Reduction of Enaminones in the Preparation of 3-Aminocyclohexanols; a Novel Preparation of Tetronic Acid

By **John V. Greenhill,* Mohamed Ramli,** and **Therezinha Tomassini,** School of Pharmacy, University of Bradford, Bradford BD7 1DP

Reduction of enaminones derived from cyclohexane-1,3-dione gives the corresponding 3-aminocyclohexanols. In the case of the *N*-unsubstituted derivative the major product is the *trans*-isomer. The position of attack of ammonia on 2-acetylcyclopentanone and 2-acetylcyclohexanone has been elucidated by reduction of the derived enaminones. In the former case the base attacks the side-chain carbonyl group, but in the latter the ring carbonyl group. Reduction of 2-(substituted amino)fumaric esters gave enaminone analogues of tetronic acid, hydrolysis of which afforded tetronic acid [4-hydroxyfuran-2(5*H*)-one] itself.

HYDROGENATION of 3-acetamidophenol over Raney nickel at high temperature and pressure has been reported [1,2] to give, after hydrolysis, 3-aminocyclohexanol (56% yield) with a *cis* : *trans* ratio of about 4 : 1. The ready preparation of enaminones from cyclohexane-1,3-dione [3]

[1] R. R. Burford, F. R. Hewgill, and P. R. Jefferies, *J. Chem. Soc.*, 1957, 2937.

[2] V. J. Traynelis and J. D. Dadura, *J. Org. Chem.*, 1961, **26**, 1813.

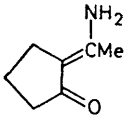
[3] J. V. Greenhill, *J. Chem. Soc.* (*C*), 1971, 2699.

suggested a possible alternative route to 3-aminocyclohexanol and to the corresponding secondary and tertiary amines.

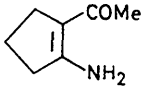
In a preliminary study, enaminones derived from piperidine and phenethylamine were treated with a range of reducing agents. With metal hydrides there was no reduction. Hydrogenation over palladium produced either N–C bond fission to give the parent amine or O–C bond fission to produce the *N*-cyclohexyl derivative of the parent amine. Best results were obtained with Raney nickel in ethanolic sodium hydroxide at 70° and 20 atm pressure: the required amino-alcohols were produced in high yields.

Application of these conditions to 3-aminocyclohex-2-enone gave, after distillation, a 75% yield of the amino-alcohol. This was converted into the benzamide, which after fractional crystallisation gave 59% of the *trans*- and 31% of the *cis*-isomer. This technique offers an alternative route to the 3-aminocyclohexanols, requires milder conditions and, at least in the case investigated, gives considerably more of the *trans*-isomer.

In the course of some synthetic work the reaction between ammonia and 2-acetylcyclopentanone was investigated. Only one enaminone (t.l.c.; column chromatography) was obtained in high yield and it was necessary to seek an unequivocal proof of structure to distinguish between the two possibilities (1) and (2). The

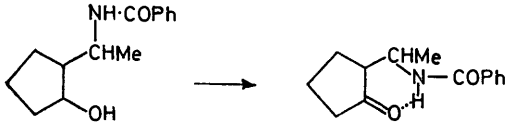


(1)



(2)

compound was resistant to metal hydride reducing agents but was converted into the amino-alcohol by hydrogenation over palladium–charcoal in glacial acetic acid. Oxidation of the benzoyl derivative (3) to the oxo-amide (4) gave a product which showed a doublet methyl signal in the n.m.r. spectrum (τ 8·78; J 7 Hz). The enaminone

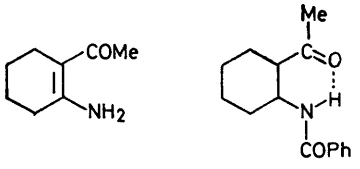


(3) (4)

must therefore have had structure (1), since the alternative (2) would produce an amido-ketone in which the methyl group would give a singlet at about τ 7·90. The i.r. spectrum of compound (4) showed a carbonyl band at 1725 cm^{-1}, presumably indicating intramolecular hydrogen bonding as shown.

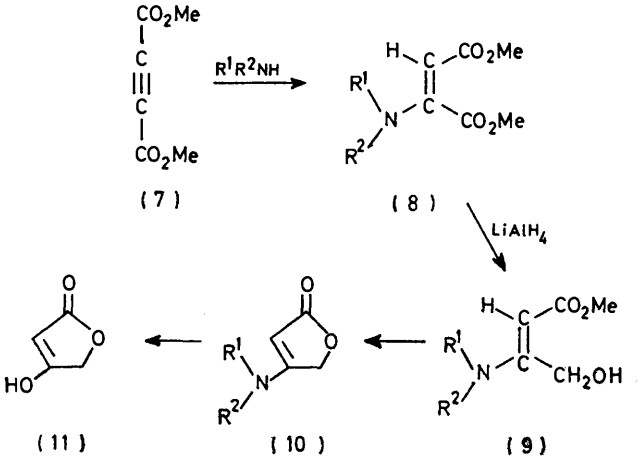
The corresponding reaction of 2-acetylcyclohexanone has previously been reported [4] to give compound (5), identified on the basis of u.v. and n.m.r. spectra. Since neither of these techniques could give an unequivocal proof of structure, we applied our method. Reduction of the only enaminone isolated (86%) to the amino-alcohol with lithium aluminium hydride was successful. Benzoylation followed by oxidation gave compound (6), which showed a singlet methyl absorption in the n.m.r. spectrum (τ 7·83). The i.r. spectrum showed a carbonyl peak at 1700 cm^{-1}.

It is evident that ammonia attacks 2-acetylcyclopentanone at the side-chain carbonyl carbon atom but its homologue at the ring site. In both cases the product would be stabilised by intramolecular hydrogen bonding [5] and by a vinylogous amide electronic interaction between the nitrogen lone pair and the carbonyl group. The difference in reaction site probably reflects the greater thermodynamic stability of exocyclic double bonds in five-membered rings and of endocyclic double bonds in six-membered rings.



(5) (6)

The need to prepare enaminone analogues of tetronic acid led us to repeat a number of the published routes to the parent compound. The most recent work on tetronic acid synthesis involves modifications [6,7] to previous methods and was repeated carefully. In our hands these methods proved difficult and gave variable results. Our experience with enaminone reduction led us to investigate the route outlined in the Scheme. The addition of



SCHEME

ammonia and amines to the acetylenic diester (7) has been carefully studied.[8] Although the reaction proceeds

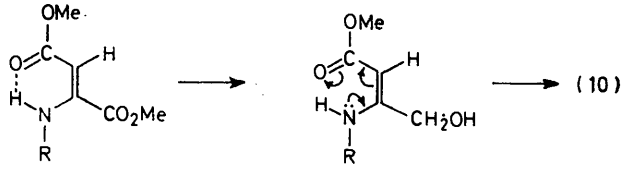
[4] D. L. Ostercamp, *J. Org. Chem.*, 1970, **35**, 1632.
[5] K. Dixon and J. V. Greenhill, *J.C.S. Perkin II*, 1974, 164.
[6] K. J. Boosen, Swiss Pat., 529,128/1972.
[7] T. P. C. Mulholland, R. Foster, and D. B. Haydock, *J.C.S. Perkin I*, 1972, 1225.
[8] R. Huigsen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, 1966, **99**, 2526; K. Herbig, R. Huigsen, and H. Huber, *ibid.*, p. 2546.

in high yield, the isomer ratio of the product depends upon the amine used.

In compound (8) one carbonyl group is part of an enaminone system whereas the other would be expected to react as a simple ester. We hoped that the latter might be more readily reduced by lithium aluminium hydride to give the alcohol (9) which might be induced to ring close to the enaminone (10).

Reactions were carried out with a series of diesters (8) and several solvents. We were unable to reduce tertiary enaminones (8; $R^1 = R^2 =$ alkyl) or primary enaminones (8; $R^1 = R^2 = H$). In all cases starting material was recovered, although after prolonged refluxing (24 h) this was sometimes accompanied by a small quantity of an intractable product. With the secondary enaminones investigated (8; $R^1 = H$, $R^2 =$ Me, Bu^t, or Ph) reaction occurred during 3 h in refluxing tetrahydrofuran. In no case was any alcohol (9) isolated, the product always proving to be the enaminone (10). Hydrolysis of this compound (followed by u.v. spectroscopy) was complete in 12 h at room temperature. Removal of the liberated amine by ion-exchange and careful evaporation of the aqueous solution below 50° avoided the formation of anhydrotetronic acid [9] and gave an essentially pure product.

The addition of secondary amines to the acetylenic diester (7) has been shown [8] to give exclusively the *cis*-product (8). Failure to reduce these compounds even with prolonged refluxing is probably due to steric hindrance by the enaminone methoxycarbonyl group. The corresponding primary and secondary enaminones (8) were shown to exist mainly in the *trans*-form, and on warming the proportion of the hydrogen-bonded, thermodynamically more stable, *trans*-isomer was further increased. Steric hindrance to the reduction of the ester group [see (12)] would then be less and it seems that



(12) (13)

the primary alcohol (13) is first formed. Inversion of the configuration would be facilitated by the partial single-bond character of the C=C link [see (13)] and ring closure could thus occur spontaneously under the reaction conditions. In view of the previously recorded experience with the reduction of enaminones it is not surprising that the product (10) is resistant to further reduction. That the primary enaminone (8; $R^1 = R^2 = H$) is not reduced is more difficult to explain, but probably reaction is prevented by complex formation between the NH_2 group and the reagent.

Enaminones have considerable potential as starting materials in synthesis. The present work has given us new routes to 3-amino-alcohols and to tetronic acid. Although overall yields of tetronic acid are no better than those achieved by other workers, we have found this the easiest way to make the compound and the route is potentially capable of further improvement.

EXPERIMENTAL

Reduction of 3-Aminocyclohex-2-enone.—A mixture of the enaminone (1 mol), aqueous 20% sodium hydroxide (20 ml), and Raney nickel (W7) [10] in ethanol (500 ml) was hydrogenated at 70° and 20 atm until uptake ceased (*ca.* 8 h). After filtration, the solution was evaporated and most of the residual water removed by azeotropic distillation with benzene. The residue was shaken with chloroform (1 l) and the solution dried ($MgSO_4$) and evaporated; the residual oil was distilled to give 3-aminocyclohexanol (75%), b.p. 130—134° at 20 mmHg (lit.,[2] 118—122° at 13 mmHg). Similarly were prepared (a) 3-methylaminocyclohexanol (52%), b.p. 130—132° at 20 mmHg (lit.,[11] 68° at 0·05 mmHg), i.r., n.m.r., and mass spectra consistent with structure; (b) 3-*piperidinocyclohexanol* (50%), b.p. 146—148° at 20 mmHg, m.p. 104—105° [from light petroleum (b.p. 80—100°)] (Found: C, 72·0; H, 11·4; N, 7·8; O, 8·6. $C_{11}H_{21}NO$ requires C, 72·1; H, 11·6; N, 7·6; O, 8·7%) [*hydrochloride*, m.p. 216—217° (from ethanol–ether) (Found: C, 59·9; H, 10·1; N, 6·4; O, 7·2. $C_{11}H_{22}ClNO$ requires: C, 60·2; H, 10·0; N, 6·4; O, 7·3%)]; (c) 3-*phenethylaminocyclohexanol* (74%), m.p. 109° [from light petroleum (b.p. 80—100°)] (Found: C, 76·7; H, 9·5; N, 6·4. $C_{14}H_{21}NO$ requires C, 76·7; H, 9·65; N, 6·4%) [*hydrochloride*, m.p. 220° (from ethanol) (Found: C, 65·6; H, 8·5; N, 5·3. $C_{14}H_{22}ClNO$ requires: C, 65·7; H, 8·6; N, 5·5%)].

cis : trans *Ratio of 3-Aminocyclohexanol.*—The distilled product of the above reaction was completely melted and stirred. To a sample (2·4 g) were added water (30 ml), aqueous 20% sodium hydroxide (12 ml), and benzoyl chloride (6 g), and the mixture was shaken for 10 min in a stoppered flask. The product was extracted with warm chloroform (6 × 50 ml) and the extracts were rapidly washed with water (10 ml) and evaporated. The residue was dissolved in the minimum of chloroform and kept at 0° overnight to yield *trans*-3-benzamidocyclohexanol (2·7 g, 59%), m.p. 170—171° (raised to 172·5—173·5° without significant loss on further recrystallisation) (lit.,[1] 169°). Addition of petroleum (b.p. 40—60°) to the filtrate gave *cis*-3-benzamidocyclohexanol (1·4 g, 31%), m.p. 149—151° (raised to 153—154° on recrystallisation from ethyl acetate) (lit.,[1] 155°).

2-(1-*Aminoethylidene*)*cyclopentanone* (1).—Ammonia was passed into a solution of 2-acetylcyclopentanone (47 g) (purified by way of its copper chelate, m.p. 240°) in ethanol (100 ml) for 2½ h and the product was set aside overnight. The solvent was evaporated off, the residue taken up in methylene chloride, and the solution washed with 5% sodium hydroxide and water (2 × 20 ml), dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica column (ethyl acetate) to give a single *product* (3·7 g, 79%), m.p. 83—84° (unchanged on recrystallisation from benzene–light petroleum) (Found: C, 67·0; H, 8·5; N, 11·5. $C_7H_{11}NO$ requires C, 67·2; H, 8·8; N, 11·2%), $\lambda_{max.}$ (EtOH) 319 nm (ε 13,600); $\nu_{max.}$ (KBr) 1520 and 1630 cm^{-1} (enaminone), τ ($CDCl_3$) 7·60 (m, $[CH_2]_3$) and 8·10 (s, Me).

2-(1-*Aminoethyl*)*cyclopentanol.*—A solution of 2-(1-amino-

[9] L. Wolff and C. Schwabe, *Annalen*, 1896, **291**, 226.
[10] H. Adkins and H. R. Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695.
[11] T. D. Perrine, *J. Org. Chem.*, 1951, **16**, 1303.

ethylidene)cyclopentanone (0·55 g) in glacial acetic acid (50 ml) was hydrogenated for 8 h at normal temperature and pressure over 10% palladium–charcoal (1 g). The solvent was removed and the residue dissolved in ether; the solution was washed with aqueous sodium hydroxide, dried, and evaporated to give the crude amino-alcohol (0·5 g). Benzoylation (PhCOCl) in 10% sodium hydroxide gave 2-(1-benzamidoethyl)cyclopentanol (3) (0·8 g), $\nu_{max.}$ (film) 1640 (amide C=O) and 3400 cm^{-1} (OH).

2-(1-*Benzamidoethyl*)*cyclopentanone* (4).—A solution of the foregoing alcohol (0·5 g) in acetone was oxidised with Jones reagent (0·5 ml) to give the *oxo-amide* (0·4 g), m.p. 91° [from petroleum (b.p. 80—100°)] (Found: C, 72·9; H, 7·4; N, 6·1. $C_{14}H_{17}NO_2$ requires C, 72·7; H, 7·4; N, 6·1%), $\nu_{max.}$ ($CHCl_3$) 1650 (amide C=O) and 1725 cm^{-1} (ketone C=O), *m/e* 231, τ ($CDCl_3$) 2·40 (5H, m, aromatic) 7·90br (8H, m, aliphatic), and 8·79 (3H, d, *J* 7 Hz, Me).

1-(2-*Aminocyclohexyl*)*ethanol*.—A solution of 1-acetyl-2-aminocyclohexene [4] [m.p. 107—108°; $\lambda_{max.}$ (EtOH) 317 nm (ε 12,700)] (15 g) in tetrahydrofuran (150 ml) was added to lithium aluminium hydride (5 g) in tetrahydrofuran (200 ml) over 1 h, and the mixture was refluxed (1 h). The product obtained after work-up with 20% sodium hydroxide and extraction with ether was distilled to give the amino-alcohol (7 g, 45%), b.p. 135—137° at 0·1 mmHg. The N-*benzoyl derivative* had m.p. 97—98° (from benzene–light petroleum) (Found: C, 72·8; H, 8·4; N, 5·4. $C_{15}H_{21}NO_2$ requires C, 72·9; H, 8·5; N, 5·7%), $\nu_{max.}$ (KBr) 1620 (amide C=O) and 3300 cm^{-1} (OH), τ ($CDCl_3$) 8·90 (3H, d, Me).

1-*Acetyl*-2-*benzamidocyclohexane*.—A solution of the foregoing alcohol (1 g) in acetone (10 ml) was treated with Jones reagent (1·2 ml) to give the *oxo-amide* (0·9 g, 90%), m.p. 158—159° [from light petroleum (b.p. 40—60°)] (Found: C, 73·8; H, 7·5; N, 5·8. $C_{15}H_{19}NO_2$ requires C, 73·5; H, 7·8; N, 5·7%), $\nu_{max.}$ (KBr) 1630 (amide C=O) and 1700 cm^{-1} (ketone C=O), τ ($CDCl_3$) 7·83 (s, Ac).

General Method for 4-(*Substituted amino*)*furan*-2(5H)-*ones*.—A solution of the dimethyl 2-(substituted amino)maleate [8] (0·01 mol) in tetrahydrofuran (100 ml) was added dropwise to lithium aluminium hydride (0·01 mol) in tetrahydrofuran (80 ml) and the mixture was refluxed for 3 h. The cooled product was treated with just enough water to decompose the reagent, dried ($MgSO_4$), and evaporated. Recrystallisation gave (a) 4-*methylaminofuran*-2(5H)-*one* (48%), m.p. 149—150° (from ethyl acetate–light petroleum) (Found: C, 53·1; H, 6·2; N, 12·4. $C_5H_7NO_2$ requires C, 53·1; H, 6·2; N, 12·4%), *m/e* 113, $\nu_{max.}$ (KBr) 1610 and 1705 cm^{-1}, τ ($CDCl_3$) 5·28 (2H, s, CH_2), 5·36 (1H, s, =CH), and 7·18 (3H, s, NH*Me*), $\lambda_{max.}$ (H_2O) 258 nm (ε 18,700); (b) 4-*t*-*butylaminofuran*-2(5H)-*one* (72%), m.p. 121—122° (from benzene–light petroleum) (Found: C, 61·8; H, 8·3; N, 9·0. $C_8H_{13}NO_2$ requires C, 61·9; H, 8·4; N, 9·0%), *m/e* 155, $\nu_{max.}$ (KBr) 1610 and 1725 cm^{-1}, τ ($CDCl_3$) 5·29 (1H, s, =CH), 5·37 (2H, s, CH_2), and 8·68 (9H, s, NH*Bu*^{t}), $\lambda_{max.}$ (H_2O) 262 nm (ε 21,000); (c) 4-*anilinofuran*-2(5H)-*one* (40%), m.p. 219—220° (from ethyl acetate) (Found: C, 68·6; H, 5·2; N, 8·0. $C_{10}H_9NO_2$ requires C, 68·5; H, 5·15; N, 8·0%), *m/e* 175, $\nu_{max.}$ (KBr) 1595, 1610, and 1690 cm^{-1}, τ [$(CD_3)_2CO$] 2·72 (5H, aromatic), 4·75 (1H, s, =CH), and 5·18 (2H, s, CH_2), $\lambda_{max.}$ (H_2O) 285 nm (ε 18,500).

Tetronic Acid.—A solution of 4-t-butylaminofuran-2(5H)-one (0·05 mol) in 2N-HCl (100 ml) was stirred for 12 h, then passed through a column containing Zeo-Karb 225 to remove t-butylamine. The column was washed with water until the washings gave no reaction with iron(III) chloride solution. The aqueous solution was evaporated to dryness at 50°. Drying *in vacuo* (KOH) gave essentially pure tetronic acid [4-hydroxyfuran-2(5H)-one] (50%), m.p. 140° (lit.,[12] 140—142°), *m/e* 100, $\nu_{max.}$ (KBr) 1595 and 1695 cm^{-1}, τ (CD_3OD) 5·05 (2H, s, CH_2) and 5·31 (1H, s, =CH), $\lambda_{max.}$ (H_2O) 225 nm (ε 13,500).

We thank Mr. R. Smith for technical assistance.

[4/2103 *Received*, 10*th October*, 1974]

[12] E. Benary, *Ber.*, 1907, **40**, 1079.