5,6,7,8-Tetrahydroquinolines. Part I. A Novel Synthesis of 7,8-Dihydroquinolin-5(6*H*)-ones

By **Adrian C. W. Curran,**† Institute of Medical Research, Wyeth Laboratories, Huntercombe Lane South, Maidenhead, Berkshire SL6 0PH

The reaction of alkyl-substituted cyclohexane-1,3-diones with β-amino-αβ-unsaturated aldehydes or ketones ($R^1CO{\cdot}CR^3{:}CR^2{\cdot}NH_2$) and, conversely, the reaction of alkyl-substituted 3-aminocyclohex-2-enones with β-ethoxy-αβ-unsaturated aldehydes or ketones ($R^1CO{\cdot}CR^3{:}CR^2{\cdot}OEt$) gives 2-, 3-, and 4-substituted 7,8-dihydroquinolin-5(6*H*)-ones which can be readily reduced to the corresponding 5,6,7,8-tetrahydroquinolines.

THIS paper describes the application of the Breitmaier reaction [1] to the synthesis of the substituted 7,8-dihydroquinolin-5(6*H*)-ones (1) and hence the 5,6,7,8-tetrahydroquinolines (2), providing a more versatile route than previously available‡ for these compounds.[1a,b,2] The 7,8-dihydroquinolin-5(6*H*)-ones (1) obtained by the reaction of cyclohexane-1,3-dione with 3-aminoacrylaldehydes (3; R^1 = H) or 4-aminobut-3-en-2-ones (3; R^1 = Me) can also be obtained by the reaction of 3-aminocyclohex-2-enone with 3-ethoxyacrylaldehydes (4; R^1 = H) or 4-ethoxybut-3-en-2-ones (4; R^1 = Me). A similar procedure for obtaining 7,8-dihydroquinolin-5(6*H*)-ones [*e.g.* (1c)] by the reaction of cyclohexane-1,3-dione with protected 1,3-dicarbonyl compounds (*e.g.* 1,1-dimethoxybutan-3-one) in the presence of ammonium acetate has appeared in the patent literature.[4]

The reaction of 3-aminocyclohex-2-enone with 3-ethoxy-2-methylacrylaldehyde (4a) in the absence of solvent (Method 1) gave the 7,8-dihydroquinolin-5(6*H*)-one (1a) in 50% yield. A similar yield was obtained when the reaction was carried out in toluene (Method 1A) or in acetic acid (Method 1B), but in the latter case a side reaction between the ethoxyacrylaldehyde (4a) and its ammonolysis product (3a) (from an exchange reaction with 3-aminocyclohex-2-enone) gave rise to a 15% yield of bis-(2-methylacryloyl)amine. The same 7,8-dihydroquinolin-5(6*H*)-one (1a) was obtained when cyclohexane-1,3-dione reacted with 3-amino-2-methylacrylaldehyde (3a) with triethylamine–piperidinium acetate as catalyst (Method 2). The various 7,8-dihydroquinolin-5(6*H*)-ones (1) obtained by Methods 1 and 2 are summarised in the Experimental section; when the same product was obtained from both methods a comparison was made by g.l.c. and n.m.r. The 7,8-dihydroquinolin-5(6*H*)-one (1a) was further identified by reduction to 3-methyl-5,6,7,8-tetrahydroquinoline (2a) which was compared with authentic material obtained from cyclohexanone and 3-amino-2-methylacrylaldehyde.[1a,b]

In its reaction with 3-aminocyclohex-2-enone, β-ethoxycrotonaldehyde diethyl acetal behaves as the enol ether (4c), giving the anticipated 7,8-dihydroquinolin-5(6*H*)-one (1c), and similarly 1,1,3,3-tetraethoxypropane with 3-amino-5,5-dimethylcyclohex-2-enone behaves as the ethoxyacrylaldehyde (4d), giving the 7,8-dihydroquinolin-5(6*H*)-one (1d).

A possible mechanism is summarised in Scheme 1 [*e.g.* for the conversion (4c) ⟶ (1c)]. Since the same products can be obtained from Methods 1 and 2 it is possible that the reactions follow a similar pathway. However an analogous reaction (in pyridine synthesis) between ethyl

† *Present address:* Reckitt and Colman Ltd., Pharmaceutical Division, Dansom Lane, Hull HU8 7DS.

‡ Since this work was completed the selective hydrogenation of quinolines [3] has provided an alternative route to the 5,6,7,8-tetrahydroquinolines (2).

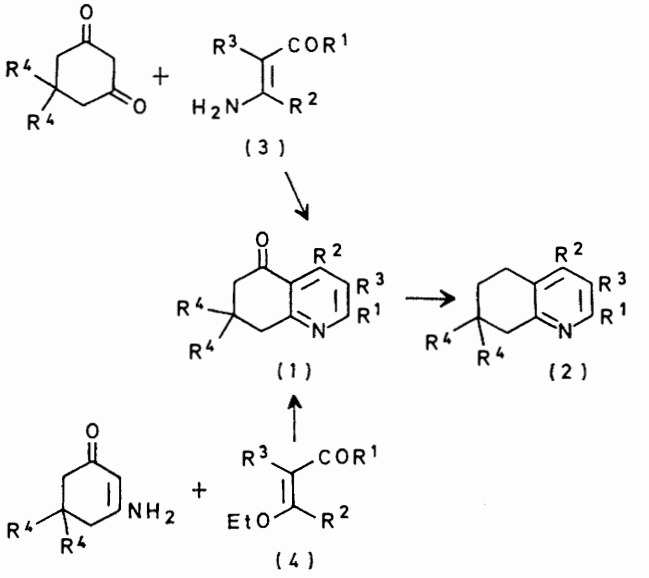
[1] E. Breitmaier and E. Bayer, (*a*) *Tetrahedron Letters*, 1970, **38**, 3291; (*b*) *Angew. Chem. Internat. Edn.*, 1969, **8**, 765; (*c*) E. Breitmaier, S. Gassenmann, and E. Bayer, *Tetrahedron*, 1970, **26**, 5907; (*d*) E. Breitmaier and S. Gassenmann. *Chem. Ber.*, 1971, **104**. 665.

[2] (*a*) F. Zymalkowski and M. Kother, *Arch. Pharm.*, 1970, **303** (8), 667; (*b*) F. Zymalkowski and J. Rimek, *ibid.*, 1961, **294**, 759; (*c*) F. Bohlmann and R. Mayer-Mader, *Tetrahedron Letters*, 1965, 171; (*d*) F. Zymalkowski and J. Rimek, *Naturwiss.*, 1960, **4**, 83.

[3] F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.*, 1975, **40**, 2729.

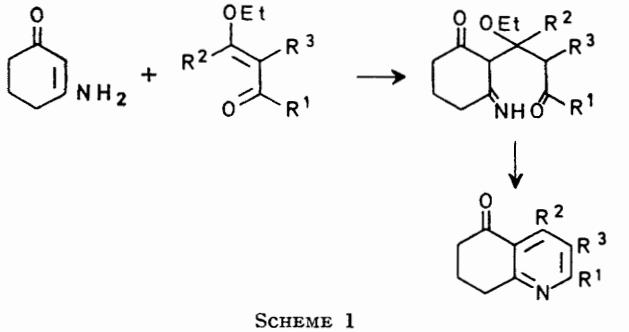
[4] Ger. Offen. 2,001,572 (*Chem. Abs.*, 1971, **75**, 152,990j).

acetoacetate and 4-aminobut-3-en-2-one (3c) has been reported [5] to give 2,4-dimethylnicotinate *via* an intermediate bisenamine and, by a similar mechanism, 4-aminopent-3-en-2-one has been reported [6] to react with dimedone in the presence of benzaldehyde to give 3-acetyl-7,8-dihydro-2,7,7-trimethyl-4-phenylquinolin-5-(6*H*)-one. Such a mechanism would predict the formation of the 7,8-dihydroquinolin-5(6*H*)-ones (1a and b)



a; $R^1 = R^2 = R^4 = H, R^3 = Me$
b; $R^1 = R^2 = H, R^3 = R^4 = Me$
c; $R^1 = Me, R^2 = R^3 = R^4 = H$
d; $R^1 = R^2 = R^3 = H, R^4 = Me$
e; $R^1 = R^2 = Me, R^3 = R^4 = H$

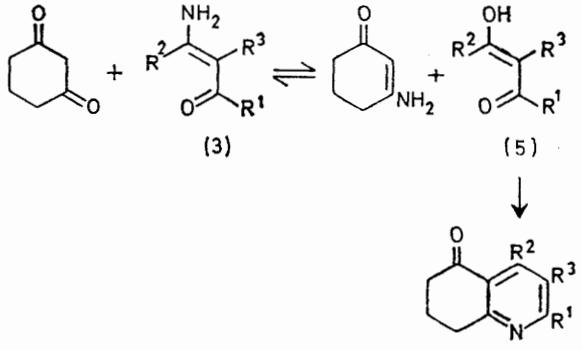
from the reaction of the aminoacrylaldehyde (3b) with cyclohexane-1,3-dione and dimedone, respectively, by Method 2 but, since 4-aminobut-3-en-2-one (3c) reacts



SCHEME 1

with cyclohexane-1,3-dione to give the 7,8-dihydro-2-methylquinolin-5(6*H*)-one (1c) rather than the 4-methyl isomer, the reaction must follow a different pathway.

To explain this inconsistency the mechanism in Scheme 2 is proposed, in which the enamine (3), under the conditions of Method 2, is in equilibrium with the β-oxoaldehyde (5), which then reacts as in Scheme 1.



SCHEME 2

Although most of this study has been directed at the more inaccessible 3-substituted 7,8-dihydroquinolin-5-(6*H*)-ones, the same approach can be applied to the synthesis of any alkyl- or aryl-substituted 7,8-dihydroquinolin-5(6*H*)-one, as shown by the reaction of the amino-ketone (3e) with cyclohexane-1,3-dione to give 7,8-dihydro-2,4-dimethylquinolin-5(6*H*)-one (1e).

EXPERIMENTAL

M.p.s were determined with a Mettler FP1 instrument, microanalyses with a Perkin-Elmer 240 instrument, i.r. spectra with a Perkin–Elmer 521 instrument, and u.v. spectra with a Pye–Unicam SP 700C instrument; g.l.c. was performed with a Perkin-Elmer F11 instrument.

Preparation of *7,8-Dihydroquinolin-5(6H)-ones* (1).—*Method* 1 (*no solvent.*) A mixture of 3-aminocyclohex-2-enone (11.1 g, 0.1 mol) and 3-ethoxy-2-methylacrylaldehyde (11.4 g, 0.1 mol), in an apparatus equipped for downward distillation, was heated at 120 °C for 16 h, during which time the theoretical volume of ethanol–water (6.5 ml) was collected. The residual oil was distilled to give *7,8-dihydro-3-methylquinolin-5(6H)-one* as an oil (7.8 g, 48%), b.p. 78—80° at 0.2 mmHg, m.p. 45—47° [needles from petroleum (b.p. 40—60°)] (Found: C, 74.8; H, 6.9; N, 8.9. $C_{10}H_{11}NO$ requires C, 74.5; H, 6.9; N, 8.7%), $\lambda_{max.}$ 234 (ε 8 000) and 291 nm (5 000), $\nu_{max.}$ 1 685 (C:O) and 900 cm^{-1} (aromatic). The *oxime* (needles from aqueous ethanol) had m.p. 180—181° (Found: C, 68.2; H, 6.9; N, 15.7. $C_{10}H_{12}N_2O$ requires C, 68.2; H, 6.9; N, 15.9%), $\nu_{max.}$ 2 500—2 900, 1 620, and 980 cm^{-1}.

Method 1A (*in toluene*). A solution of 3-aminocyclohex-2-enone (11.1 g, 0.1 mol) and 3-ethoxy-2-methylacrylaldehyde (11.4 g, 0.1 mol) in toluene (25 ml) was heated under reflux for 18 h and the cooled solution was washed with 2N-hydrochloric acid (2 × 20 ml). The combined washings were made alkaline with 4N-sodium hydroxide and extracted (3 × 25 ml) with chloroform. The combined, dried ($MgSO_4$) extracts were distilled to give 7,8-dihydro-3-methylquinolin-5(6*H*)-one as an oil (7.6 g, 48%), b.p. 78—80° at 0.2 mmHg, m.p. 43—45°.

Method 1B (*in acetic acid*). A solution of 3-aminocyclohex-2-enone (24.1 g, 0.22 mol) and 3-ethoxy-2-methylacrylaldehyde (27.7 g, 0.24 mol) in glacial acetic acid (55 ml) was heated under reflux for 24 h, cooled to 0 °C, and filtered giving *bis-(2-methylacryloyl)amine* (5 g, 15%), m.p. 252—

[5] N. K. Kochetkov, A. Gonsales, and A. N. Nesmeyanov, *Doklady Akad. Nauk S.S.S.R.*, 1951, **79**, 609 (*Chem. Abs.*, 1955, **49**, 15894).

[6] E. Grinstein, E. Stankevics, and G. Duburs, *Khim. geterotsikl. Soedinenii*, 1967, **6**, 1118 (*Chem. Abs.*, 1968, **69**, 77095).

253° (plates from ethanol) (Found: C, 62.5; H, 7.5; N, 9.2. $C_8H_{11}NO_2$ requires C, 62.7; H, 7.2; N, 9.2%), $\nu_{max.}$ 3 220 (NH), 2 720, and 1 600—1 650 cm^{-1} (C:O). The acetic acid solution was evaporated *in vacuo* and the residual oil was dissolved in chloroform (100 ml) and washed with 2N-hydrochloric acid (2 × 25 ml); the combined washings were made alkaline with 4N-sodium hydroxide and extracted (3 × 50 ml) with chloroform. The combined, dried ($MgSO_4$) extracts were distilled to give 7,8-dihydro-3-methylquinolin-5(6*H*)-one as an oil (13.5 g, 40%), b.p. 78—80° at 0.2 mmHg, m.p. 43—45°.

Method 2. A mixture of cyclohexane-1,3-dione (22.4 g, 0.2 mol), 3-amino-2-methylacrylaldehyde (17 g, 0.2 mol), triethylamine (10 ml), and piperidinium acetate (0.25 g) was heated with stirring at 120 °C for 24 h, cooled, and dissolved in 2N-hydrochloric acid (50 ml); the solution was extracted (3 × 50 ml) with ethyl acetate and the extracts were discarded. The acidic solution was made alkaline with 4N-sodium hydroxide and extracted (3 × 50 ml) with chloroform. The combined, dried ($MgSO_4$) extracts were distilled to give 7,8-dihydro-3-methylquinolin-5(6*H*)-one (17 g, 52%) as an oil, b.p. 79° at 0.2 mmHg, m.p. 43—45°.

By the methods indicated the following 7,8-dihydroquinolin-5(6*H*)-ones were obtained: (i) 7,8-*dihydro*-3,7,7-*trimethylquinolin*-5(6H)-*one*, Method 1 from 3-amino-5,5-dimethylcyclohex-2-enone and 3-ethoxy-2-methylacrylaldehyde (53%) b.p. 80° at 0.2 mmHg; *hydrochloride* m.p. 232—234° (needles from propan-2-ol) (Found: C, 63.8; H, 7.1; N, 6.1. $C_{12}H_{15}NO$,HCl requires C, 63.8; H, 7.1; N, 6.2%); Method 2 from 5,5-dimethylcyclohexane-1,3-dione and 3-amino-2-methylacrylaldehyde (40%); (ii) 7,8-*dihydro*-2-*methylquinolin*-5(6H)-*one*, Method 1 from 3-aminocyclohex-2-enone and 4-ethoxybut-3-en-2-one (72%) b.p. 64—66° at 0.05 mmHg (lit.,[4] b.p. 142—144° at 14 mmHg); *hydrochloride* m.p. 223—225° (needles from propan-2-ol) (Found: C, 60.7; H, 6.3; N, 6.8. $C_{10}H_{11}NO$,HCl requires C, 60.7; H, 6.1; N, 7.1%); Method 1 from 3-aminocyclohex-2-enone and β-ethoxycrotonaldehyde (72%); Method 2 from cyclohexane-1,3-dione and 4-aminobut-3-en-2-one (68%); (iii) 7,8-*dihydro*-7,7-*dimethylquinolin*-5(6H)-*one*, Method 1 from 3-amino-5,5-dimethylcyclohex-2-enone and 1,1,3,3-tetraethoxypropane (36%), b.p. 61° at 0.2 mmHg; *hydrochloride* m.p. 219° (needles from propan-2-ol) (lit.,[2a] m.p. 213°) (Found: C, 62.6; H, 6.8; N, 6.5. $C_{11}H_{13}NO$,HCl requires C, 62.4; H, 6.7; N, 6.6%); (iv) 7,8-*dihydro*-2,4-*dimethylquinolin*-5(6H)-*one*, Method 1 from cyclohexane-1,3-dione and 4-aminopent-3-en-2-one (60%), m.p. 63—64° [needles from petroleum (b.p. 40—60°)] (Found: C, 75.5; H, 7.7; N, 8.1. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.1%).

5,6,7,8-*Tetrahydro*-3-*methylquinoline*.—A mixture of 7,8-dihydro-3-methylquinolin-5(6*H*)-one (20 g), hydrazine hydrate (14 ml), diethylene glycol (150 ml), and sodium hydroxide (14 g) was heated under reflux for 1 h. The condenser was replaced by a Dean–Stark water separator and the heating was continued for 3 h. The cooled mixture was diluted with water (200 ml) and extracted with ether (3 × 150 ml) and the combined, dried ($MgSO_4$) extracts were distilled to give 5,6,7,8-tetrahydro-3-methylquinoline (17 g, 93%) as an oil, b.p. 116° at 18 mmHg, g.l.c. (3% SE 30; 150°) t_R 3.5 min, (10% MS200; 150 °C) t_R 5.5 min, $\nu_{max.}$ (film) 1 600, 1 565, 1 245, and 710 cm^{-1}, identical with authentic material.[1a]

5,6,7,8-*Tetrahydro*-3,7,7-*trimethylquinoline*.—7,8-Dihydro-3,7,7-trimethylquinolin-5(6*H*)-one was reduced by the procedure used for the quinolone (1a), giving 5,6,7,8-*tetrahydro*-3,7,7-*trimethylquinoline* as an oil (98%), b.p. 59° at 0.2 mmHg, g.l.c. (2% OV17; 150 °C) t_R 6 min. The picrate was isolated as the quarter hydrate as yellow needles (from ethanol), m.p. 173—174° (Found: C, 52.6; H, 4.9; N, 13.5. $C_{18}H_{20}N_4O_7$,0.25H_2O requires C, 52.9; H, 5.0; N, 13.7%), $\nu_{max.}$ 2 040, 1 550, and 1 340 cm^{-1}.

[5/2004 *Received*, 13*th October*, 1975]