Tetrahedron Letters No. 17, pp. 1397-1400, 1970. Pergamon Press. Printed in Great Britain.

# Stereochemical control in the hydrolysis of an ynamine-cyclopentenone adduct : a stereoselective route to diastereoisomeric 2-(1-cyclopentyl 3-oxo) propionic acids.

Jacqueline Ficini et Alain Krief

Laboratoire de Chimie Organique de Synthèse
8, rue Cuvier - Paris (5e)

(Received in UK 24 February 1970; accepted for publication 12 March 1970)

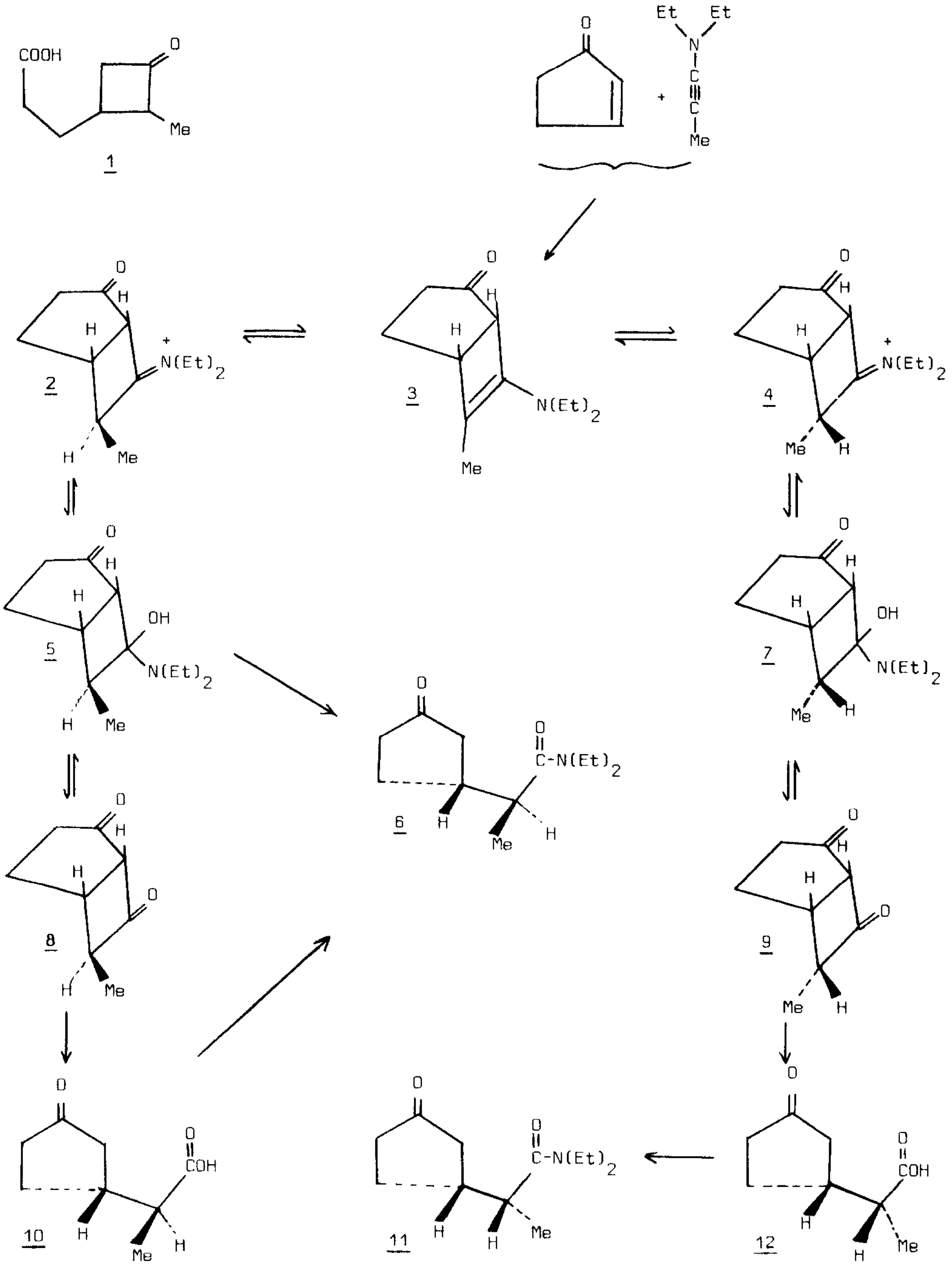
We have previously reported, that N,N diethylaminopropyne[1] reacts with open chain α-β ethylenic ketones, to give 2-amino γ pyrans via a heterocyclisation reaction[2], whereas carbocyclisation takes place with cyclopentenone to give the amino-bicycloheptenone 3 in 70 % yield.

We now report that the hydrolysis of the adduct 3 occurs with high stereoselectivity and that it is possible to control the stereochemical course of the hydrolysis by proper adjustment of the pH of the medium.(Scheme I).

Under acidic conditions (excess 10 % aquesous hydrochloric acid), the adduct 3 leads to the keto-acid 12 : bp 121° (0,1 mm); $n_D^{26}$ 1.4758; nmr ($CDCl_3$) δ 1.24 ppm (d, 3, J=6 Hz, $CH_3$). This acid, which gives the corresponding amide 11 : bp 90° (0,04 mm) $n_D^{26}$ 1.4766; 2,4 DNPH mp 154°, via its acid chloride is a single diastereoisomer, free of 10. In contrast, and as expected, methylmalonic diester reacts with cyclopentenone, under Michael conditions, to give a 50/50 mixture of the two diastereoisomeric keto-acids 12 and 10 : nmr ($CDCl_3$) δ 1.25 ppm (d, 3, J=6 Hz, $CH_3$), from which are separated the two corresponding keto-amides 11 : 2,4 DNPH mp 154° and 6 : 2,4 DNPH mp 214°.

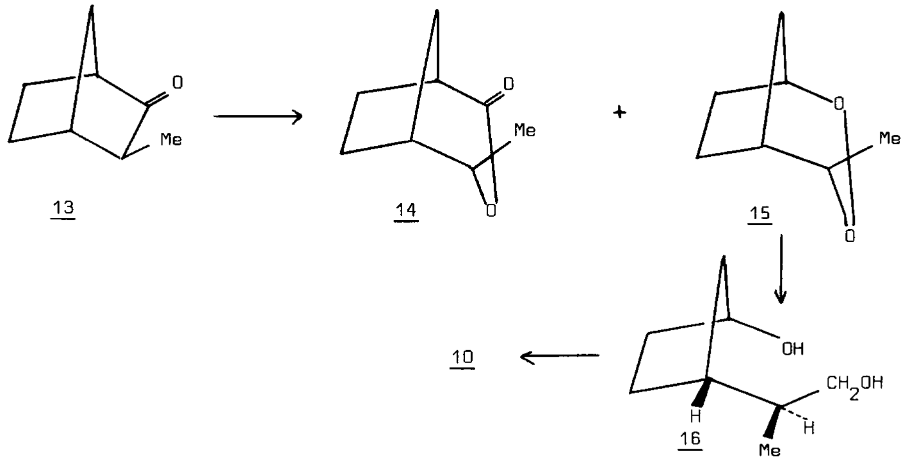
In contrast to the results under acidic conditions, basic hydrolysis of 3 (catalytic amount 1°/₀₀ aqueous sodium hydroxide), affords the diastereoisomeric keto-amide 6 : bp 110° (0,08 mm); $n_D^{21}$ 1.4760; 2,4 DNPH mp 214°, in 60 % yield.

SCHEME I


COOH
O
Me
1
O
Et
Et
N
C
C
Me
+
O
H
H
+
N(Et)2
H
Me
2
O
H
H
N(Et)2
Me
3
O
H
H
+
N(Et)2
Me
H
4
O
H
H
OH
N(Et)2
H
Me
5
O
H
H
OH
N(Et)2
Me
H
7
O
O
C-N(Et)2
H
Me
H
6
O
H
H
O
H
Me
8
O
H
H
O
Me
H
9
O
O
COH
H
Me
H
10
O
O
C-N(Et)2
H
H
Me
11
O
O
COH
H
H
Me
12

The stereochemistry of the keto-acids 12 and 10 was established by the unambiguous synthesis of 10 from the known methylnorcamphor[4] 13. Baeyer-Villiger oxidation of 13 with p. nitroperbenzoïc acid[5] gives, in methylene chloride, a 50/50 mixture of the two lactones 14 and 15 in 70 % yield. (Scheme II).

SCHEME II



The lactone 15 : bp 57° (0.15 mm); mp 33°; $n_D^{25}$ 1.4792; nmr ($CDCl_3$) δ 1.34 ppm (d, 3, J=7.6 Hz, $CH_3$), can be separated from its isomer 14 : bp 110° (4 mm); $n_D^{22}$ 1.4789; nmr ($CDCl_3$) δ 1.36 ppm (d, 3, J=6.4 Hz, $CH_3$), by treatment with dilute sodium hydroxide in the cold, which cleaves the lactone ring of 14 but not the more hindered one of 15. The crucial methylated center of 15 is not equilibrated in these conditions. Lithium aluminium hydride reduction of 15 leads to the alcohol 16 : bp 112° (0.04 mm); $n_D^{19}$ 1.4855; bisphenylurethane mp 140°, which is oxidized with Jones reagent to the keto-acid 10 : nmr ($CDCl_3$) δ 1.25 ppm (d, 3, J=6 Hz, $CH_3$), yielding the corresponding keto-amide 6 : 2,4 DNPH mp 214°.

The stereoselectivity observed in the hydrolysis of the adduct 3, can be rationalized by assuming that protonation of the enamine 3 gives kinetically immonium ion 4, in which the proton is added on the less hindered side of the molecule, rather than immonium ion 2. The immonium ion 4 can be equilibrated to the thermodynamically more stable isomer 2 via the enamine 3, but in acidic medium the steps : $4 \rightarrow 7 \rightarrow 9 \rightarrow 12$, leading to the keto-acid 12 are sufficiently faster than the reactions : $4 \rightarrow 3 \rightarrow 2$ or $9 \rightarrow 8$, so that equilibration does not take place. The hypothesis that aqueous acid hydrolysis is kinetically controlled is supported by the fact that if immonium ion 4 is allowed to equilibrate, i.e., if the adduct 3 is treated for 30 min. with dry hydrogen chloride in ether, before addition of a 10 N aqueous hydrochloric acid solution, the dione 8 : nmr ($CCl_4$) δ 1,28 ppm (d, 3, J=7 Hz, $CH_3$); ir (film) 1790, 1732 $cm^{-1}$, which can be isolated in 30 % yield, affords the keto-acid 10 free of diastereoisomer 12, in a quantitative yield. An interesting point is that, under these conditions, hydrolysis of enamine 3 gives also the keto-acid 1 : bp 109° (0.04 mm); $n_D^{22}$ 1.4642; 2,4 DNPH mp 86°, in 45 % yield, whereas under normal acidic conditions (diluted aqueous hydrochlorid acid), this acid is only detected (vpc) in 1 % yield, together with the keto-acid 12.

Under basic conditions equilibration of the α methyl group via : $4 \rightleftharpoons 3 \rightleftharpoons 2$ or $9 \rightleftharpoons 8$, takes place faster than formation of the cleavage product, and 6 is then produced via 5.

The nigh steric control which can be achieved in the hydrolysis of the ynamine cyclopentenone adduct, can be very useful in synthesis. We are presently carrying out experiments with cyclenones other than cyclopentenone to determine the generality of this stereoselectivity and the factors which may limit its occurence.

## Bibliography

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