Tetrahedron Vol 29, pp. 715 to 718 Pergamon Press 1973 Printed in Great Britain

HETEROCYCLIC STEROIDS—VII[1]

REARRANGEMENT OF 1-DIETHYLAMINO-5-(*m*-METHOXYPHENOXY)-PENT-2-YNE

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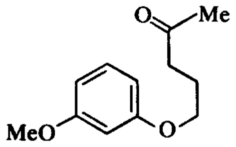
(*Received in the UK* 14 *October* 1972; *Accepted for publication* 13 *November* 1972)

Abstract—Thermal rearrangement of diethylamino-5-(*m*-methoxyphenoxy)-pent-2-yne (**3**) gives 1-(*m*-methoxyphenoxy)-pent-3,4-diene (**14**) in about 8% yield. Hydration of the latter yields 1-(*m*-methoxyphenoxy)-pentan-4-one (**6**), which has been synthesised by an unambiguous route. A mechanism of formation of the allene (**14**) from the amine (**3**) has been suggested.

We have recently reported[1] the synthesis of trione (**1**), an intermediate in the synthesis of 6-oxa-oestrone derivative (**2**) according to Scheme 1.

When the above reactions were carried out with the crude acetylene amine (**3**), as expected, ketol (**5**) and trione (**1**) were formed. However, when the distilled amine (**3**) (b.p. 190°/2 mm) was used, unexpectedly the major product obtained was not the ketol (**5**) or trione (**1**) but another ketone, to which structure **6** has been assigned on the basis of the data mentioned below.

Elemental analysis and mass spectrometry (M^+) corroborated the molecular formula $C_{12}H_{16}O_3$. The presence of *m*-methoxyphenoxy moiety was indicated by UV absorption maxima at 222 (ϵ 5,700), 274 (1,970) and 280 nm (1,800). The compound exhibits bands in the IR spectrum (neat) at 1709 (sat. C=O) and 1597 cm^{-1} (aromatic C=C). The NMR signals were assigned as follows: 1·82–2·15 (m, 2H, CH_2), 2·08 (s, 3H, $COCH_3$), 2·4–2·7 (m, 2H, CH_2CO), 3·72 (s, 3H, OMe), 3·88 (t, $J = 6$Hz, 2H, O-CH_2), 6·25–6·5 (m, 3H, aromatic protons) and 6·9–7·2 (m, 1H, aromatic proton). The ion structures† (**7–11**) assigned to the major fragments *m/e* 150, 124, 95, 94 and 85 respectively lent further support to the structure.



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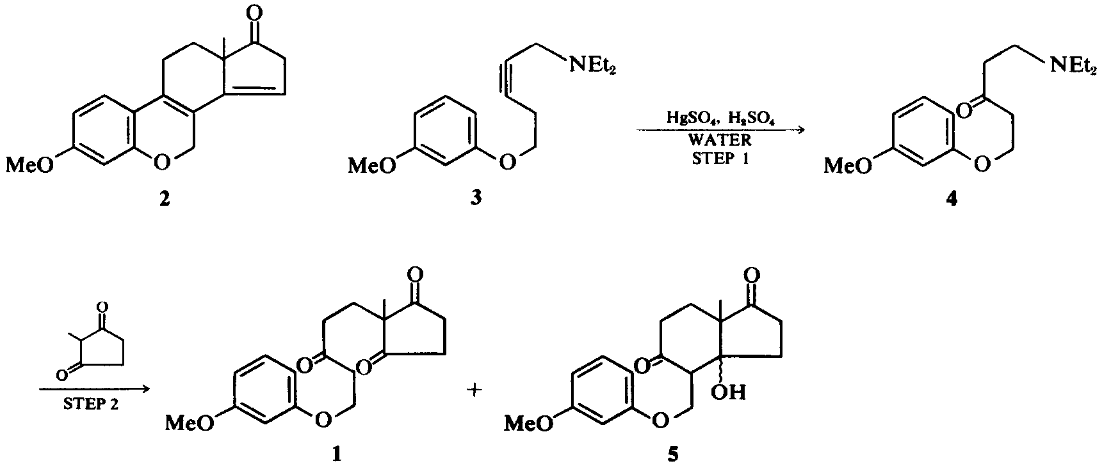

2 **3** **4**

1 **5**

Scheme 1

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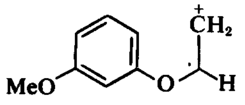
[†] The mass spectral fragments envisaged in this paper have been supported by the occurrence of metastable peaks.



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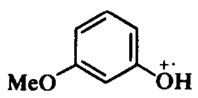

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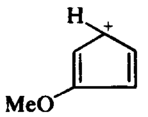

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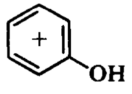

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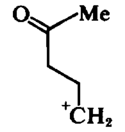

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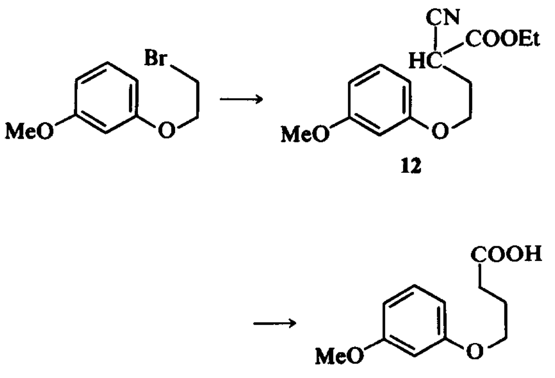
Structure of the ketone (**6**) was further confirmed by its conversion to the acid (**13**) *via* iodoform reaction. This acid was alternatively[2] synthesised as shown in Scheme 2.



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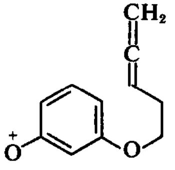
SCHEME 2

Finally, the structure of the ketone (**6**) was established by an unambiguous synthesis involving the condensation of *m*-methoxyphenol with ethylene ketal of 1-bromopentan-4-one in presence of sodium hydroxide.

Initial experiments on the synthesis of the ketol (**5**) or trione (**1**) showed that the ketone (**6**) is not formed during the condensation stage (Step 2 in Scheme 1) but during the hydration step (Step 1 in Scheme 1), as the methyl ketone (**6**) could be isolated after hydration of the distilled amine (**3**).

A careful analysis of the TLC of the distilled amine (**3**) showed the presence in minor amounts of a new compound which could be separated by column chromatography. This compound has been assigned the allene structure (**14**) on the basis of elemental analysis and spectral characteristics The presence of *m*-(methoxyphenoxy) moiety was inferred by UV absorption maxima at 222 (ϵ 7,900), 274 (2,330) and 280 nm (2,160). In the IR spectrum, it showed the characteristic allene absorption at 1960 cm^{-1}. The olefinic protons of the allene double bonds appeared as a perturbed quintet at 4·68 ($J = 3$ Hz, 2H) and a quintet at 5·19 ($J = 6$ Hz, 1H). The ions (*m/e*) 175, 162, 124, and 95, corresponding to the fragments (**15**, **16**, **8** and **9**) support this structure. The yield of allene (**14**) could be improved by refluxing the amine (**3**) in tetralin for 24 hr under an atmosphere of nitrogen.



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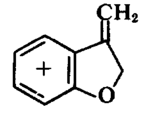

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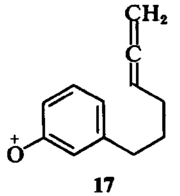
On hydration, the allene (**14**) gave the ketone (**6**), whereas the distilled acetylene amine (**3**) devoid of this allene (**14**) did not give the ketone (**6**).

The presence of the hetero O atom in the acetylene amine (**3**) does not seem to be essential for its conversion to **14**, as allene (**14a**) is formed even from acetylene amine (**3a**) under the conditions of formation of **14** from **3**. The structure of this allene (**14a**) was again clearly proved by its spectral data. The NMR spectrum indicated allene protons at 4·67 (pert. q, $J = 3$ Hz, 2H) and 5·12 (q, $J = 6$ Hz, 1H), while the mass spectral ions (*m/e*) 173, 160, 134 and 121 corresponding to fragments (**17–20**) supported this structure.



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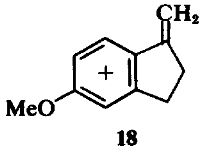

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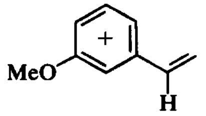

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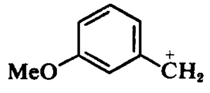

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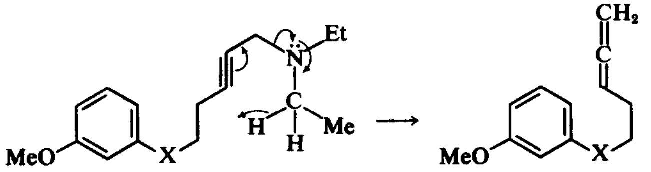
This thermal rearrangement is not base catalysed as the amine (**3**) remained unchanged on treatment with sodium ethoxide or sodamide.

On the basis of the above evidences, it is very clear that the methyl ketone (**6**) is formed from the allene (**14**), which in turn is generated by a thermal rearrangement of the amine (**3**) depicted below.



3: X = 0
3a: X = CH_2

14: X = 0
14a: X = CH_2

Similar type of thermal rearrangement of acetylenes involving 6-membered transition state has been reported.[3-10]

EXPERIMENTAL

M.ps (hot stage) and b.ps reported herein are uncorrected. UV (EtOH soln) spectra were measured on a Unicam SP700A spectrophotometer. IR spectra were measured on a Perkin-Elmer model 137B and Carl Zeiss URIO spectrophotometers. NMR spectra were taken in CCl_4 on a Varian HA 100 spectrometer (unless otherwise mentioned) using TMS as internal standard and all chemical shifts are reported in δ values. Neutral alumina and silica gel were used for column chromatography and TLC respectively. Solvent extracts were dried over Na_2SO_4.

Isolation of 5-(m-*methoxyphenoxy*)-*pentan*-2-*one* (**6**) *in the preparation of* 1-(2,5-*diketo*-1-*methylcyclopentyl*)-5-(m-*methoxyphenoxy*)-*pentan*-3-*one* (**1**). Distilled **3** (4 g)[1] was kept with mercuric sulphate (0·22 g) in water (12·6 ml) containing conc H_2SO_4 (0·63 ml) at 75° for 3 hr under N_2. The cooled soln was basified with 3N NaOH, extracted with ether and washed with 5% NaOHaq. Removal of solvent *in vacuo* gave the product (2·34 g) suspected to be **4**. This crude product (1·4 g) and 2-methylcyclopentan-1,3-dione (1·4 g) in dry MeOH (5·6 ml) were refluxed for 10 hr. Most of the MeOH was removed *in vacuo*. The residue was extracted with benzene and the soln was washed with $NaHCO_3$aq, 3N HCl, dil NaOHaq and water. The crude material, after the removal of benzene, showed in TLC three spots of R_f values 0·18, 0·26 and 0·8 (5:1 benzene-EtOAc). Preparative TLC of the crude product led to three fractions, the ketol **5** (0·015 g), the trione **1** (0·005 g) and the ketone **6** (0·12 g, R_f 0·8), b.p. 115–120°/2 mm (bath temp). (Found: C, 69·25; H, 7·64. $C_{12}H_{16}O_3$ requires: C, 69·21; H, 7·74%).

2-*Cyano*-4-(m-*methoxyphenoxy*)-*ethyl butyrate* (**12**). Ethyl cyanoacetate (5·65 g) in toluene (10 ml) was added dropwise to NaOEt (from 1·15 g Na in 3 ml super dry EtOH) in toluene (20 ml). After stirring for 2 hr, a soln of 2-(*m*-methoxyphenoxy)-ethyl bromide (23·1 g) in toluene (20 ml) was added and the mixture refluxed for 24 hr. The mixture was extracted with ether and washed with water several times. Solvents were removed *in vacuo* and the residue distilled to yield the ester (3·62 g, 27·5%), b.p. 160°/5·7 × 10^{-4} mm; (Found: C, 63·86; H, 6·46; N, 5·78. $C_{14}H_{17}NO_4$ requires: C, 63·87; H, 6·46; N, 5·32%); IR ν_{max}^{neat} 1600 (aromatic C=C), 1735 (ester C=O) and 2260 cm^{-1} (C≡N).

4-(m-*Methoxyphenoxy*)-*butyric acid* (**13**). The cyanoester **12** (1 g) was refluxed with 20% HClaq (60 ml) for 20 hr and the excess HCl was removed *in vacuo*. Residue was taken up in ether, washed with water and extracted with 5% $NaHCO_3$aq. The bicarbonate washings were acidified and extracted with ether. Solvent was removed, the residue was crystallized from light petrol (40–60°) to give the acid (0·29 g, 35%); m.p. 69–70° (lit.[2] 70–71°); (Found: C, 62·59; H, 6·63. $C_{11}H_{14}O_4$ requires: C, 62·86; H, 6·67%); IR ν_{max}^{nujol} 1590 (C=C), 1720 (acid C=O) and 3160 cm^{-1} (acid OH); NMR* 1·8–2·8 (m, 4H), 3·78 (s, OCH_3), 4·02 (t, $J = 6$ Hz, 2H, -OCH_2), 6·38–6·65 (m, 3H, aromatic protons), 7–7·4 (m, 1H, aromatic proton) and 9·38 (s, 1H, OH).

5-(m-*Methoxyphenoxy*)-*pentan*-2-*one* (**6**). A mixture of 9% ethanolic NaOH (2 ml) and *m*-methoxyphenol (0·54 g) were refluxed for 15 min. The ethylene ketal of 1-bromopentan-4-one[11] (1 g) was added during 1½ hr in six portions. The mixture was refluxed for 18 hr and alcohol was removed. The residue was treated with dil HCl and the mixture extracted with ether. The ether extract was successively washed with water, 5% NaOHaq and water. Ether was removed and the residue (0·54 g) was purified by preparative TLC to give **6** (0·15 g, 16%); b.p. 128–130°/3 mm (bath temp). UV, IR and NMR were identical with **6** isolated in the first reaction.

Iodoform reaction of 5-(m-*methoxyphenoxy*)-*pentan*-2-*one*. To a homogeneous soln of **6** (0·25 g) in a mixture of water and dioxane (5 ml) was added dropwise 5% NaOHaq followed by KI-I_2 reagent (prepared by dissolving 5 g KI and 2·5 g I_2 in 25 ml water) until a definite dark colour of iodine persisted. The mixture was allowed to stand for a few min and then warmed for 15 min, when more of iodoform separated. Excess of I_2 was removed by adding more of NaOHaq with shaking. The soln was extracted with chloroform and washed with 5% NaOHaq. The alkali extract was acidified after adding $NaHSO_3$ and extracted with ether. The residue obtained after removing ether (0·18 g, 71%) was treated with norite and crystallised from light petrol (40–60°), m.p. 69–70°.

1-(m-*Methoxyphenoxy*)-*penta*-3,4-*diene* (**14**). A soln of **3** (1 g) in tetralin (6 ml) was refluxed under N_2 (bath temp 270°) for 24 hr. Tetralin was distilled off *in vacuo* and the residue was purified by short path distillation. The distilled material showed a weak allene absorption in the IR spectrum (1960 cm^{-1}). This material on purification by column chromatography followed by short path distillation gave **14** (59 mg); b.p. 75°/2 mm (bath temp); (Found: C, 75·88; H, 7·59. $C_{12}H_{14}O_2$ requires: C, 75·76; H, 7·43%); IR ν_{max}^{neat} 1960 (C=C=C) and 1610 cm^{-1} (aromatic C=C); NMR† 2·26–2·6 (symmetric m, 2H, $C\underline{H}_2$-CH), 3·72 (s, 3H, OMe), 3·9 (t, $J = 6$ Hz, 2H, $OC\underline{H}_2$-), 6·2–6·5 (m, 3H, aromatic) and 6·8–7·28 (m, 1H, aromatic).

1-(m-*Methoxyphenyl*)-*hexa*-4,5-*diene* (**14a**). A soln of **3a**[12] (1 g) in tetralin (6 ml) was refluxed under N_2 (bath

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*NMR was taken in $CDCl_3$ on a varian A60 spectrometer.

†NMR data for similar type of allenes (XCH_2CH_2-CH=C=CH_2) are known in literature.[13,14]

temp 270°) for 24 hr. After the usual work up, the pure **14a** (50 mg), b.p. 65°/2 mm was obtained. (Found: C, 82·88; H, 8·49. $C_{13}H_{16}O$ requires: C, 82·94; H, 8·57%); IR ν_{max}^{neat} 1960 (C=C=C) and 1619 cm^{-1} (aromatic C=C), UV λ_{max} 222 (ϵ 10,000), 272 (2,820) and 279 nm (2,630), NMR 1·5–2·3 (complex m, 4H, $2CH_2$), 2·63 (t, $J = 7·2$ Hz, 2H, benzylic protons), 3·78 (s, 3H, OCH_3), 6·68–6·87 (m, 3H, aromatic protons) and 7·08–7·38 (m, 1H, aromatic proton).

Acknowledgement—The authors are thankful to Prof. G. R. Pettit, Arizona State University, Arizona, USA for the mass spectra and Prof. D. K. Banerjee of this department for useful discussions. Two of us (G. G. and K. M. D.) are thankful to Council of Scientific and Industrial Research, New Delhi, for financial assistance.

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