# A New Synthesis of Ethyl 2-Methyl-4-oxocyclohex-2-enecarboxylate (Hagemann's Ester) and its Methyl and t-Butyl Analogues

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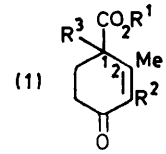
Regioselective cyclisations of esters of 2-acetyl-5-oxohexanoic acid led to (i) alkyl 2-methyl-4-oxocyclohex-2-enecarboxylates (alkyl = Bu$^t$, Et, or Me) (catalysed by pyrrolidinium acetate), (ii) esters of 4-pyrrolidino-2-methylcyclohexa-1,3-dienecarboxylic acid (in the presence of pyrrolidine), and (iii) alkyl 4-methyl-2-oxocyclohex-3-enecarboxylates (catalysed by hydrogen chloride).

ETHYL 2-METHYL-4-OXOCYCLOHEX-2-ENECARBOXYLATE (1a) (Hagemann's ester [1]) is a versatile synthetic intermediate.[2] It is commonly made *via* the condensation of 2 equiv. of ethyl acetoacetate with 1 equiv. of formaldehyde in the presence of a catalytic amount of piperidine.[3-5] The ethoxycarbonyl group α to the ketone is selectively removed from the intermediate (2) by heating with sodium ethoxide in ethanol,[3] whence Hagemann's ester is obtained in *ca.* 50% overall yield. Other less satisfactory methods for its preparation have been recorded.[6] The investigation described here was prompted by our need in other synthetic work for a convenient large-scale synthesis of the t-butyl analogue (1b).

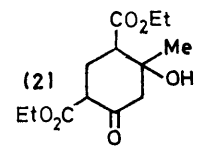
As a possible approach to the t-butyl ester (1b) and an improved route to the esters (1a) and (1c), we investigated the cyclisation of esters (3a—c) of 2-acetyl-5-oxohexanoic acid. In general, dioxo-esters of type (3) can undergo aldol cyclisation in two ways, giving either the δ-keto-ester (1) or its structural isomer, the β-keto-ester (4).[7] The relative amounts of these isomers formed will be determined by kinetic and/or equilibrium factors depending on the conditions used. Much previous work [8] indicated that this cyclisation led, under acidic or basic conditions, to mainly the β-keto-ester (4). It has been claimed [9] that compound (3a) gives Hagemann's ester (1a) in low yield, by catalysis with sodium ethoxide, but the insufficient characterisation of the product does not rule out the possibility that it was compound (4a) or a mixture of the esters (1a) and (4a). However, it has been conclusively demonstrated,[10,11] that whereas acid-catalysed cyclisation of (3d) gives the ester (4d) as expected, the use of piperidinium acetate as catalyst effects cyclisation to give mainly the ester (1d).

The dioxo-esters (3a—c) were prepared by base-catalysed Michael addition of the appropriate ester of acetoacetic acid to but-3-en-2-one.[12] We have found that cyclisation of these dioxo-esters proceeds rapidly in the presence of catalytic quantities of pyrrolidine and acetic acid, and gives the esters (1a), (1b), or (1c), respectively, uncontaminated by isomers [no signals from the isomer (4a) are observed in the 100 MHz $^1$H n.m.r. spectrum of the ester (1a)]. The overall yield of this simple two-step procedure is 70—75 for (1a), *ca.* 50 for (1b), and 55% for (1c).

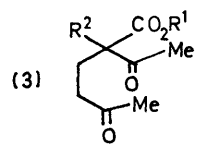


(1)

a; R$^1$ = Et, R$^2$ = H, R$^3$ = H
b; R$^1$ = Bu$^t$, R$^2$ = H, R$^3$ = H
c; R$^1$ = Me, R$^2$ = H, R$^3$ = H
d; R$^1$ = Et, R$^2$ = H, R$^3$ = Me
e; R$^1$ = Et, R$^2$ = various, R$^3$ = H
f; R$^1$ = Bu$^t$, R$^2$ = $CH_2Ph$, R$^3$ = H

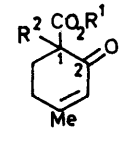


(2)



(3)

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



(4)

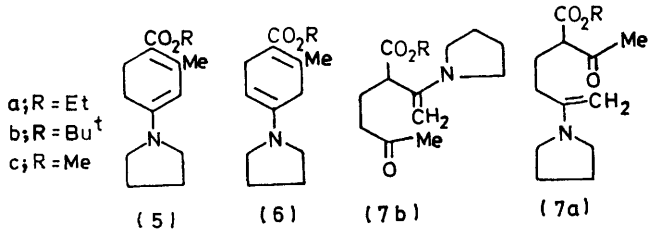
a; R$^1$ = Et, R$^2$ = H
c; R$^1$ = Me, R$^2$ = H
d; R$^1$ = Et, R$^2$ = Me

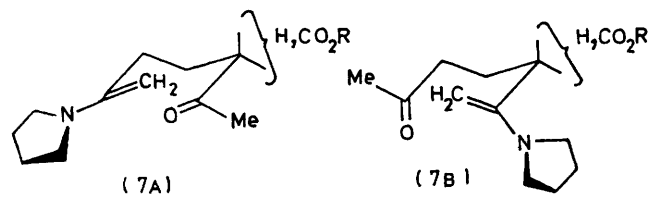
To assess the purity of the synthetic esters (1a) and (1c) we followed Henecka's procedure [12] (*i.e.* catalysis of cyclisation by hydrogen chloride) to prepare (4a) from (3a) and (4c) from (3c). Their $^1$H n.m.r. spectra agree with the assigned structures and also show that each compound is initially contaminated with *ca.* 15% of the isomers (1a) and (1c), respectively. Pure β-keto-ester (4c) can be obtained by crystallisation of a once-distilled

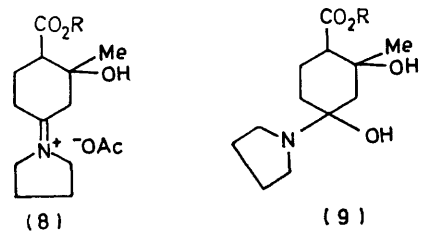
[1] C. T. L. Hagemann, *Ber.*, 1893, **26**, 876.
[2] R. E. Ireland, 'Organic Synthesis,' Prentice-Hall, New York, 1969, p. 75; D. Nasipuri, G. Sarkar, R. Roy, and M. Guha, *J. Indian Chem. Soc.*, 1966, **43**, 383, and references therein; W. S. Johnson, *Accounts Chem. Res.*, 1968, **1**, 1; M. Ohashi, *Chem. Comm.*, 1969, 893; O. R. Ghatak and N. R. Chatterjee, *J. Chem. Soc.* (*C*), 1971, 190.
[3] P. Rabe and D. Spence, *Annalen*, 1905, **342**, 328; P. Rabe and F. Rahm, *Ber.*, 1905, **38**, 969.
[4] L. I. Smith and G. F. Rouault, *J. Amer. Chem. Soc.*, 1943, **65**, 631.
[5] M-M. Claudon, R. Cornubert, H. Lemoine, and R. Malzieu, *Bull. Soc. chim. France*, 1958, 843.
[6] E. C. Horning, M. G. Horning, and E. J. Platt, *J. Amer. Chem. Soc.*, 1949, **71**, 1771; M. S. Newman and H. A. Lloyd, *J. Org. Chem.*, 1952, **17**, 577.
[7] H. Henecka, 'Chemie der Beta-dicarbonylverbindungen,' Springer-Verlag, Berlin, 1950, p. 263.
[8] R. N. Lacey, *J. Chem. Soc.*, 1960, 1625, and references therein.
[9] H. M. E. Cardwell and F. J. McQuillin, *J. Chem. Soc.*, 1949, 708; C. Mannich and J-P. Fourneau, *Ber.*, 1938, **71**, 2090.
[10] H. Plieninger and T. Suehiro, *Chem. Ber.*, 1956, **89**, 2789; for further examples of such piperidine acetate-catalysed cyclisations see H. Plieninger, L. Arnold, and W. Hoffmann, 1965, **98**, 1399.
[11] R. Brettle and D. Seddon, *J. Chem. Soc.* (*C*), 1970, 1320.
[12] H. Henecka, *Chem. Ber.*, 1948, **81**, 179.

sample of the product. The main difference between the $^1$H n.m.r. spectra of the esters (1a) and (4a) [c ˝c) and (4c)] is in the appearance of the 1-H signal a˘ ˘ triplet ($\tau$ 6·79) in the case of the δ-isomer (1a), but as a quartet ($\tau$ 6·86) for the β-isomer (4a).

When a small excess of neat pyrrolidine is added to any of the esters (1a—c) or (3a—c), rapid exothermic reactions occur and the yellow crystalline dienamines (5a—c) are formed almost quantitatively. Though unstable in air, they may be used to characterise the esters (1a—c). Under similar conditions, a crystalline product could not be obtained from the isomeric ester (4a). The structures (5a—c) follow unambiguously from spectroscopic and analytical data (see Experimental section). In particular, their formulation as conjugated dienamines (5) rather than unconjugated dienamines (6) is consistent with a strong absorption in the visible spectrum [for (5a) $\lambda_{max.}$ 386 nm (ε 31,600)] and a singlet for the olefinic proton in the n.m.r. spectrum [$\tau$ 5·53 for (5a)]. The dienamines are resistant to hydrolysis [on the evidence of n.m.r. spectra, there was an 83% recovery of (5a) from refluxing in 2M-hydrochloric acid for



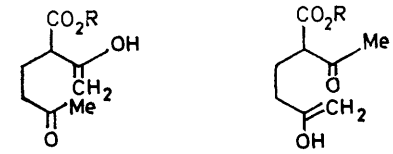

1 h and 98% recovery on subjecting it to conditions (in aqueous methanol) used for the preparation of the ester (1a)] and they are not therefore intermediates in the cyclisation of the esters (3a—c) to (1a—c) when pyrrolidinium acetate is used as catalyst.

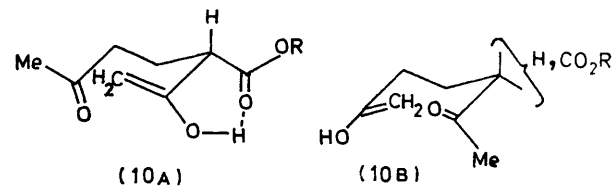
* However, there is no explicit evidence for an enamine intermediate. The reaction between the ester (3c) and pyrrolidine in [$^2H_4$]methanol was followed by $^1$H n.m.r. spectroscopy. During the rapid formation (*ca.* 5 min at 33°) of the dienamine (5c), no resonances were detected which could be ascribed to an intermediate such as the enamine (7a).

† Product equilibration does not occur.

Under conditions otherwise identical to those used with pyrrolidinium acetate, triethylammonium acetate fails to cyclise the ester (3a). Furthermore, product equilibration does not occur in the pyrrolidinium acetate-catalysed cyclisation of compound (3a), since the β-isomer (4a) is recovered unchanged from conditions used to prepare compound (1a). It is therefore likely (*cf.* refs. 13 and 14) that with pyrrolidinium acetate as catalyst the cyclising step involves the intramolecular condensation of an enamine * with a ketone carbonyl group, followed by elimination of water and hydrolysis of an intermediate immonium ion. Of four possible enamines, two [(7a) and (7b)] can cyclise to six-membered rings. The preferred formation of the ester (1a) may be due to (7a) undergoing cyclisation faster than (7b), as the latter has a much greater degree of steric crowding in the transition state required for a cyclisation [*cf.* (7A) and (7B)], with maximal orbital overlap of the double bond π-electrons with the lone-pair electrons on nitrogen. Cyclisation of the enamine (7a) gives the intermediate (8). In the absence of acid this is dehydrated and deprotonated (or deprotonated and dehydrated) to the dienamine (5). Although an immonium ion such as (8) could be attacked by water to yield the amino-alcohol (9), under non-acidic conditions further conversion of the N–C–OH system of (9) into a carbonyl group may not occur, as this would necessitate loss of the pyrrolidino-anion, a poor leaving group, even if solvent-assisted by proton transfer. However, in the presence of acetic acid the ion (8) can be trapped by attack of water, protonation on nitrogen, and loss of pyrrolidine to give, after dehydration, Hagemann's ester (1a).

The alternative direction of cyclisation of the dioxo-esters (3a) and (3c) under acidic catalysis probably goes through enols as intermediates (*cf.* pp. 9—11 of ref. 13). The preferred formation of the ester (4a) † may be due to the faster cyclisation of enol (10a) compared with (10b),




for the following reasons: (i) the carbonyl group in (10a) is less hindered than that in (10b); (ii) the preferred conformations for cyclisation, (10A) and (10B) can be

[13] A. T. Nielson and W. J. Houlihan in *Org. Reactions*, 1968, **16**, 7—9, 50—53, and references therein.

[14] T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Letters*, 1965, 3889.

stabilised by an intramolecular hydrogen-bond only in the case of (10A); and (iii) the carbonyl group of the ester can act as a general base catalyst, thereby increasing the nucleophilicity of the enolic double bond of (10a).

Several synthetic uses of Hagemann's ester have involved the preparation of 2-substituted 3-methylcyclohex-2-enones through alkylation of its anion and removal with alkali of the ethoxycarbonyl group from the intermediate (1e).[2] Poor yields have been experienced in this latter reaction.[15] We have examined the potential of the t-butyl analogue (1b) as a starting material in such syntheses since the t-butoxycarbonyl group is labile to mild acid. Benzylation of the ester (1b) to compound (1f) was effected smoothly on treating its potassium salt with benzyl bromide in acetonitrile. The t-butoxycarbonyl group was removed from the ester (1f) on heating in benzene containing a catalytic amount of toluene-*p*-sulphonic acid and gave 2-benzyl-3-methylcyclohex-2-enone in 72% overall yield.

## EXPERIMENTAL

*Materials.*—Methyl acetoacetate (B.D.H.), ethyl acetoacetate (B.D.H.), t-butyl acetoacetate (Aldrich), pyrrolidine (B.D.H.), and potassium t-butoxide (Kodak) were of satisfactory purity for direct use. AnalaR solvents were used in all reactions. But-3-en-2-one (Koch–Light) was stabilised with 10% water and was dried and distilled [16] immediately before use. $^1$H N.m.r. spectra were taken for *ca.* 10% solutions in carbon tetrachloride at 60 MHz (Perkin-Elmer R12) or at 100 MHz (Varian HA100) using tetramethylsilane as internal standard, i.r. spectra for *ca.* 3% solutions in carbon tetrachloride using 0·25 mm NaCl cells (Perkin-Elmer 257), and u.v. spectra for methanolic solutions in quartz cells (Unicam SP 800). Mass spectra were run on an A.E.I. MS 902 machine (University of Hull service). Full spectroscopic data have not been included for compounds (3a—c), (4c), (5b), and (5c). In the case of (3a—c), the n.m.r., i.r., and mass spectra were unexceptional, whilst for compounds (4c), (5b), and (5c) the spectral data paralleled those for (4a) or (5a). A Honeywell F and M instrument with an SE 30 column (2 ft) at 175° was used for g.l.c.

*Ethyl* (3a), *t-Butyl* (3b), *and Methyl* (3c) *2-Acetyl-5-oxohexanoate.—General procedure.* But-3-en-2-one (*ca.* 1 mol) was added dropwise to a stirred mixture of an ester of acetoacetic acid (1 mol. equiv.) and methanolic sodium methoxide (0·015 mol. equiv.), keeping the temperature of the reaction below 20°. After 18 h at 20° [(3a) and (3c)] or 35° (3b) g.l.c. showed the reactions to be complete. Dichloromethane was added and the mixture was washed with small portions of M-hydrochloric acid. The organic layer was dried and evaporated and the residue was fractionally distilled giving the *ester* (3a), (3b), or (3c) as an oil: (3a) (88%), b.p. 110—121° at 0·1—0·3 mmHg (lit.,[12] 127—129° at 4·5 mmHg), $\lambda_{max.}$ 249 nm (ε 325); (3b) (71%), b.p. 110—116° at 0·1 mmHg, $\lambda_{max.}$ 258 nm (ε 246) (Found: $M^+$, 228·1359. $C_{12}H_{20}O_4$ requires $M$, 228·1361); and (3c) (75%), b.p. 112—120° at 0·2 mmHg, $\lambda_{max.}$ 257 nm (ε 253) (Found: $M^+$, 186·0890. $C_9H_{14}O_4$ requires $M$, 186·0892).

[15] R. A. Barnes and M. Sedlak, *J. Org. Chem.*, 1962, **27**, 4562; see however ref. 18.

*Esters* (1a), *t-Butyl 2-Methyl-4-oxocyclohex-2-enecarboxylate* (1b), *and* (1c).—The ester (3a) (100 g, 0·5 mol), glacial acetic acid (4·5 g, 0·075 mol), and pyrrolidine (4·0 g, 0·055 mol) in 9 : 1 methanol–water (100 ml) were refluxed for 1 h. The solvent was distilled off and the residue was dissolved in ether (250 ml). After being washed with small portions of M-hydrochloric acid and dilute aqueous sodium hydrogen carbonate, the solution was dried and evaporated. The resulting red oil was distilled, giving the ester (1a) as a pale yellow oil (76·5 g, 84%), b.p. 105° at 0·2 mmHg (lit.,[4] 142—144°/15 mmHg); τ 4·19 (q, *J ca.* 1·4 Hz, 3-H), 5·83 (q, *J* 7·2 Hz, $CH_2{\cdot}CH_3$), 6·79 (t, $w_{\frac{1}{2}}$ 9 Hz, 1-H), 7·4—8·0 (m, $[CH_2]_2$), 8·01 (d, *J ca.* 1 Hz, $CH_3C$=), and 8·72 (t, *J* 7·1 Hz, $CH_3{\cdot}CH_2$) [identical with a spectrum of (1a) prepared by Rabe's method [3,4]]; $\nu_{max.}$ 1728s, 1672s, and 1633m cm$^{-1}$; $\lambda_{max.}$ 234 nm (ε 13,500); semicarbazone, m.p. 156° (lit.,[3] 169°). The esters (1b) and (1c) were prepared in the manner described for (1a) except that solvent was omitted, the reaction mixture was heated for 30 min at 80° (bath), and the quantities of catalysts were 0·2 mol. equiv. (pyrrolidine) and 0·25 mol. equiv. (acetic acid): (1b) (76%; *ca.* 90% pure by g.l.c.), b.p. 94° at 0·1 mmHg; τ 4·21 (1H, q), 6·85 (1H, t, $w_{\frac{1}{2}}$ *ca.* 8 Hz), 7·4—7·9 (4H, m), 8·00 (3H, d, *J ca.* 0·5 Hz), and 8·52 (9H, s); $\nu_{max.}$ 1724s, 1674s, and 1632m cm$^{-1}$; $\lambda_{max.}$ 234·5 nm (ε 15,700); *m/e* 210(1%), 154(22), 137(20), 110(23), 109(30), and 57(100) found: $M^+$, 210·1247. $C_{12}H_{18}O_3$ requires $M$, 210·1255); (1c) (73%), b.p. 86—90° at 0·2 mmHg (lit.,[17] 135° at 2 mmHg).

*Ester* (4a) *and Methyl 4-Methyl-2-oxocyclohex-3-enecarboxylate* (4c).—Treatment of esters (3a) or (3c) with hydrogen chloride in benzene followed by *NN*-dimethylaniline (140°/2 h) essentially as described,[12] gave the esters (4a) or (4c) as pale yellow oils (40%): (4a), b.p. 90° at 0·1 mmHg (lit.,[12] 119—120° at 3·5 mmHg); τ 4·23 (q, *J ca.* 1 Hz, 3-H), 5·88 (q, *J* 7·1 Hz, $CH_2{\cdot}CH_3$), 6·86 (q, $w_{\frac{1}{2}}$ 13 Hz, 1-H), 7·6—8·0 (m, $[CH_2]_2$), 8·05 (s, $CH_3CH$=), and 8·75 (t, *J* 7·1 Hz, $CH_3{\cdot}CH_2$); $\nu_{max.}$ 1740s, 1680s, and 1636mw cm$^{-1}$; $\lambda_{max.}$ 236 nm (ε 13,700); *semicarbazone*, m.p. 163° (from ethanol) (Found: C, 55·3; H, 7·15; N, 17·75. $C_{11}H_{17}N_3O_3$ requires C, 55·2; H, 7·15; N, 17·55%); and (4c), b.p. 85—90° at 0·1 mmHg, needles, m.p. 52—53° (from acetone–hexane) (Found: C, 64·2; H, 6·9. $C_9H_{12}O_3$ requires C, 64·25; H, 7·2%).

*Ethyl* (5a), *t-Butyl* (5b), *and Methyl* (5c) *Esters of 2-Methyl-4-pyrrolidinocyclohexa-1,3-dienecarboxylic Acid.—General procedure* (0·01—0·1 *molar scale*). The ester (1) [or (3)] was mixed with pyrrolidine (4% excess). An exothermic reaction occurred; the mixture became yellow, and finally solidified. The solid was taken up in M-hydrochloric acid and after washing with ether, the aqueous extract was basified. The precipitated solid was filtered off, washed with water, and dried (yield *ca.* 90%). Alternatively, the ester (1) [or (3)] was refluxed (Fo) min with and 1 equiv. of pyrrolidine in methanol. Evaporation gave the crystalline product (5). Recrystallisation of these crude products (3 × from hexane) gave analytical samples: (5a) yellow *plates* which darkened in air, m.p. 71—71·5°; τ 5·53 (1H, s, H-3), 5·92 (2H, q, $CH_2{\cdot}CH_3$), 6·72 (4H, m, $CH_2{\cdot}N{\cdot}CH_2$), 7·5—8·2 (8H, m, 2 × $[CH_2]_2$), 7·86 (3H, s, $CH_3C$=), and 8·73 (3H, t, $CH_3{\cdot}CH_2$); $\nu_{max.}$ 1683s and 1615m

[16] L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 697.

[17] E. Schwenk and E. Bloch, *J. Amer. Chem. Soc.*, 1942, **64**, 3050.

$cm^{-1}$; $\lambda_{max.}$ 386 nm (ε 31,600); *m/e* 235(98%), 206(1 190(54), and 162(100) (Found: *M*, 235·1561. $C_{14}H_{21}N\cup_2$ requires 235·1572); (5b) yellow *needles*, m.p. 79—80° (Found: C, 72·85; H, 9·45; N, 5·45. $C_{16}H_{25}NO_2$ requires C, 72·95; H, 9·55; N, 5·3%); and (5c) yellow *crystals*, m.p. 85° (Found: C, 70·55; H, 8·6; N, 6·3. $C_{13}H_{19}NO_2$ requires C, 70·55; H, 8·65; N, 6·35%).

*t-Butyl 3-Benzyl-2-methyl-4-oxocyclohex-2-enecarboxylate* (1f) *and 2-Benzyl-3-methylcyclohex-2-enone* (with M. R. Adams).—Ester (1b) (5·92 g, 0·028 mol) in dry acetonitrile (40 ml) was added dropwise to potassium t-butoxide (3·26 g, 0·029 mol) under nitrogen at 0°. After stirring for 10 min, benzyl bromide (5·0 g, 0·029 mol) in acetonitrile (10 ml) was added dropwise. The mixture was allowed to warm to room temperature and after 2 h was filtered and evaporated. The residue was distilled giving the *ester* (1f) (6·95 g, 83%) as an oil, b.p. 128—130° at 0·01 mmHg; τ 2·88 (5H, s), 6·33 (2H, s), 6·85 (1H, t, $w_{\frac{1}{2}}$ 8 Hz), 7·5—8·0 (4H, m), 8·09 (3H, s), and 8·60 (9H, s); $\nu_{max.}$ 1730s, 1675s, and 1630mw $cm^{-1}$; $\lambda_{max.}$ 243 nm (ε 9850); *m/e* 300 ($M^+$) and 229 (100%) (Found: C, 75·2; H, 7·95. $C_{19}H_{24}O_3$ requires C, 75·95; H, 8·05%).

The ester (1f) (6·1 g, 0·020 mol) and toluene-*p*-sulphonic acid (0·2 g) in dry benzene (80 ml) were refluxed for 24 h under nitrogen. The solution was washed with aqueous sodium hydrogen carbonate and, after drying, the benzene was removed. 2-Benzyl-3-methylcyclohex-2-enone [3·5 g, 87%; overall yield from (1b) 72%] was obtained as a pale yellow oil, b.p. 90° at 0·05 mmHg (lit.,[15] 123—126° at 0·3 mmHg). I.r. and u.v. spectra were in agreement with previously reported [18] data.

We thank Professor J. W. Cornforth for suggesting this investigation and for discussions, Dr. W. R. Bowman for discussions on the mechanism of the pyrrolidine-catalysed reactions, and the S.R.C. for a research studentship (to A. L. B.).

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[18] O. R. Ghatak, J. J. Chrakraiarty, and A. K. Banerjii, *Tetrahedron*, 1968, **24**, 1577.