Reactions Between Enaminones and Enones. Part 1. Some Unexpected Products from the Condensation of 3-Aminocyclohexenones with Methyl Vinyl Ketone

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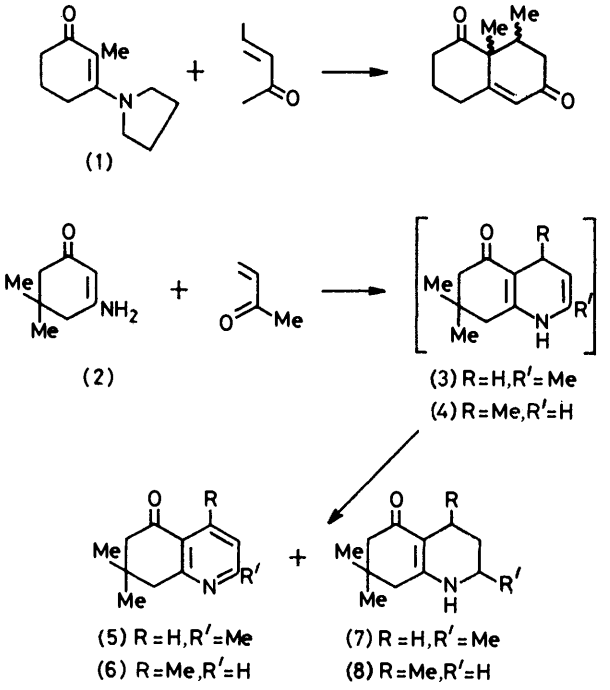
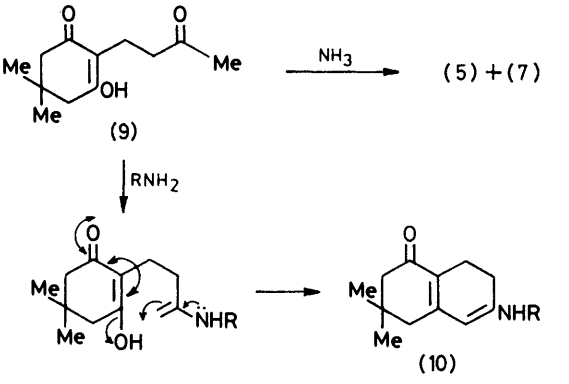
Methyl vinyl ketone readily undergoes acid-catalysed condensation with 3-amino-5,5-dimethylcyclohex-2-enone to give an unstable dihydropyridine which spontaneously disproportionates. The same mixture is obtained when 2-(3-oxobutyl)dimedone reacts with ammonia in toluene, but in xylene a single, tetracyclic product is obtained. In the absence of acid, the dihydropyridine can be trapped by an excess of methyl vinyl ketone to give a hexahydropyranoquinoline. Some primary amines react with 2-(3-oxobutyl)dimedone to give dienaminones.

REACTIONS between conjugated enones and the electron-rich sites of enaminones centred on the oxygen, nitrogen, and α-C atoms have not been widely exploited. A number of reactions on 6-aminouracils have been reported to give useful heterocyclic products.[1,2] Of the simple enaminones which have been employed, 1-aminobut-1-en-3-one is reported to condense with 2-alkylacroleins to give 3-acetyl-5-alkylpyridines.[3] An interesting use of a tertiary enaminone (1) as the starting point in the synthesis of calarene,[4] was shown [5] to involve initial attack at α-C despite considerable steric hinderance. Evidence so far available suggests that generally initial alkylation at α-C is followed by ring closure, but in one case, the use of the enaminone anion induced the initial alkylation on the nitrogen atom.[1] We are now undertaking a systematic investigation



into reactions of this type and already have evidence that they will make several synthetic intermediates available.

Treating 3-amino-5,5-dimethylcyclohex-2-enone (2) with methyl vinyl ketone in acidic conditions gave a mixture of products, (5) and (7), presumably *via* disproportionation of the quinoline (3). This intermediate (3) would be formed by alkylation at C-2 followed by dehydration. However, the spectral evidence for the



SCHEME 1 R = $PhCH_2$, Pr^i, and Bu^t

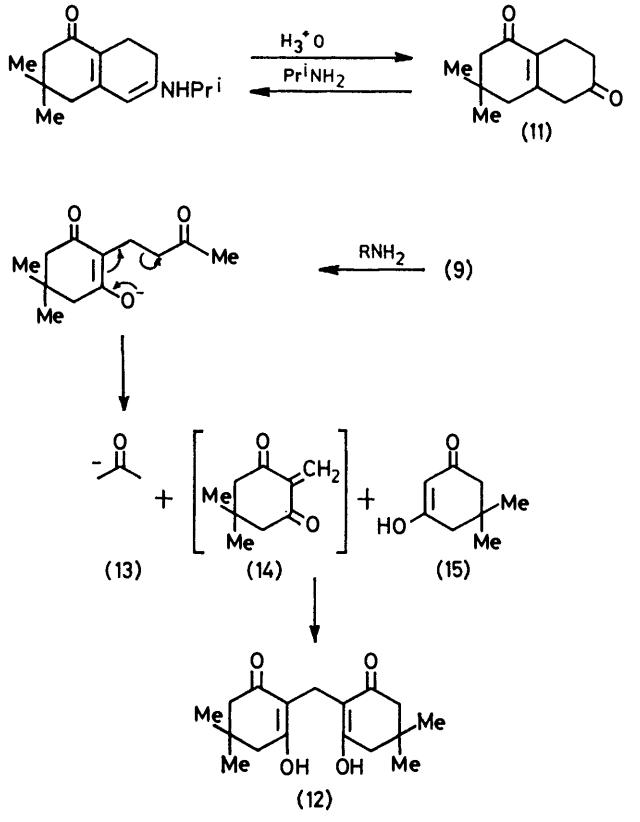
isolated products did not eliminate the alternative possibility that *N*-alkylation followed by ring closure at C-2 had given intermediate (4) which would disproportionate to compounds (6) and (8).

To solve this problem, the trione (9) was prepared by reaction between dimedone (15) and methyl vinyl ketone and carefully purified. Compound (9) with ammonia in refluxing toluene gave the same mixture of products (5) and (7). Disproportionation of the intermediate had been induced by heat whereas previous reports of similar disproportionations all made use of either acid or metal catalysis.[6]

When the trione (9) was refluxed with a number of primary amines in toluene or xylene a series of crystalline yellow dienaminones (10) was obtained, which presumably arose *via* the route outlined in Scheme 1. Compounds (10) had u.v. spectra characteristic of dienaminones.[7] Compound (10; R = Pr^i) was readily hydrolysed to the dione (11) with aqueous acid and the dione could be converted back to (10; R = Pr^i) by reaction with isopropylamine.

Although the dienaminones (10) were readily obtained in a pure form on cooling the reaction, the best yields that could be achieved were usually below 50%. Upon

investigation it was discovered that the mother liquors contained the bisdimedone (12). When secondary amines were used (morpholine or pyrrolidine) the characteristic yellowing of the solution was not seen, and the only product isolated was the bisdimedone (12). A possible explanation for this surprising result is shown in Scheme 2. Deprotonation of the trione (9) by the



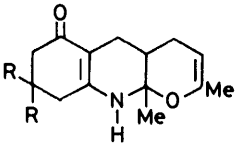
SCHEME 2

amine could lead to production of acetone anion (13) and methylenedimedone (14). Reverse Michael reaction of the trione (induced by heat or by side-chain α-C deprotonation) could produce free dimedone (15). Undoubtedly, intermediate (14) and dimedone would react rapidly together to give the observed product (12). A reaction between equimolar amounts of trione (9), dimedone, and piperidine gave 59% of the pure, dry bisdimedone (12)—a much higher yield than was obtained in any other reaction. The added dimedone must have been responsible for this increase otherwise the yield could not have exceeded 50%. Also, acetone was shown to be present in the reaction distillate. Likewise acetone was obtained from the isopropylamine reaction. In both cases the acetone was isolated in the form of its 2,4-dinitrophenylhydrazone.

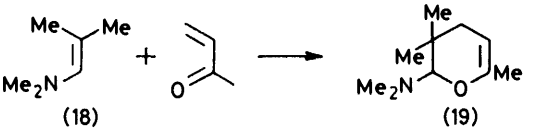
When the enaminone (2) was treated with an excess of methyl vinyl ketone in the absence of acid, a substantial yield of a new compound ($C_{16}H_{23}NO_2$, high-resolution mass spectrometry and elemental analysis) was obtained. It transpired that a second molecule of the enone had trapped the intermediate (3) to give the adduct (17). A similar compound (16) was prepared from 3-aminocyclohex-2-enone.

The u.v. and i.r. spectra for compound (17) were characteristic for the enaminone system. Strong bands at 1 580 and 1 520 cm^{-1} in a Nujol mull moved to 1 600 and 1 500 cm^{-1} in chloroform solution, but a medium strength band at 1 680 cm^{-1} did not change in frequency. The behaviour of the stronger pair is due to coupling between ν(C=O) and ν(C=C) which causes both band frequencies to be sensitive to their environment.[8] The very low frequency of the latter band is consistent with its position along the ring junction of two fused six-membered rings.[8] A previous, very thorough, investigation of reaction between a simple enamine (18) and methyl vinyl ketone to give the dihydropyran (19) assigned a band at 1 682 cm^{-1} to ν(C=C) of the enol-ether.[9] The band at 1 680 cm^{-1} in (17), which was too weak to be due to a carbonyl group could arise from a similar enol-ether structure.

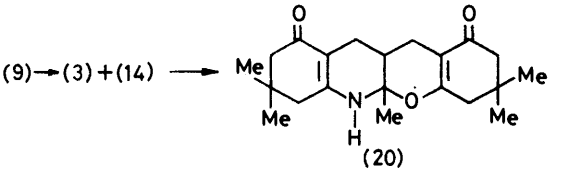
Compound (16) had very similar u.v. and i.r. spectra, but was more soluble than (17) and provided more satisfactory n.m.r. spectra. The ^1H spectrum (100 MHz, $CDCl_3$) showed a multiplet (1 H) at τ 5.60 for the vinyl proton and singlets (3 H) at τ 8.30 (broadened) and 8.58 for methyl groups on unsaturated and quaternary carbon respectively. A resonance at τ 4.94 disappeared on deuteriation and is assigned to the N–H proton. Resonances in the proton-decoupled ^{13}C spectrum were assigned as shown in the Table and confirm the structure given for compound (16). Without proton decoupling C-2, C-5a, C-6, C-9a, and C-10a remained as singlets and C-3 and C-4a became doublets.



(16) R = H, (17) R = Me



(18) (19)



(20)

When the reaction between the trione (9) and ammonia was conducted in refluxing xylene rather than toluene another unexpected product was obtained. In this case the enamine intermediate (3) had been trapped by the methylenedimedone (14) to give the tetracyclic product (20). Compound (20) ($C_{21}H_{29}NO_3$, high-resolu-

tion mass spectrometry and elemental analysis) had u.v. absorption characteristics of both the enaminone group and the vinylogous ester. Likewise in the i.r. where a band (in $CHCl_3$) at 1 500 cm^{-1} was characteristic for enaminone ν(C=C) in an annulated system [8] while a very strong, broad band at 1 620 cm^{-1} was due to the vinylogous ester superimposed on the enaminone ν(C=O). This was confirmed by the spectrum of the mull which showed ν(C=C) at 1 515 cm^{-1}, ν(C=O) at 1 585 cm^{-1}, and vinylogous ester absorption at 1 620 (strong) and 1 645 cm^{-1} (medium).[10]

^{13}C Chemical shifts for compound (16) in $CDCl_3$ (p.p.m. from $SiMe_4$)

δ	194.0	156.6	145.9	104.5	91.9
C	6	9a	2	5a	3
δ	82.2	36.0	31.6	27.4	24.3
C	10a	4/5	4a	5/4	7/9
δ	22.6	21.7	21.1	19.6	
C	9/7	8	2/10a-Me	10a/2-Me	

EXPERIMENTAL

2,7,7-Trimethyl-7,8-dihydroquinolin-5(6H)-one (5) *and 2,7,7-Trimethyl-1,2,3,4,7,8,-hexahydroquinolin-5(6H)-one* (7).—*Method* (1). A solution of 3-amino-5,5-dimethylcyclohex-2-enone (1.39 g, 10 mmol) and methyl vinyl ketone (1.4 g, 20 mmol) in propionic acid (20 ml) was refluxed for 1 h. The solvent was removed under reduced pressure and the residue dissolved in toluene and chromatographed on an alumina column. Elution with toluene gave (a) *2,7,7-trimethyl-7,8-dihydroquinolin-5(6H)-one* (0.77 g, 40%) as an oil, i.r. ν(neat) 1 590 (pyridine ring) and 1 685 cm^{-1} (C=O); u.v. (H_2O) $\lambda_{max.}$ 238 (ε 9 000) and 285 nm (8 000); (0.1M HCl) $\lambda_{max.}$ 234 (ε 6 900) and 281 nm (11 400); n.m.r. ($CDCl_3$) τ 1.76 (1 H, d) and 2.76 (1 H, d, aromatic H), 6.92 (2 H, s, 8-CH_2), 7.40 (2 H, s, CH_2, 7.33 (3 H, s, 2-Me), and 8.82 (6 H, s, 7,7-Me_2). It gave a *hydrochloride*, m.p. 245 °C (decomp.) (from ethanol–diethyl ether) (Found: C, 63.5; H, 7.5; Cl, 15.7; N, 6.3. $C_{12}H_{16}ClNO$ requires C, 63.9; H, 7.1; Cl, 15.7; N, 6.2%); i.r. (disc) 1 635 (protonated pyridine) and 1 690 cm^{-1} [ν(C=O)]. The *hydrobromide* had m.p. 271 °C (decomp.) (from ethanol) (Found: C, 53.1; H, 6.1; Br, 29.5; N, 5.2. $C_{12}H_{16}BrNO$ requires C, 53.3; H, 5.9; Br, 29.6; N, 5.2%). (b) *2,7,7-Trimethyl-1,2,3,4,-7,8-hexahydroquinolin-5(6H)-one* (0.6 g, 31%) had m.p. 181—182 °C (from toluene), i.r. ν(KBr) 1 520 and 1 570 (enaminone system), and 3 300 cm^{-1} [ν(N–H)]; u.v. $\lambda_{max.}$ (H_2O) 307 nm (ε 24 100); $\lambda_{max.}$ (0.1M-HCl) 292 nm (ε 19 100); n.m.r. τ($CDCl_3$) 6.57 (1 H, m, NCH), 7.80 (8 H, m, 4 × CH_2), 8.80 (3 H, d, $NCCH_3$), and 8.99 (6 H, s, 2 × CH_3); the doublet at τ 8.80 collapsed to a singlet on irradiation at τ 6.57. The *hydrochloride* had m.p. 229—230 °C (from ethanol–diethyl ether) (Found: C, 62.3; H, 8.4; Cl, 15.9; N, 6.4. $C_{12}H_{20}ClNO$ requires C, 62.8; H, 8.7; Cl, 15.5; N, 6.1%); i.r. (KBr) 1 540 and 1 610 cm^{-1}.

Method (2).—Ammonia was passed into a solution of 5,5-dimethyl-2-(3-oxobutyl)cyclohexane-1,3-dione (2.5 g) in toluene (50 ml) during 3 h refluxing under a Dean–Stark water separator. About 0.15 ml of water was collected (theoretical 0.21 ml). The solvent was evaporated and the residue dissolved in chloroform and chromatographed on a silica column to give the *dihydroquinolinone* (0.9 g, 40%) identical (i.r., n.m.r., and m.p. of salts) with the material described above. Elution with 5% methanol in chloroform gave the *hexahydroquinolinone* (0.77 g, 34%) identical (m.p., i.r., and n.m.r.) with the material described above.

5,5-Dimethyl-2-(3-oxobutyl)cyclohexane-1,3-dione (9).—To a solution of dimedone (14 g, 0.1 mol) and sodium hydrogencarbonate (8.4 g, 0.1 mol) in water (200 ml) was added a solution of redistilled methyl vinyl ketone (10 g, 0.14 mol) in water (50 ml) and the mixture was maintained at 75 °C for 3 h. The cooled solution was washed with ethyl acetate (4 × 100 ml) to remove 5,5-dimethyl-2,2-di-(3-oxobutyl)-cyclohexane-1,3-dione (4 g, 14%), m.p. 107—108 °C (lit.,[11] m.p. 105—107 °C). The solution was acidified (HCl), extracted with ethyl acetate (5 × 100 ml), and the extract dried ($MgSO_4$). Evaporation of the solvent gave the *trione* (14.7 g, 70%), m.p. 119—120 °C (from toluene–light petroleum, b.p. 40—60 °C) (lit.,[11] m.p. 120—122 °C).

6-Isopropylamino-3,3-dimethyl-3,4,7,8-tetrahydronaphthalen-1(2H)-one (10; R = Pr^i).—A solution of the trione (9) (6.3 g, 30 mmol) and isopropylamine (1.98 g, 36 mmol) in xylene (120 ml) was refluxed for 1 h. Water produced (1.2 ml, the theoretical quantity) was removed continuously (Dean–Stark apparatus). Evaporation of the solvent to a low volume and refrigeration gave the *dienaminone* (3.3 g, 47%), m.p. 168—169 °C (from toluene) (Found: C, 77.7; H, 10.1; N, 5.8. $C_{15}H_{23}NO$ requires C, 77.3; H, 9.9; N, 6.0%); i.r. $\nu_{max.}$ (KBr) 1 490, 1 595, 1 615, and 3 250 cm^{-1}; u.v. $\lambda_{max.}$ (EtOH) 405 nm (ε 29 000); $\lambda_{max.}$ (H_2O) 239 (6 700), 259 (5 200), and 415 nm (ε 32 600); $\lambda_{max.}$ (0.1M-HCl) 252 (8 100) and 380 nm (21 200); n.m.r. τ ($CDCl_3$) 5 30 (H, s, =CH), 6.36 (1 H, septet NCH), 7.70 (8 H, m, 4 × CH_2), 8.79 [6 H, d, $NCH(CH_3)_2$], and 9.00 (6 H, s, 2 × CH_3). After recrystallisation, the toluene was evaporated to give 2,2′-methylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (1.2 g, 27%), m.p. 190—191 °C (from ethanol) identical with an authentic sample (m.p. and mixed m.p. and i.r.). When the reaction was repeated using a fractionating column and the distillate passed into a volume of Brady's Reagent containing 2,4-dinitrophenylhydrazine (1 g), within 10 min, a precipitate formed of acetone 2,4-dinitrophenylhydrazone (1.1 g, 15%), m.p. 125 °C, identical (mixed m.p., and i.r.) with an authentic sample.

By similar techniques to the above were obtained (i) *3,3-dimethyl-6-t-butylamino-3,4,7,8-tetrahydronaphthalen-1(2H)-one* (10; R = Bu^t) after 14 h under reflux in toluene (8.1%), m.p. 192—193 °C (from toluene) (Found: C, 77.8; H, 10.1; N, 5.9. $C_{16}H_{25}NO$ requires C, 77.7; H, 10.1; N, 5.7%); i.r. (KBr) 1 495, 1 590, 1 610, and 3 400 cm^{-1}; u.v. $\lambda_{max.}$ (EtOH) 405 (ε 29 600); $\lambda_{max.}$ (H_2O) 238 (ε 5 000), 261 (3 600), and 417 nm (ε 34 400); $\lambda_{max.}$ (0.1M-HCl) 256 (ε 7 500) and 390 nm (25 500); n.m.r. τ($CDCl_3$) 5.13 (1 H, s, =CH), 7.76 (8 H, m, 4 × CH_2), 8.62 [9 H, s, $N(CH_3)_3$], 8.99 (6 H, s, 2 × CH_3). (ii) *6-Benzylamino-3,3-dimethyl-3,4,7,8-hexahydronaphthalen-1(2H)-one* (10; R = CH_2Ph), after 6 h under reflux in toluene (71%), m.p. 152—153 °C (from toluene) (Found: C, 80.8; H, 8.2; N, 5.3. $C_{19}H_{23}NO$ requires C, 81.1; H, 8.2; N, 5.0%); i.r. $\nu_{max.}$ (KBr) 1 500, 1 590, 1 610, and 3 300 cm^{-1}; u.v. $\lambda_{max.}$ (EtOH) 403 nm (ε 26 800); $\lambda_{max.}$ (H_2O) 412 nm (ε 26 000); $\lambda_{max.}$(0.1M HCl) 255 (ε 8 700) and 394 nm (ε 25 500); n.m.r. τ ($CDCl_3$) 2.70 (5 H, s, Ph), 5.26 (1 H, s, =CH), 5.72 (2 H, d, $PhCH_2$), 7.70 (8 H, m, 4 × CH_2), and 9.03 (6 H, s, 2 × CH_3).

Reaction of the Trione with Dimedone and Piperidine.—A solution of the trione (9) (2.1 g, 10 mmol), dimedone (1.4 g, 10 m mol), and piperidine (0.85 g, 10 mmol) in xylene (250 ml) was refluxed (2 h) under a fractionating column and the distillate passed directly into a volume of

Brady's Reagent containing 2,4-dinitrophenylhydrazine (1 g). The precipitate was collected to give acetone dinitrophenylhydrazone (0.1 g, 4%) identical with an authentic sample (m.p., mixed m.p., and i.r.). The solvent was removed from the reaction mixture and the residue recrystallised to give 2,2'-methylenebis(5,5-dimethyl-3-hydroxycyclohex-2-enone) (1.72 g, 59%), m.p. 190 °C (from ethanol) identical with an authentic sample (m.p., mixed m.p., and i.r.).

3,3-*Dimethyl*-3,4,7,8-*tetrahydronaphthalene*-1,6-*dione* (11).—A solution of the dienaminone (10; R = Pr^i) (0.6 g, 2.5 mmol) and 10% HCl (0.9 ml, 2.5 mmol) in water (10 ml) was stirred at room temperature 0.5 h and then set aside overnight. Extraction with diethyl ether gave, after drying and evaporation, the liquid *dione* (0.3 g, 63%), i.r. $\nu_{max.}$ (neat) 1 645 (C=C), 1 670 (conjugated C=O), and 1 720 cm^{-1} (C=O); n.m.r. τ($CDCl_3$) 6.96 (2 H, s, CH_2 position 5), 7.50 (8 H, m, 4 × CH_2), and 8.94 (6 H, s, 2 × CH_3). The dione was added to a solution of isopropylamine (0.4 g, 5 mmol) in xylene (50 ml) and refluxed 1 h. On evaporation of the solvent it gave the dienaminone (10; R = Pr^i) (0.2 g), m.p. 167—169 °C, identical with the starting material (mixed m.p. and i.r.).

4,4a,5,7,8,9,10,10a-*Octahydro*-2,8,8,10a-*tetramethylpyrano*[2,3-b]*quinolin*-6-*one* (17).—A solution of 3-amino-5,5-dimethylcyclohex-2-enone (1.39 g, 10 mmol) and redistilled methyl vinyl ketone (2.1 g, 30 mmol) in ethanol (20 ml) was refluxed for 6 h. The solution was cooled and the precipitate collected to give the *product* (1.1 g, 42%), m.p. 212—213 °C (from ethanol) (Found: C, 73.6; H, 8.8; N, 5.4. $C_{16}H_{23}NO_2$ requires C, 73.6; H, 8.8; N, 5.4%); i.r, $\nu_{max.}$ (mull) 1 515 and 1 580 (enaminone system), 1 680 (C=C), and 3 300 cm^{-1} (NH); ($CHCl_3$) 1 500 and 1 600 (enaminone system), 1 688 cm^{-1} (C=C), and 3 440 cm^{-1} (NH); u.v. $\lambda_{max.}$ (H_2O) 302 nm (ε 23 400); $\lambda_{max.}$ (0.1 M-HCl) 296 nm (ε 16 000).

4,4a,5,7,8,9,10a-*Octahydro*-2,10a-*dimethylpyrano*[2,3-b]-*quinolin*-6-*one* (16).—A solution of 3-aminocyclohex-2-enone (1.1 g) in redistilled methyl vinyl ketone (5 ml) was refluxed for 3 h. After cooling the precipitate was collected to give the *product* (0.7 g, 30%), m.p. 166—167 °C (from ethyl acetate) (Found: C, 72.2; H, 8.3; N, 6.0. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%); i.r. $\nu_{max.}$ (mull) 1 515 and 1 585 (enaminone system), 1 680 (C=C), and 3 280 cm^{-1} (NH); $\nu_{max.}$ ($CHCl_3$) 1 500 and 1 600 cm^{-1} (enaminone system), 1 685 (C=C), and 3 440 cm^{-1} (NH).

3,4,5a,6,7,8,9,11,11a,12-*Decahydro*-3,3,5a,8,8-*pentamethyl*[1]*benzopyrano*[2,3-b]*quinoline*-1,10(2H)-*dione* (20).—Ammonia was passed into a refluxing solution of 5,5-dimethyl-2-(3-oxobutyl)cyclohexane-1,3-dione (2.1 g) in xylene (150 ml) for 7 h. Evaporation of the solvent gave the *product* (0.7 g, 41%), m.p. 205 °C (from toluene–light petroleum, b.p. 40—60 °C) (Found: C, 73.3; H, 8.5; N, 4.1. $C_{21}H_{29}NO_3$ requires C, 73.5; H, 8.5; N, 4.1%); i.r. $\nu_{max.}$ (mull) 1 515 and 1 585 (enaminone system), 1 620 and 1 650 (vinylogous ester system), and 3 290 cm^{-1} (NH); $\nu_{max.}$ ($CHCl_3$) 1 500 (enaminone), 1 620 (enaminone and vinylogous ester), and 3 430 cm^{-1} (NH); u.v. $\lambda_{max.}$ (EtOH) 262 (ε 21 300) and 293 nm (22 000); $\lambda_{max.}$ (H_2O) 268 (ε 19 200) and 300 nm (20 900); $\lambda_{max.}$ (0.1M-HCl) 265 (ε 19 200) and 301 nm (ε 23 300); $\lambda_{max.}$ (0.1M-NaOH) 295 nm (ε 28 800); n.m.r. τ($CDCl_3$) 7.82 (13 H, m, 6 × CH_2 plus CH), 8.56 (3 H, s, CH_3), and 9.00 (12 H, s, 4 × CH_3). ^{1}H N.m.r. spectra were recorded at 60 MHz except that for compound (16) which was at 100 MHz.

We thank Dr. G. Bedford and Mr. P. J. Taylor for helpful discussions and Mr. R. S. Smith for help with the i.r. and u.v. spectra.

[8/804 *Received*, 2*nd May*, 1978]

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