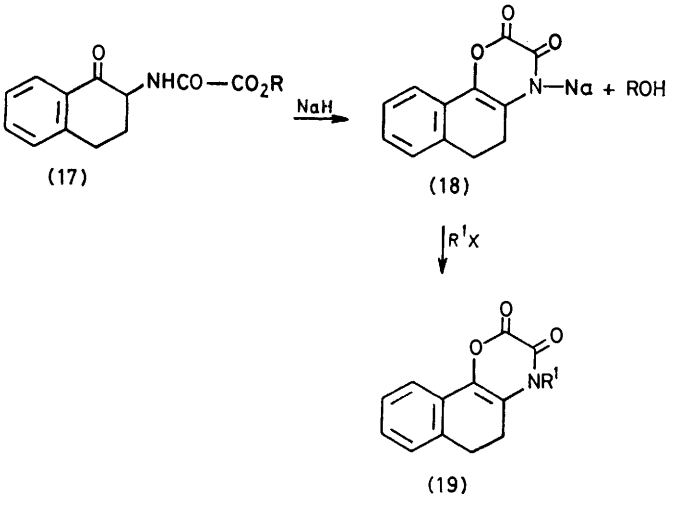
Alkylation of keto-urethanes took a different course, which eventually proved to be of considerable preparative value. Thus, the keto-urethane (14; R^1 = Me) on treatment with sodium hydride (1 mol equiv.) in dimethylformamide solution readily formed a sodio-derivative which reacted rapidly with methyl iodide. The major, highly crystalline and sparingly soluble, product ($\nu_{max.}$ 1 750vs cm^{-1}) proved to be the *N*-methyloxazolinone (15; R = Me) arising from ring-closure involving elimination of methanol during reaction with sodium hydride. A somewhat improved yield could be



obtained by removal of methanol produced during the reaction by azeotropic distillation. These oxazolinones proved resistant to many reagents including strong alkali and both acid- and base-catalysed methanolysis. It was this latter finding that prompted us to attempt the reaction in the presence of 2 mol equiv. of sodium hydride, whereupon excellent yields (>80%) of *N*-alkyloxazolinones were routinely obtained in both the dihydro-naphthalenone and -acenaphthenone series; the reaction appeared to be of wide application, since other halides such as prop-2-ynyl bromide and benzyl chloride could be used to give similarly high yields of the corresponding *N*-prop-2-ynyl and -benzyl compounds (16; R = CH_2–C≡CH and CH_2Ph, respectively); the benzyl ester (14; R^1 = CH_2Ph) behaved similarly but not the t-butyl ester (14; R^1 = Bu^t) which was recovered unchanged. In addition these *N*-alkyl derivatives could be obtained from the parent oxazolinone (15; R = H) by reaction with alkyl halides in the presence of anhydrous potassium carbonate in refluxing acetone.

We were misled by earlier literature statements [4] that oxazolinones were resistant to strong acids and there was a considerable delay before we found that, in fact, these compounds are readily split by a mixture of propan-2-ol and concentrated hydrochloric acid (2 : 1) at 95 °C for 1.5 h to give an essentially quantitative yield of the desired *N*-alkylaminoketones. The ready isolation of these oxazolinones, on account of their sparing solubility and strong crystallising properties, and their subsequent facile hydrolysis, makes available a wide group of substituted aminoketones for the first time.

Prior to achieving this breakthrough, we examined a similar series of reactions with the homologous oxamic esters (17; R = Me or Et) in the expectation, fully realised, that the resulting oxaziniediones (19) would be more susceptible to ring-opening.

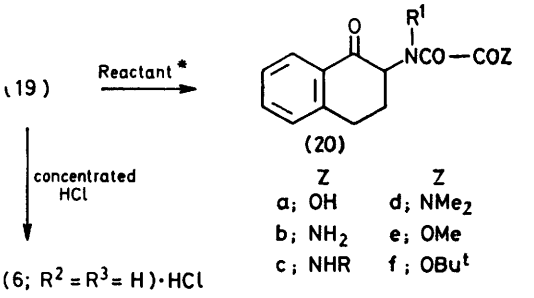


(17) (18) (19)

The initial cyclisation in this case appeared to be accompanied by a substantial back-reaction, and forcing conditions involving removal of ethanol or methanol were required. Surprisingly, the deep yellow sodio-compound (18) proved sparingly soluble even in hot dimethylformamide, and could be isolated by filtration and converted to the parent compound (19; R^1 = H) by protonation, or reacted *in situ* with alkyl halides to give (19; R^1 = Alkyl) in reasonable yield. Like the corresponding oxazolinones, these oxaziniediones were high melting, sparingly soluble and with strong crystallising powers which facilitated their isolation in a pure condition; indeed, many crystallised spontaneously from the hot solvent dimethylformamide, during its evaporation *in vacuo*. Surprising also was the strikingly yellow colour of both the parent dione (19; R^1 = H) and its *N*-alkyl derivatives. The i.r. absorption spectra of these compounds are characteristic and worthy of comment. In the region 2 500—1 600 cm^{-1}, all the simple members described herein, and more complex ones to be described later, possess a particularly strong band at 1 770—1 760 cm^{-1} (enol-lactam) and two strong bands at *ca.* 1 680 and 1 665—1 655 cm^{-1}, provisionally attributed to double bond (C=C–O) [5] and amide I absorptions, respectively. An unexpected and valuable finding was the reaction of the sodio-compound (18) with chloroacetone to give the *N*-acetonyl derivative (19; $R^1 = CH_2COMe$) in high yield.

As will be reported later, two particularly important ring systems which we planned to use proved unstable under the prolonged reaction conditions required for reasonable conversions, and we were forced to look for milder procedures. Eventually, it was found that treatment of the oxamic esters (17) in dimethylformamide solution with potassium t-butoxide at room temperature led to the rapid separation of the sparingly-soluble potassium salt (19; R^1 = K); reaction with methyl iodide was complete in *ca.* 1 min and furnished the *N*-methyldione (19; R^1 = Me) in 87% yield. Addition to dilute mineral acid gave the parent dione (19; R^1 = H) in similar yield, by far the best procedure. Reactions using chloroacetone as alkylating agent proved particularly informative. Under the same conditions, but after a much longer reaction time, the *N*-acetonyldione was obtained in only 55% yield. In contrast was the 90% crude yield obtained when the sodio-derivative (18) (obtained from the parent dione and sodium hydride) was employed and the 67% yield when the potassium salt was generated from the parent dione and potassium t-butoxide. It seemed possible that these lower yields could be attributed to the operation of a fission reaction involving attack of t-butoxide ion on the *N*-alkyldione and this was readily demonstrated when treatment of the *N*-methyldione (19; R^1 = Me) with potassium t-butoxide (preferably >1 mol) in tetrahydrofuran brought about a rapid conversion to the ' open ' t-butyl oxamic ester (20f; R^1 = Me). This reaction, involving the release of a masked carbonyl function under such mild conditions, has obvious synthetic uses which will be reported later.

As expected, these oxaziniediones proved sensitive to both acidic and nucleophilic reagents, particularly the latter. Thus, for example, the sparingly soluble *N*-benzyldione (19; $R^1 = CH_2Ph$) in suspension in methanol



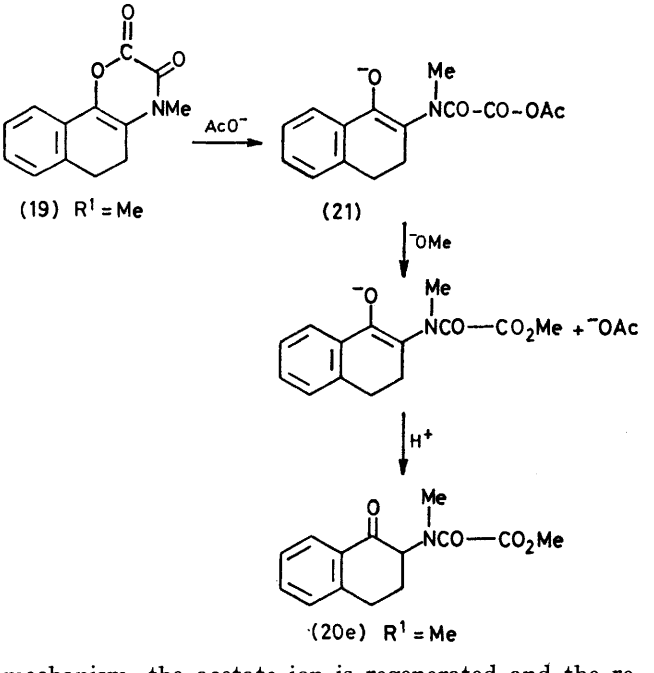
*(a) OH^-; (b) NH_3; (c) RNH_2; (d) Me_2NH; (e) OMe^- or H^+–MeOH; (f) Bu^tO^-

was brought into solution with evolution of heat in <1 min on addition of either dilute sodium hydroxide or dimethylamine to give the oxamic-derivatives (20a and d, respectively; $R^1 = CH_2Ph$).

Equally rapid was ring-opening by methanol in the

presence of a catalytic amount of magnesium methoxide to give the methyl ester (20e; $R^1 = CH_2Ph$), which was also obtained more slowly by acid-catalysed methanolysis; other examples are reported in the Experimental section. Complete hydrolysis could be effected by treatment with concentrated hydrochloric acid–propan-2-ol to give the known [6] (benzylamino)tetralone (6; $R^1 = CH_2Ph$, $R^2 = R^3 = H$) hydrochloride; the corresponding (acetonylamino)tetralone (6; $R^1 = CH_2COMe$, $R^2 = R^3 = H$) hydrochloride was obtained similarly from the 4-acetonyldione (19; $R^1 = CH_2COMe$) in virtually quantitative yield, this method proving far superior to that described earlier by us.[6]

An alternative and very mild methanolysis procedure was discovered when examining the action of methanolic potassium acetate on our oxazinediones. Amongst the many curious reactions undergone by derivatives of oxalic acid, one of the more interesting, first reported in 1893,[7] is the action of potassium acetate on alcoholic solutions of oxalic esters which gives rise to potassium alkyl oxalates in good yield. It was expected by analogy that the *N*-methyldione (19; $R^1 = Me$) on reaction with methanolic potassium acetate would furnish the potassium salt of the ' open ' oxamic acid, but the extremely rapid reaction gave instead the corresponding methyl ester (20e; $R^1 = Me$) in almost quantitative yield, presumably *via* the mixed anhydride (21). By this



mechanism, the acetate ion is regenerated and the reaction should only require a catalytic quantity, as was found to be the case.

Methanolysis of oxazinediones can also be catalysed by organic bases as was found during an attempted reaction of the *N*-methyldione (19; $R^1 = Me$) in methanolic suspension with t-butylamine, when rapid solution took place followed by separation of the methyl ketooxamate (20e; $R^1 = Me$) in 62% yield; triethylamine (1.0 or 0.1 mol equiv.) furnished the same ester with equal rapidity and in 93% yield, thus providing an even milder ring-opening procedure. In tetrahydrofuran, t-butylamine at 40 °C slowly furnished the expected *N*-t-butyloxamide (20c; $R = Bu^t$, $R^1 = Me$).

EXPERIMENTAL

Unless stated otherwise, i.r. spectra of solids were determined for Nujol mulls and u.v. spectra were measured for solutions in 96% ethanol. Anhydrous reagents were high-grade commercial materials which had been stood over 4A molecular sieves for at least 48 h before use. All evaporations were carried out with a rotary evaporator *in vacuo*. Petrol refers to light petroleum, b.p. 60—80 °C.

Starting Amides.—These were prepared from 2-amino-3,4-dihydronaphthalen-1(2*H*)-one [8] and 4-amino-3,4-dihydroacenaphthen-5(2a*H*)-one [3] hydrochlorides by one or more of the following methods: (*A*) A solution of the amine salt in ice–water was treated with acetic anhydride or alkyl chloroformate (1.2 mol) with vigorous stirring, and an excess of sodium hydrogencarbonate added in portions. Stirring was continued until gas evolution ceased and the product obtained by filtration.

(*B*) A suspension of the amine salt (1 mol) in anhydrous dichloromethane was stirred under nitrogen in an ice–water bath and the acylating agent (*e.g.* acetic–formic anhydride,[9] ethyl and methyl oxalyl chlorides, methanesulphonyl chloride, trimethylacetyl chloride, and di-t-butyl dicarbonate) (1.5 mol) added; triethylamine (2.5 mol) was then added portionwise so as to keep the temperature below 12 °C. Stirring was continued for 15 min, whereupon water was added, the cooling bath removed and the mixture stirred for a further 30 min. The organic phase was washed successively with 0.5M-hydrochloric acid, 0.1M-sodium hydrogencarbonate, and water, dried ($MgSO_4$), and evaporated to yield, after trituration with ether, the crystalline amide.

(*C*) As for (*B*) except that triethylamine was omitted and trifluoroacetic anhydride (2.25 mol) added over 5 min when a clear solution was obtained. Toluene (100 ml) was added and the mixture evaporated.[10]

When the starting salt was hydrated and the acylating agent water-sensitive, appropriate additional equivalents of the latter and triethylamine [in (*B*) but not (*C*)] were employed.

The naphthalenone amides thus prepared are listed in Table 1; also prepared by method (*B*) were 4-acetamido-3,4-dihydroacenaphthen-5(2a*H*)-one [3] and 4-*formamido*-3,4-*dihydroacenaphthen*-5(2aH)-*one* as needles (from ethanol), m.p. 168 °C; $\nu_{max.}$ 3 280 (N–H), 1 680 (C=O), 1 640 (amide I), and 1 530 (amide II) cm^{-1} (Found: C, 72.2; H, 6.0; N, 6.4. $C_{13}H_{13}NO_2$ requires C, 72.5; H, 6.1; N, 6.5%).

General Procedures for Alkylation of α-Amidoketones.—(A) *Monoalkylation.* Sodium hydride (80% dispersion in oil; 0.1 mol) was covered with dimethylformamide (50 ml) under nitrogen and a solution of the amidoketone (0.1 mol) in dimethylformamide (100 ml) added with stirring at such a rate as to control foaming and keep the temperature below 40 °C. When evolution of gas ceased, alkyl halide (0.2 mol) was added cautiously with cooling, and the mixture kept at room temperature for 0.5 h, and if necessary at 60 °C until neutral, whereupon solvent was removed *in vacuo* (bath temperature <100 °C). Addition of water usually afforded crystalline material which was

obtained by filtration; otherwise the product was isolated with benzene.

In this manner were prepared *2-acetamido-2-methyl-3,4-dihydronaphthalen-1(2H)-one* (6; R^1 = Ac, R^2 = H, R^3 = Me) (75%) as prisms (from 2-methoxyethanol), m.p. 164 °C; $\nu_{max.}$ 3 220—3 110 (bonded N–H), 1 685 (C=O), 1 620 (amide I) and 1 540 (amide II) cm^{-1} (Found: C, 71.9; H, 7.2; N, 6.3. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%): *2-acetamido-2-prop-2-ynyl-3,4-dihydronaphthalen-1(2H)-one* (6; R^1 = Ac, R^2 = H, R^3 = CH_2–C≡CH) (65%) as needles (from 2-methoxyethanol), m.p. 146 °C; $\nu_{max.}$ 3 360 (N–H), 3 260 (C≡CH), 1 680 (C=O), 1 650 (amide I) and 1 510 (amide II) cm^{-1} (Found: C, 74.3; H, 6.1; N, 5.6. $C_{15}H_{15}NO_2$ requires C, 74.6; H, 6.3; N, 5.8%): *4-acetamido-4-methyl-3,4-dihydroacenaphthen-5(2aH)-one* (8; R^1 = Ac, R^2 = H, R^3 = Me) (82%) as prisms (from xylene), m.p. 193 °C; $\nu_{max.}$ 3 260 (N–H), 1 685 (C=O), 1 635 (amide I) and 1 550 (amide II) cm^{-1} (Found: C, 74.2; H, 7.3; N, 5.7. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.0; N, 5.8%): 2-(N-*methyltrifluoroacetamido*)-*3,4-dihydronaphthalen-1(2H)-one* (6; R^1 = $COCF_3$, R^2 = Me, R^3 = H) (4 h reaction time at 50 °C) (95%) as felted needles (from CCl_4–petrol), m.p. 123 °C; $\nu_{max.}$ 1 715 (sh), 1 700 (sh), and 1 685 (sh) (amide I), and 1 675 (C=O) cm^{-1} (Found: C, 57.5; H, 4.6; N, 5.0. $C_{13}H_{12}F_3NO_2$ requires C, 57.6; H, 4.45; N, 5.2%).

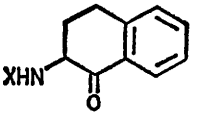
(B) CN-*Dimethylation*. A solution of the formamidoketone (0.1 mol) in dimethylformamide (100 ml) was added with high-torque stirring under nitrogen to a suspension of sodium hydride (0.2 mol) in the same solvent (200 ml) as in (A) and the mixture, which had become semi-solid, kept at 40—50 °C for 0.5 h; methyl iodide (0.3 mol) was then added with cooling and when neutral, the reaction mixture worked up as in (A). In this way were prepared *2-methyl-2-(N-methylformamido)-3,4-dihydronaphthalen-1(2H)-one* (6; R^1 = CHO, R^2 = R^3 = Me) (crude yield 100%) as needles [from petrol–benzene (5 : 1)], m.p. 91 °C; $\nu_{max.}$ 1 690 (C=O) and 1 662 (amide I) cm^{-1} (Found: C, 71.75; H, 7.0; N, 6.4. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%): *4-methyl-4-(N-methylformamido)-3,4-dihydroacenaphthen-5(2aH)-one* (8; R^1 = CHO, R^2 = R^3 = Me) (crude yield 93%) which crystallised in prisms [from benzene–petrol (2 : 1)], m.p. 157 °C; $\nu_{max.}$ 1 685 (C=O) and 1 652 (amide I) cm^{-1} (Found: C, 74.1; H, 7.1; N, 5.7. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.0; N, 5.8%). These alkylations could also be effected more conveniently but in lower yield under identical conditions in tetrahydrofuran solution using solid potassium t-butoxide (Aldrich, 3 mol) as base and an excess of methyl iodide.

Hydrolysis of Amidoketones.—(*A*). The amide (1 g) was refluxed with 5M-hydrochloric acid (6 ml) for 6 h and the solution, after treatment with charcoal, evaporated to dryness. The residue was then dissolved in propan-2-ol (10 ml) and re-evaporated to dryness. After repeating this procedure, the residual gum was boiled with acetone (10 ml) when the aminoketone hydrochloride crystallised spontaneously; yield >95% and of sufficient purity for subsequent use.

In this manner were prepared: *2-amino-2-methyl-3,4-dihydronaphthalen-1(2H)-one* (6; R^1 = R^2 = H, R^3 = Me) *hydrochloride* as small needles (from propan-2-ol–diethyl ether), m.p. 254 °C; $\nu_{max.}$ 2 620, 2 540, and 2 500 (NH_3^+), and 1 690 (C=O) cm^{-1} (Found: C, 62.1; H, 6.5; N, 6.5. $C_{11}H_{14}ClNO$ requires C, 62.4; H, 6.7; N, 6.6%): and *4-amino-4-methyl-3,4-dihydroacenaphthen-5(2aH)-one* (8; R^1 = R^2 = H, R^3 = Me) *hydrochloride* as prisms (from propan-2-ol–diethyl ether), m.p. 287 °C; $\nu_{max.}$ 2 620, 2 560, and 2 520 (NH_3^+), and 1 690 (C=O) cm^{-1} (Found: C, 65.7; H, 6.7; N, 5.9. $C_{13}H_{16}ClNO$ requires C, 65.7; H, 6.8; N, 5.9%).

(*B*) The amide (1 g) was boiled with propan-2-ol–concentrated hydrochloric acid (2 : 1) (15 ml) for 1.5 h and worked up as in (*A*). Thus were prepared *2-methylamino-3,4-dihydronaphthalen-1(2H)-one* (6; R^1 = R^3 = H, R^2 = Me) *hydrochloride* as needles (from propan-2-ol plus a few drops of 2M-hydrochloric acid), m.p. 215 °C, $\nu_{max.}$ 2 680, 2 470, and 2 425 (NH_2Me^+), and 1 680 (C=O) cm^{-1} (Found: C, 62.6; H, 6.7; N, 6.6. $C_{11}H_{14}ClNO$ requires C, 62.4; H, 6.7; N, 6.6%): and *2-methyl-2-methylamino-3,4-dihydronaphthalen-1(2H)-one* (6; R^1 = H, R^2 = R^3 = Me) *hydrochloride* as prisms (from the same solvent mixture), m.p. 207 °C; $\nu_{max.}$ 2 700—2 640 and 2 420 (NH_2Me^+), and 1 685 (C=O) cm^{-1} (Found: C, 63.8; H, 7.1; N, 6.1. $C_{12}H_{16}ClNO$ requires C, 63.85; H, 7.15; N, 6.2%): 4-

TABLE 1



X	Method of preparation	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N	$\nu_{max.}$(cm^{-1}) N–H	C=O	Amide I	Amide II
CHO [a]	B	127	70.0	5.9	7.4	$C_{11}H_{11}NO_2$	69.8	5.9	7.4	3 315	1 685	1 650	1 510(sh)
COMe [b]	A	126	70.8	6.45	6.8	$C_{12}H_{13}NO_2$	70.9	6.45	6.9 [c]	3 260	1 685	1 635	1 545
$COCMe_3$ [d]	B	101	73.5	7.9	5.6	$C_{15}H_{19}NO_2$	73.4	7.8	5.7	3 300	1 690	1 638	1 545
$COCF_3$ [e]	C	129	56.0	3.9	5.3	$C_{12}H_{10}F_3NO_2$	56.0	3.9	5.45	3.280	1 685	1 705	1 555
SO_2Me [f]	B	127	55.1	5.5	5.9	$C_{11}H_{13}NO_3S$	55.2	5.5	5.9	3 240	1 690		
CO_2Me [g]	A	125	65.8	6.0	6.3	$C_{12}H_{13}NO_3$	65.7	6.0	6.4	3 290	1 680	1 718	1 540
CO_2CH_2Ph [a]	A	85	73.4	5.9	4.7	$C_{18}H_{17}NO_3$	73.2	5.8	4.7	3 300	1 685	1 710	1 515
CO_2Bu^t [h]	B	122	69.2	7.3	5.2	$C_{15}H_{19}NO_3$	68.9	7.3	5.4	3 370	1 685	1 710	1 530
$COCO_2Me$ [a]	B	134	63.1	5.3	5.7	$C_{13}H_{13}NO_4$	63.15	5.3	5.7	3 220	1 740,[i] 1 690(sh)	1 675	1 535
$COCO_2Et$ [e]	B	119	64.4	5.7	5.4	$C_{14}H_{15}NO_4$	64.4	5.8	5.4	3 310	1 745,[i] 1 700	1 672	1 535

[a] Needles from benzene. [b] Needles from benzene–petrol. [c] Calculated (F. Zymalkowski and J. Rimek, *Arch. Pharm.*, 1961, **294**, 281). [d] Needles from petrol. [e] Needles from CCl_4. [f] Prisms from MeOH. [g] Needles from 95% EtOH. [h] Laths from petrol. [i] α-Keto-ester.

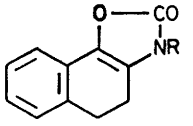
methyl-4-methylamino-3,4-dihydroacenaphthen-5(2aH)-one (8; R^1 = H, R^2 = R^3 = Me) *hydrochloride* as prisms (from 2M-hydrochloric acid), m.p. 288 °C, $\nu_{max.}$ 2 625, 2 580, and 2 410 (NH_2Me^+), and 1 680 (C=O) cm^{-1} (Found: C, 66.6; H, 6.9; N, 5.5. $C_{14}H_{18}ClNO$ requires C, 66.8; H, 6.8; N, 5.6%).

Alkylation of Keto-urethanes.—(1) *With sodium hydride* (1 mol). The reaction was carried out and worked up exactly as above in (*A*) except that the solvent was benzene–dimethylformamide (1 : 2) (300 ml per 0.1 mol) and the flask was attached to a Fenske column (20 cm in length) fitted with a variable take-off head. After addition of urethane was completed, the reaction mixture was heated with stirring, and the methanol which was formed in the reaction removed slowly as its azeotrope with benzene in the usual manner (3—5 h); treatment with acetic acid or alkyl halide and isolation of product was carried out as before. Yields varied from 50—60% of the theoretical.

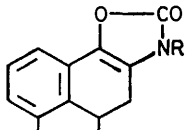
2 460, and 2 380 (NH_2Me^+), and 1 690 (C=O) cm^{-1} (Found: C, 65.8; H, 6.8; N, 5.8. $C_{13}H_{16}ClNO$ requires C, 65.6; H, 6.8; N, 5.9%).

5,6-Dihydronaphth[1,2-b]-*1,4-oxazine-2,3(4H)-diones* (19).—(a) *From oxamic esters* (18; R = Me or Et). (1) *With sodium hydride.* The reaction was carried out exactly as described above for keto-urethanes [method (A)] (600 ml of mixed solvents per 0.1 mol). Surprisingly, the reaction with sodium hydride did not occur until the internal temperature reached 70 °C and it was kept there until gas evolution ceased and then heated to boiling; elimination of methanol or ethanol took 3 h. The cooled mixture could be filtered to give, after washing with ether, the yellow sodio-derivative (18) (75%) which was decomposed by stirring with glacial acetic acid (50 ml per 0.05 mol) for 10 min, followed by addition of water (100 ml) to give the parent *dione* (19; R^1 = H) (70%) as golden yellow prisms (from diethylene glycol–dimethyl ether), m.p. 276 °C;

TABLE 2



(15)



(16)

Compound	M.p. (°C)	Found % C	H	N	Formula	Required % C	H	N	$\nu_{max.}$ cm^{-1})
(15; R = H) [a,b]	203	70.8	5.0	7.4	$C_{11}H_9NO_2$	70.6	4.85	7.5	3 250—3 080 (bonded NH), 1 750 (oxazolinone), 1 720
(15; R = Me) [c,d]	143	71.5	5.6	6.9	$C_{12}H_{11}NO_2$	71.6	5.5	7.0	1 750
(15; R = CH_2–C≡CH) [e]	136	75.1	5.0	6.25	$C_{14}H_{11}NO_2$	74.65	4.9	6.2	3 230 (C≡CH), 2 105 (C≡C), 1 755
(15; R = CH_2Ph) [e]	155	77.7	5.4	5.1	$C_{18}H_{15}NO_2$	78.0	5.45	5.05	1 745 (br)
(16; R = Me) [e]	201	74.1	5.8	6.1	$C_{14}H_{13}NO_2$	74.0	5.8	6.2	1 745 (br)
(16; R = CH_2–C≡CH) [e]	169	76.8	5.4	5.7	$C_{16}H_{13}NO_2$	76.5	5.2	5.6	3 260 (C≡CH), 2 125 (C≡C), 1 750 (br)

[a] Needles from 2-methoxyethanol. [b] $\lambda_{max.}$ 226, 292, and 304 (sh) nm (log ε 4.13, 4.19, and 4.09); δ [$(CD_3)_2SO$] 2.68 (2 H, d, *J* 8 Hz, CH_2), 2.95 (2 H, d, *J* 8 Hz, CH_2), 7.0—7.3 (4 H, m, Ar-H), and 11.0 br (1 H, NH). [c] Rhombs from EtOH. [d] $\lambda_{max.}$ 226, 294, and 306 (sh) nm (log ε 4.28, 4.20, and 4.11); δ ($CDCl_3$) 2.62 (2 H, d, *J* 7 Hz, CH_2), 3.05 (2 H, d, *J* 7 Hz, CH_2), 3.18 (3 H, s, NMe), and 7.0—7.25 (4 H, m, Ar-H). [e] Needles from EtOH.

(2) *With sodium hydride* (2 mol). Reaction conditions were exactly those described for *CN*-dialkylation (see earlier) except that the reaction with sodium hydride was carried out at 45—50 °C; yields were usually >80%.

(3) The *N*-alkyl compounds could also be prepared by treatment of the parent oxazolinone (15; R = H) (0.1 mol) with alkyl halide (0.3 mol) in acetone (200 ml) in the presence of anhydrous potassium carbonate (dried for 16 h at 160 °C; [11] 0.3 mol) with stirring at reflux temperature for 6 h; filtration and evaporation then furnished the product in essentially quantitative yield. Compounds prepared by the above routes are listed in Table 2.

N-*Alkylaminoketones.*—Hydrolysis of the appropriate oxazolinones (Table 2) by the propan-2-ol–concentrated hydrochloric acid technique [see (*B*) above] furnished the following amine hydrochlorides in virtually quantitative yield: 2-methylamino- and 2-benzylamino-3,4-dihydronaphthalen-1(2*H*)-one (6; R^1 = R^3 = H, R^2 = Me and CH_2Ph) hydrochlorides, identical with material described above and earlier,[6] respectively: *4-methylamino-3,4-dihydroacenaphthen-5(2aH)-one* (8; R^1 = R^3 = H, R^2 = Me) *hydrochloride* as prisms (from propan-2-ol plus a few drops of 2M-hydrochloric acid), m.p. 224 °C; $\nu_{max.}$ 2 715, 2 490, $\lambda_{max.}$ 213, 250, and 289 nm (log ε 4.16, 4.15, and 3.38); $\nu_{max.}$ 3 200—3 00 (bonded N–H), and 1 765, 1 690, and 1 675 (amide I) cm^{-1}; δ[$(CD_3)_2SO$] 2.55 (2 H, d, *J* 9 Hz, CH_2), 2.83 (2 H, d, *J* 9 Hz, CH_2), 7.05—7.35 (4 H, m, Ar-H), and 11.5 (1 H, br NH) (Found: C, 66.75; H, 4.2; N, 6.5. $C_{12}H_9NO_3$ requires C, 67.0; H, 4.2; N, 6.5%). Alternatively, the sodio-derivative without isolation could be alkylated by addition of alkyl halide and the product isolated as previously to give *4-acetonyl-5,6-dihydronaphth*[1,2-b]-*1,4-oxazine-2,3(4H)-dione* (19; R^1 = CH_2COMe) as yellow prisms (from acetonitrile) (62%), m.p. 223 °C; $\nu_{max.}$ 1 758, 1 728 (MeCO), 1 687, and 1 662 (amide I) cm^{-1} (Found: C, 66.2; H, 4.8; N, 5.3. $C_{15}H_{13}NO$ requires C, 66.4; H, 4.8; N, 5.2), and *4-benzyl-5,6-dihydronaph*[1,2-b]-*1,4-oxazine-2,3(4H)-dione* as yellow rhombs (19; R^1 = CH_2Ph) (from benzene), m.p. 167 °C; $\nu_{max.}$ 1 755, 1 680, and 1 655 (amide I) cm^{-1} (Found: C, 74.9; H, 4.9; N, 4.6. $C_{19}H_{15}NO_3$ requires C, 74.7; H, 4.95; N, 4.6%).

(2) *With potassium t-butoxide.* A solution of potassium t-butoxide (Aldrich; 6.05 g, 54 mmol) in dimethylformamide (30 ml) was added in one lot with powerful stirring under nitrogen to a solution of the oxamic ethyl ester (13.05 g, 50 mmol) in dimethylformamide (300 ml) whereupon

a deep red colour developed and heat was evolved. Within a short time a yellow solid began to precipitate and stirring became difficult; over the next 15 min the orange mass turned yellow and stirring became easier. After a further 15 min the alkyl halide (100 mmol) was added and stirring was continued at room temperature, and if necessary at 50—60 °C, until the mixture was neutral, whereupon most of the solvent was removed *in vacuo*; addition of water furnished the crystalline product. The *4-methyl derivative* (19; R^1 = Me) (87%) formed yellow prisms (from diethyleneglycol dimethyl ether), m.p. 203 °C; $\lambda_{max.}$ 213, 225, 279 (sh), 287, 299 (sh), and 347 nm (log ε 4.06, 4.06, 3.96, 3.98, 3.88, and 3.71); $\nu_{max.}$ 1 765, 1 680, and 1 665 (amide I) cm^{-1} (Found: C, 68.0; H, 4.9; N, 6.2. $C_{13}H_{11}NO_3$ requires C, 68.1; H, 4.8; N, 6.1%); the corresponding 4-acetonyldione was also obtained similarly in 55% yield. In addition, the parent dione could be obtained most conveniently in 84% yield by portionwise addition of the yellow suspension of its potassium salt (50 mmol) to a mixture of 2M-hydrochloric acid (50 ml), water (600 ml), and ice (to 1 l) with stirring and subsequent filtration.

(b) *From the parent dione* (19; R^1 = H). (1) *With sodium hydride.* Sodium hydride (150 mg of an 80% dispersion in oil, 5 mmol) was added to a solution of the dione (1.08 g, 5 mmol) in dimethylformamide (30 ml) at 60 °C; after 0.5 h, chloroacetone (930 mg, 10 mmol) was then added and during the next 15 min, the insoluble sodium salt had completely dissolved and the solution was virtually neutral. After a further 15 min at 60 °C, the solvent was removed *in vacuo* and the residue treated with water, dried, and washed with a little ether to give the 4-acetonyl derivative (1.2 g of crude material), m.p. 204—208 °C (90%).

(2) *With potassium t-butoxide.* A solution of the base (1.55 g, 13.8 mmol) in dimethylformamide (12 ml) was added in one portion with stirring under nitrogen to a solution of the dione (2.71 g, 12.6 mmol) in dimethylformamide (65 ml). The deep red solution soon became unstirrable and 5 min later, chloroacetone (2.3 g, 25 mmol) was added. The mixture was shaken manually for a short time and then stirred for 15 min when a neutral hazy solution was obtained. Solvent was then removed *in vacuo* and the residue triturated with water and then a little methanol to give the 4-acetonyl derivative (19; R^1 = CH_2COMe) (2.30 g, 67%), m.p. 212—214 °C.

(3) *With potassium carbonate.* The reaction was effected exactly as in (1) except that anhydrous potassium carbonate (dried at 160 °C for 16 h; [11] 3 mol) was used in place of sodium hydride and the reaction time at 60 °C was 3 h. By use of prop-2-ynyl bromide, the *4-prop-2-ynyl-oxazinedione* (19; R^1 = CH_2–C≡CH) (46%) was obtained as yellow prisms (from toluene), m.p. 205 °C; $\nu_{max.}$ 3 230 (C≡CH), 2 120 (C≡C), and 1 765, 1 675, and 1 655 (amide I) cm^{-1} (Found: C, 71.3; H, 4.4; N, 5.5. $C_{15}H_{11}NO_3$ requires C, 71.1; H, 4.4; N, 5.5%); the 4-benzyl derivative was likewise secured in 35% yield.

Reactions of Some N-*Alkyloxazinediones* (19).—(a) *With* OH^-. 2M-sodium hydroxide (1.2 ml) was added to a suspension of the *N*-benzyl compound (19; R^1 = CH_2Ph) (600 mg) in methanol (4 ml) whereupon heat was evolved. The clear solution was evaporated and the residue after treatment with 2M-hydrochloric acid was extracted with chloroform. Evaporation and crystallisation from ether (25 ml) gave N-*benzyl*-N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthalenyl*)*oxamic acid* (20a; R^1 = CH_2Ph) *etherate* as colourless needles (570 mg), m.p. 73 °C with evolution of gas; $\nu_{max.}$ 3 550—3 100w,br (bonded OH), 1 725 (CO_2H), 1 690 (C=O), and 1 660 (amide I) cm^{-1} (Found: C, 69.3; H, 6.6; N, 3.8. $C_{19}H_{17}NO_4 \cdot (C_2H_5)_2O$ requires C, 69.5; H, 6.9; N, 3.5%). Crystallisation from 50% EtOH furnished the corresponding neutral *ethyl ester hydrate* as needles m.p. 91 °C; $\nu_{max.}$ 1 730 (CO_2Et), 1 690 (C=O), and 1 660 (amide I) cm^{-1} (Found: C, 68.1; H, 6.1; N, 4.05. $C_{21}H_{21}NO_4 \cdot H_2O$ requires C, 68.3; H, 6.3; N, 4.0%).

(b) *With* H^+–H_2O. (1) Hydrolysis of the same dione with propan-2-ol–concentrated hydrochloric acid (2 : 1) (15 parts) for 1.5 h at 95 °C and isolation as previously gave 2-benzylamino-3,4-dihydronaphthalen-1(2*H*)-one (6; R^1 = CH_2Ph, R^2 = R^3 = H) hydrochloride, identical with material prepared previously.[6]

(2) A suspension of the *N*-acetonyldione (19; R^1 = CH_2COMe) (9 g) in propan-2-ol (100 ml) and concentrated hydrochloric acid (50 ml) was heated on a steam-bath for 45 min, and the solution worked up by the general method to give 2-(acetonylamino)-3,4-dihydronaphthalen-1(2*H*)-one (6; R^1 = CH_2COMe, R^2 = R^3 = H) hydrochloride, (8.2 g, 97%), m.p. 204 °C.[6]

(c) *With methanol.* The catalyst was added to a suspension of the dione (19) (3 mmol) in methanol (5 ml) either at room (R) or reflux (RF) temperature and when reaction was complete the methyl ester (20e) was isolated by filtration after either cooling to 3 °C (A) or dilution with water (B).

R^1	Catalyst	Temp.	Time/min	Isolation procedure	Yield (%)
Me	Toluene-4-sulphonic acid (20 mg)	RF	480	A	79 *
CH_2Ph	Toluene-4-sulphonic acid (20 mg)			B	80 (crude)
Me	KOAc (588 mg)	R	2	B	91
Me	KOAc (25 mg)	R	2	B	90
Me	$Mg(OMe)_2$ (0.1 ml; 4M)	R	2	B	92
Me	Bu^tNH_2 (1.2 ml)	R	5	A	62
Me	Et_3N (0.42 ml)	R	5	A	93
Me	Et_3N (0.04 ml)	R	5	A	93
Me	β-alanine (25 mg)	RF	15	A	72

* M.p. 110—112 °C; pale yellow, presumably due to traces of starting dione.

The products obtained accordingly were *methyl* N-*methyl*-N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthalenyl*)*oxamate* (20e; R^1 = Me) as needles [from benzene–petrol (1 : 1)], m.p. 115—116 °C; $\nu_{max.}$ 1 740 (α-keto-ester), 1 690 (C=O), and 1 655 (amide I) cm^{-1} (Found: C, 64.4; H, 5.8; N, 5.2. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%): and *methyl* N-*benzyl*-N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthyl*)*oxamate* (20e; R^1 = CH_2Ph) as prisms (from benzene), m.p. 147 °C; $\nu_{max.}$ 1 740 (α-keto-ester), 1 692 (C=O), and 1 655 (amide I) cm^{-1} (Found: C, 71.3; H, 5.7; N, 4.2. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.7; N, 4.2%), identical with material obtained by reaction of the parent amine hydrochloride [6] and methyl oxalyl chloride.

(d) *With* $^-OBu^t$. A solution of potassium t-butoxide (Aldrich, 1.7 g, 15 mmol) in tetrahydrofuran was added to a suspension of the dione (19; R^1 = Me) (2.29 g, 10 mmol) in tetrahydrofuran (30 ml): an immediate deep red colour developed and most of the dione dissolved; after 5 min, when some remaining larger particles had gone into solution, acetic acid (1.5 ml) was added followed by water. The mixture was extracted with chloroform and the organic extracts washed with 0.1M-sodium hydrogencarbonate, dried (Na_2SO_4), and evaporated to give a gum which was

dissolved in hot ether (15 ml); on cooling to 3 °C, the ether solution deposited almost pure *t-butyl* N-*methyl*-N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthalenyl*)*oxamate* (20f; R^1 = Me) (2.0 g) as needles, m.p. 112—114 °C. The ester still had a slight yellow colour due to the presence of a small quantity of starting dione and was purified by dissolution in methanol followed by addition of 2M-sodium hydroxide (1 ml) and after 2 min, dilution with water when the pure colourless ester separated. It crystallised from petrol as a gelatinous mass of micro-needles, m.p. 113—114 °C; $\nu_{max.}$ 1 725 (ester), 1 700 (C=O), and 1 655 (amide I) cm^{-1} (Found: C, 67.25; H, 7.1; N, 4.7. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%). When 1 mol equiv. of base was employed, the crude ester contained significantly more starting dione (deeper yellow in colour, m.p. 110—150 °C).

(e) *With primary and secondary amines.* (1) Ammonia (*d* 0.88, 2 ml) was added in one portion to a stirred suspension of the parent dione (19; R^1 = H) (645 mg, 3 mmol) in methanol (5 ml). Heat was evolved and in less than 1 min, the yellow dione was replaced by the colourless amide (650 mg, 93%) which was obtained by filtration. N-(1,2,3,-4-*Tetrahydro*-1-*oxo*-2-*naphthalenyl*)*oxamide* (20b; R^1 = H) formed needles (from 2-methoxyethanol), m.p. 238 °C; $\nu_{max.}$ 3 380, 3 320, and 3 200 br (N–H), 1 700, 1 685 (C=O), 1 655 (amide I), and 1 545 (amide II) cm^{-1} (Found: C, 61.95; H, 5.15; N, 12.0. $C_{12}H_{12}N_2O_3$ requires C, 62.1; H, 5.2; N, 12.1%).

N-*Methyl*-N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthalenyl*)-*oxamide* (20b; R^1 = Me), prismatic needles (from 50% ethanol), m.p. 184 °C; $\nu_{max.}$ 3 370, 3 230br, and 3 100w (N–H), 1 690 (C=O), and 1 665 and 1 625w (amide I) cm^{-1} (Found: C, 63.3; H, 5.8; N, 11.2. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%) was obtained similarly from the *N*-methyldione.

(2) The following amides were also prepared similarly, except that the clear solutions obtained after the reaction with ethanolic (30%) monomethyl- and dimethyl-amines were evaporated to dryness to give crystalline products: N-*methyl*-N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthalenyl*)*oxamic acid methylamide* (20c; R = R^1 = Me) as needles (from methanol), m.p. 126 and 141 °C; $\nu_{max.}$ 3 360 (N–H), 1 690 (C=O), 1 665 and 1 635 (amide I), and 1 535 (amide II) cm^{-1} (Found: C, 64.6; H, 6.2; N, 10.75. $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.2; N, 11.0%): and N-*benzyl*-N-(1,2,3,4-*tetrahydro*-1-*oxo*-2-*naphthalenyl*)*oxamic acid dimethylamide* (20d; R^1 = CH_2Ph) as prisms (from methanol), m.p. 158 °C; $\nu_{max.}$ 1 685 (C=O) and 1 640br (CON< and $CONMe_2$) cm^{-1} (Found: C, 71.8; H, 6.3; N, 8.2. $C_{21}H_{22}N_2O_3$ requires C, 72.0; H, 6.3; N, 8.0).

(3) Anhydrous t-butylamine (438 mg, 6 mmol) was added to a stirred suspension of the dione (19; R^1 = Me) (687 mg, 3 mmol) in tetrahydrofuran (10 ml), and the mixture heated at 40 °C for 0.5 h and then filtered. Evaporation furnished a yellow mixture of product and starting dione (720 mg), m.p. 141—178 °C. Treatment with 2M-sodium hydroxide as in the above t butyl ester preparation furnished N-*methyl*-N-(1,2,3,4 *tetrahydro*-1-*oxo*-2-*naphthalenyl*)*oxamic acid t-butylamide* (20c; R^1 = Me, R = Bu^t) (320 mg) as colourless prisms (from ethanol), m.p. 155 °C; $\nu_{max.}$ 3 270 (N–H), 1 702 (C=O), 1 672 (amide I), 1 638 (CON<), and 1 540 (amide II) cm^{-1} (Found: C, 67.3; H, 7.3; N, 9.2. $C_{17}H_{22}N_2O_3$ requires C, 67.5; H, 7.3; N, 9.3%).

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