Tetrahedron. Vol. 34, pp. 951 to 954. Pergamon Press 1978. Printed in Great Britain

AROMATIZATION OF ALIPHATIC COMPOUNDS—II[1]

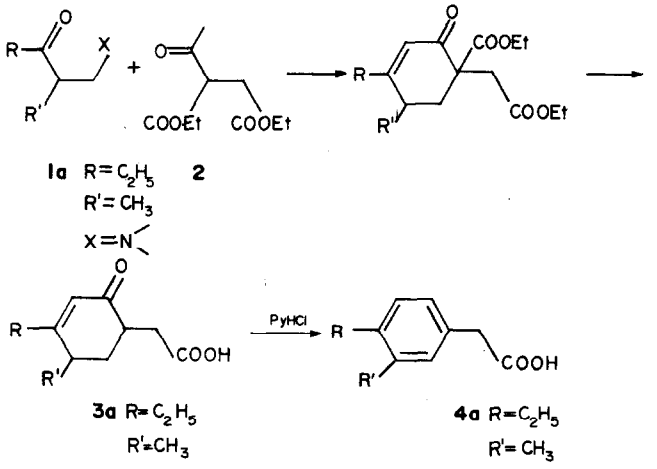
ON THE AROMATIZATION OF SOME ALKYL SUBSTITUTED CYCLOHEXENONES

LEANDRO BAIOCCHI,* MARILENA GIANNANGELI and MICHELE BONANOMI
Department of Chemistry, F. Angelini Research Institute, Viale Amelia 70, 00181 Rome, Italy

(*Received in the UK 9 August 1977; Accepted for publication 2 September 1977*)

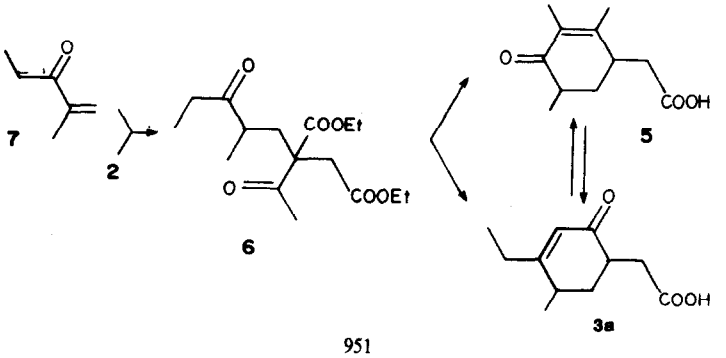
Abstract—2,3,5-Trimethyl-4-oxo-cyclohex-2-en acetic acid **5** treated with PyHCl aromatizes to the corresponding 2,3,5-trimethyl-benzene acetic acid **9** through a mechanism different from that leading to arylacetic acids from 2-oxo-cyclohex-3-en acetic acids **3**. 2,3,4,6-Tetrakyl cyclohexenone **11**, lacking the 2-carboxymethyl group, also aromatizes to tetralkyl benzene **13**.

Substituted aryl-acetic acids, useful as anti-inflammatory agents can be obtained according to the scheme outlined in the following chart:[1-3]



As previously described,[1,4] by condensing Mannich bases **1** in which R′ = H with diethyl acetyl succinate **2**, after hydrolysis of the reaction mixture only mono-substituted cyclohexenonacetic acids were obtained. We then found that, after refluxing **2** and **1a** in KOH/BuOH for 16 h and saponifying the resulting mixture, an acid was separated whose NMR spectrum showed signals due to methyl resonance but not to vinylic protons. On this basis we assigned structure **5** to the compound. Despite a correct elemental analysis, **5** showed two peaks upon GLC analysis, indicating that it was a diastereoisomeric mixture. This result was not quite unexpected since the succinate **6** may be thought of as the first product of the reaction between **1a** and **2** which can then give **3a** or **5** through cyclization, saponification and decarboxylation.

It is known that when two different cyclohexenones can be obtained from asymmetric 1,5-diketones, it is possible, by varying the reaction conditions, to obtain different ratios of the two compounds, the less substituted one being the product of kinetic control of the reaction, and the more substituted one that of thermodynamic control.[5] We thus prepared **6** by reaction **2** with vinyl ketone corresponding to **1a**, i.e. **7**, at room



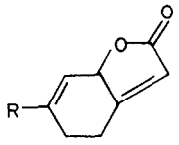
temperature with catalytic amounts of the base. We then treated it with varying amounts of 1N NaOH at reflux for 2.5 h and found that besides the diastereoisomers of **5**, there was another pair later identified as **3a**. The ratio of these compounds **3a/5** was related to the quantity of NaOH employed (see Table 1).

Table 1.

Moles 1N NaOH per mole of **6**	**3a/5**
1	3.5
2	2.2
3	0.4
4	0

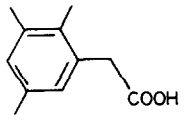
From these results, it was possible to choose suitable conditions to obtain a mixture of **3a** and **5** particularly rich in **3a**; after treatment of this mixture with diazomethane, the methyl ester of **3a** was separated by means of column chromatography.

The methyl ester of **3a**, when treated with PyHCl at 220° for 30 min gave, nearly quantitative yield, 4-ethyl-3-methyl-benzene-acetic acid **4a**. Nevertheless, it did not seem necessary to prepare **3a** in order to aromatize this compound to **4a**. Better overall yields of **4a** were obtained when **6** was treated directly with PyHCl at reflux. The preparation of arylacetic acids from suitable 1,5-diketo-esters is the subject of a patent assigned to our laboratory.[3] Having already postulated in our previous paper,[1] in which the new synthesis of arylacetic acids was published, the lactones **8** as key intermediates in the aromatization step, we thought it interesting to treat **5**, which cannot give a similar lactone, with PyHCl.



8

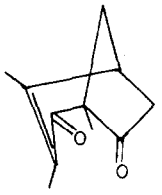
Considerable amounts of unreacted **5** were recovered after heating for 2 h at 220°, conditions which are known to be suitable for the aromatization of several type **3** compounds. However, the presence of a considerable quantity of aromatic protons was noted in the NMR spectrum of the reaction mixture. Protracted heating (20 h) produced complete transformation of **5** into 2,3,5-trimethyl-benzene-acetic acid **9**.



9

This rather unexpected result induced us to investigate this reaction more carefully.

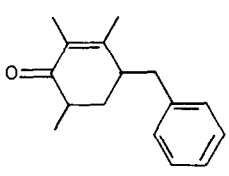
We could detect by GLC analysis the presence of small quantities of an unknown substance together with **9** and unreacted **5** in the aromatization mixture, after 30 min of heating. This substance was separated and, on the basis of its elemental analysis, UV, IR, NMR and mass spectra the bicycloctendione structure **10** was assigned.



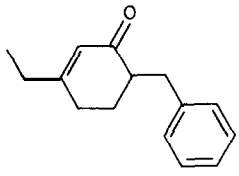
10

This compound **10** seems to derive from intramolecular attack of the acylium ion on the carbon atom α to the ketonic C=O. This behaviour resembles the synthesis of 1-benzyl-bicyclo[3.3.1]nonan-4,6-dione by means of PTSA in decalin.[6] Compound **10**, when treated with PyHCl at reflux gave **9** in good yields. In order to clarify whether **10** is a forced intermediate in the conversion of **5** into **9**, we attempted the aromatization of an analogue of **5** which was lacking the acidic moiety.

We selected 4-benzyl-2,3,6-trimethyl cyclohexenone **11** which we obtained from **1a** and diethyl-benzyl-acetoacetate. Once again we obtained a mixture of the two possible cyclohexenones **11** and **12** from which **12** was separated as mixture of diastereoisomers by means of repeated spinning band distillations.

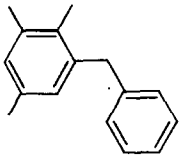


11



12

Compound **11** can be obtained by very long alkaline heating of **12** or of the crude reaction mixture.[5] When treated with PyHCl at 220° for 20 h **11** gave 1-benzyl-2,3,5-trimethylbenzene **13** in reasonable yields.

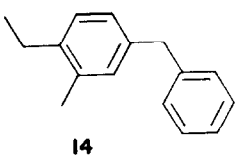


13

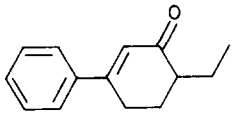
This result showed that **10** is not an essential intermediate in the conversion of **5** into **9** but only a collateral product. Moreover, the aromatization of **5** and **11** does not seem to contradict the mechanism proposed for the aromatization of type **3** compounds.

We think that in these cases a non-specific mechanism of dehydration is operating through carbonium ions in the aromatization of cyclohexenones lacking the 2-carboxymethyl group, which proceeds very slowly. This kind of reaction can proceed only when the substituents present in the cyclohexenone ring prevent the occurrence of other reactions such as aldol or Michael condensations. The positions 2 and 4 seem the ones to be protected. While **12** gives the corresponding **14** in good yields, **15** in similar conditions is transformed in a mixture of polymeric material in which only traces of aromatized products are present.

Further studies concerning this new synthesis of alkylbenzenes are in progress.



14



15

EXPERIMENTAL

M.ps were determined on a Büchi apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer 257 spectrometer and NMR spectra with a Perkin–Elmer Hitachi R 24 spectrometer (with tetramethylsilane as internal standard). Mass spectra were recorded as a LKB 9000 spectrometer. Gas chromatographic analyses were performed on a Perkin–Elmer F11 apparatus equipped with F.I.D. and OV 17 1.5% glass column (1.2 m × 4 mm ϕi). UV spectra were taken with a Beckmann DK_2 Spectrometer.

2,3,5 - Trimethyl - 4 - oxo - cyclohex - 2 - en - acetic acid **5**

To a solution of KOH (2.8 g) in methanol (10 ml), n-butanol (150 ml), diethylacetylsuccinate[7] (21.6 g) and 1 - dimethylamino - 2 - methyl - pentan - 3 - one[8] (14.3 g) were added; the resulting solution was refluxed for 16 h. After removal of the low boiling materials on a steam bath under reduced pressure, the residue was refluxed with 100 ml of 2N NaOH until complete dissolution (about 2 h). The alkaline solution was acidified and the oil which separated was chromatographed on silica gel with $CHCl_3$, MeOH, H_2O = 81:15:4 (lower layer), fractions showing a single spot in TLC were collected and evaporated. The residue after recrystallization from cyclohexane-benzene (3:1) gave **5** (2 g), m.p. 116–118°; ν_{max} ($CHCl_3$) 1710, 1660 cm^{-1}; δ($CDCl_3$) 1.12 (3H, d, J, 7 Hz, C<u>H</u>$_3$–CH), 1.76 (3H, s, C<u>H</u>$_3$–C=), 1.95 (3H, s, C<u>H</u>$_3$–C=), 2.5 (4H, m, <u>CH</u>–CH$_3$,<u>CH</u>$_2$,<u>CH</u>–C<u>H</u>$_2$), 2.62 (2H, s, –<u>CH</u>$_2$–COOH), 10.4 (1H, s, COOH). Found: C, 67.8; H, 8.2. $C_{11}H_{16}O_3$ requires: C, 67.3; H, 8.2%.

Diethyl - 1 - acetyl - 1 - (2 - methyl - 3 - oxo - pentyl)succinate **6**

Sodium (0.3 g) was dissolved in ethanol (30 ml), diethylacetylsuccinate (38 g) was added and the resulting solution cooled to 0°. 2-Methyl-1-penten-3-one **7** (34.6 g) was added over 30 min the mixture left to stand at room temp. for 12 h, and poured into water, the oil which separated was taken up in ether. After removal of the solvent the residue was distilled to give oily fraction (20 g), b.p. 168–171° (0.8 mmHg); δ ($CDCl_3$) 0.9–1.4 (12 H, m, –CH_3), 1.85 (2H, m, CH_2–CH–), 2.3 (3H, s, CH_3–CO), 2.3–2.85 (3H, m, CH_2–CO, –CH–CO), 2.9 (2H, s, <u>CH</u>$_2$–COOEt), 4.12 (4H, 2q, J 8 Hz, 2CH_2, –CH_3). Found: C, 61.9; H, 8.0. $C_{16}H_{26}O_6$ requires: C, 61.1, H, 8.3%.

2-Methyl-1-penten-3-one **7**

Prepared in 63% yield by distillation of 1 - dimethylamino - 2 - methyl - penten - 3 - one - hydrochloride heated to 210–220°, b.p. 105–109° (lit.[9] 117–119°).

Action of NaOH *on* **6**

Four different samples of **6** (200 mg each) were heated under reflux with 1N NaOH (3,6,9,12 ml respectively) for 2.5 h. The cooled mixtures were acidified and extracted with ether. The extracts were shaken with aqueous sodium bicarbonate: the alkaline solutions were acidified and the oils which separated taken up with ether. After treatment with diazomethane the solutions were analysed by GLC (OV 17, 1.5%, T = 165°; F.I.D.). The results are shown in Table 1, the ratios **3a/5** were calculated from the relative peak areas of **3a** and **5** methyl esters without corrections.

Methyl - 4 - ethyl - 5 methyl - 2 oxo - cyclohex - 3 - en - acetate (methylester of **3a**)

A suspension of **6** (10 g) in 1N NaOH (30 ml) was refluxed for 2.5 h. The resulting solution was acidified and the oil which separated taken up in ether. The ethereal solution was dried over Na_2SO_4 and treated with diazomethane. The residue (7.8 g) obtained after removal of the solvent was chromatographed on silica gel with hexane:ethyl-acetate (9:1) to give the methyl ester of **3a** (1.2 g), b.p. 175° (20 mmHg); ν_{max} (film) 1735, 1670 cm^{-1}; δ ($CDCl_3$) 0.98–1.35 (6H, 2CH_3–), 1.75–3.20 (8H, m), 3.72 (3H, s, CH_3–O), 5.82 and 5.93 (1H, s, CH=). (The NMR spectrum is very complex due to the superimposition of the signals of the diasteroisomers). Found: C, 68.7; H, 8.5. $C_{12}H_{18}O_3$ requires: C, 68.5; H, 8.6%.

4 - Ethyl - 3 - methyl - benzeneacetic acid **4a**

(a) *From methyl ester of* **3a**. The methyl ester of **3a** (0.7 g) and PyHCl (3.5 g) were heated for 30 min in an oil bath at 230°. The warm reaction mixture was poured into water and the solid which separated was collected and recrystallized from petroleum ether to give **4a** (0.5 g) m.p. 54–57°, δ($CDCl_3$), 1.2 (3H, t, J 7 Hz, C<u>H</u>$_3$–CH_2), 2.25 (3H, s, CH_3–Ph), 2.55 (2H, q, J 7 Hz, CH_3–<u>CH</u>$_2$–Ph), 3.55 (2H, s, Ph–CH_2–COOH) 7.05 (3H, s, Ph), 11.65 (1H, s, COOH). Found: C, 74.2; H, 7.9. $C_{11}H_{14}O_2$ requires: C, 74.1; H, 7.9%.

(b) *From* **6**. Compound **6** (2 g) and PyHCl (10 g) were heated for 30 min in an oil bath at 230°. The reaction mixture treated as above gave 0.7 g of **4a**, m.p. undepressed on admixture with the sample obtained from **3a** methyl ester.

2,3,5-Trimethyl-benzene acetic acid **9**

Compound **5** (2 g) and PyHCl (10 g) were heated at 230° for 20 h. The mixture was poured into water and the oil which separated taken up with ether. After removal of the solvent, a residue (1.4 g) was obtained which, when recrystallised from cyclohexane, gave (**9**), m.p. 130–132° (0.8 g); ν_{max} ($CHCl_3$) 1710 cm^{-1}; δ ($CDCl_3$) 1.15 (3H, s, CH_3–Ph), 1.25 (6H, s, CH_3–Ph), 3.62 (2H, s, Ph–<u>CH</u>$_2$–COOH), 6.9 (2H, s, Ph), 11.1 (1H, s, COOH). Found: C, 74.1; H, 7.9. $C_{11}H_{14}O_2$ requires: C, 74.1; H, 7.89%.

2,3,5 - Trimethyl - bicyclo[3.2.1]oct - 2 - en - 4,6 - dione **10**

Methyl ester **5** (6 g) and PyHCl (30 g) were heated at 230° for 30 min. The reaction mixture was poured into water and the oil which separated taken up with ether and treated with diazomethane. After removal of the solvent, the residue (4 g) showed on GLC (OV 17 1.5%, T = 140°) the presence of unreacted **5**, **9** and an unknown peak. This residue was chromatographed on SiO_2; elution with a mixture of hexane-ethyl-acetate (6:4) afforded the pure unknown substance as an oil (85 mg). GLC mass, NMR, IR and UV spectra are in agreement with the structure of **10**; *m/e* 178 (59%), 146 (17), 121 (13), 109 (21), 98 (16), 80 (13), 69 (100); ν_{max} (film) 1665, 1745 cm^{-1}, δ ($CDCl_3$) 1.23 (3H, s, CH_3–C), 1.7 (3H, s, CH_3–C=), 2.03 (3H, s, CH_3–C=), 2.25–2.60 (3H, m), 2.72 (1H, d, J 5 Hz, HC<u>H</u>), 2.93 (1H), d, J 4 Hz, <u>H</u>CH) λ_{max} 256 nm (ϵ = 6300) (ethanol).

9 from **10**

10 (60 mg) and PyHCl (0.3 g) were heated at 230° for 1 h. Following the above described procedures, **9** was obtained (35 mg) (identified by mixed m.p.).

4 - Benzyl - 2,3,6 - trimethyl - cyclohex - 2 - enone **11**

To a solution of KOH (0.9 g) in methanol (9 ml) 1 - dimethylamino - 2 - methyl - pentan - 3 - one (4.7 g), ethyl - 2 - benzyl - acetoacetate[10] (7.2 g) and butanol (36 ml) were added and the mixture was heated under reflux for 20 h. After removal of the low boiling materials the residue was poured into water (20 ml) and the oil which separated taken up with ether. The residue was distilled to give an oily mixture (3 g) b.p. 171–188° showing on GLC (OV 17 1.5%, T = 190°, F.I.D.) the presence of two diastereomeric mixtures. This mixture was heated with 2N NaOH (150 ml) until GLC showed the presence of only the stereoisomers with the shorter retention time. The oil taken up with ether gave (**11**) (1 g) b.p. 160–3° 1 mmHg); ν_{max} ($CHCl_3$) 1655 cm^{-1}; δ ($CDCl_3$) 1.03 and 1.11 (3H, d, J 6 Hz; CH_3–CH), 1.78 (3H, s, CH_3–C=), 1.92 (3H, s, CH_3–C=), 2.07–3.55 (6H, m) 7.21

(5H, s, Ph). Found: C, 84.0; H, 8.9. $C_{16}H_{20}O$ requires: C, 84.2; H, 8.8%.

6 - *Benzyl* - 3 - *ethyl* - 4 - *methyl* - *cyclohex* - 2 - *enone* **12**

Following the procedure described for the preparation of **11**, an oil (60 g) was obtained, b.p. 178–82° (1 mmHg), starting from 1 - dimethylamino - 2 - methyl - pentan - 3 - one (103 g), ethyl-2-benzyl acetoacetate (160 g), butanol (800 ml), KOH (20 g) and methanol (200 ml). By means of three spinning band distillations it was possible to obtain from this oil the diastereoisomers **12** having the longer retention time on GLC (10 g); ν_{max} (CCl_4) 1675 cm^{-1}; $\delta(CDCl_3)$ 1.03 (3H, t, J 6 Hz, CH_3–CH_2–), 1.13 (3H, d, J 6 Hz, CH_3–CH–), 5.8 and 5.85 (1H, s, CH=), 7.15 (5H, s, Ph). Found: C, 83.8; H 8.9. $C_{16}H_{20}O$ requires: C, 84.2; H, 8.8% (The NMR spectrum of this diastereoisomeric mixture is very complex).

11 *from* **12**

12 (5 g) and 2N NaOH (150 ml) were heated at reflux for 10 days. The mixture was taken up with ether, the solvent removed under reduced pressure and the residue distilled to give an oil (3.5 g) identified (IR and NMR) as **11** by comparison with a sample obtained as above.

1-*Benzyl*-2,3,5-*trimethyl benzene* **13**

11 (2 g) and PyHCl (10 g) were heated at 230° for 20 h. The mixture was poured into water and the oil which separated was taken up with ether. After removal of the solvent a NMR assay (succinic anydride as internal standard) of the residue (1.3 g) showed the presence of 92% of aromatized product. This residue was distilled to give **13** (0.9 g), b.p. 140–143° (1 mmHg); δ ($CDCl_3$) 2.05 (3H, s, CH_3–Ph), 2.21 (6H, s, CH_3–Ph), 3.92 (2H, s, CH_2–Ph), 6.85 (2H, s, Ph), 7.18 (5H, s, Ph). Found: C, 90.7; H, 8.7. $C_{16}H_{18}$ requires: C, 91.4; H, 8.6%.

1 - *Benzyl* - 4 - *ethyl* - 3 - *methyl* - *benzene* **14**

12 (1 g) and PyHCl (5 g) were heated at 230° for 20 h. Following the described procedure, a residue (0.7 g) was obtained, from which a NMR assay (succinic anydride as internal standard) of 82% in aromatized product, was calculated. This residue was distilled to give **14** (0.2 g), b.p. 145° (1 mmHg); δ ($CDCl_3$) 1.19 (3H, t, J 7 Hz, CH_3–CH_2), 2.21 (3H, s, CH_3–Ph), 2.55 (2H, q, J 7 Hz, CH_2–CH_3), 7.00 (3H, s, pH), 7.22 (5H, s, Ph). Found: C, 90.6; H, 8.7. $C_{16}H_{18}$ requires: C, 91.4: H, 8.6%.

6 - *Ethyl* - 3 - *phenylcyclohex-2-enone* **15**

To a solution of KOH (14.5 g) in methanol (40 ml), β-dimethylaminopropiophenone hydrochloride (40 g), ethyl - 2 ethyl - acetoacetate (38 g) and butanol (400 ml) were added and the mixture was heated at reflux for 20 h. After removal of the low boiling materials, the residue was heated with 2N NaOH (700 ml) at reflux for 20 h. The mixture was taken up with ether, the solvent evaporated under reduced pressure and the residue distilled to give **15** (8 g), b.p. 154° (1 mmHg) δ (CCl_4) 6.25 (1H, s, CH=), 7.32 (5H, m, Ph). Found: C, 84.3; H, 8.2; $C_{14}H_{16}O$ requires: C, 84.0; H, 8.1%.

Treatment of **15** *with* PyHCl

15 (0.5 g) and PyHCl (2 g) were heated at 230° for 18 h. The mixture was poured into water and taken up with ether (10 ml). 1 ml of the ethereal solution with diphenyl (2 mg) added as internal standard was analysed by GLC (OV 17 1.5%, T = 160°, FID). This analysis showed the presence of traces (< 5%) of 4-ethylbiphenyl.

REFERENCES

[1]Part I: G. Palazzo and L. Baiocchi, *Tetrahedron Letters* 4739 (1968).
[2]*Br. Pat.* 1265800.
[3]*Belg. Pat.* 837588 (15/7/1976).
[4]L. Baiocchi, *Boll. Chim. Farm.* **107**, 762 (1968).
[5]R. N. Lacey, *J. Chem. Soc.* 1639 (1960).
[6]R. Fusco and F. Tenconi, *Tetrahedron Letters* 1313 (1965).
[7]*Organic Syntheses, Coll. Vol. II*, 262 (1946).
[8]A. N. Kost and V. V. Ershov, *Zhur. Obscheir Khim.* **27**, 1722 (1957).
[9]J. Colonge *et al.*, *Bull. Soc. Chim. Fr.* 619 (1965).
[10]J. T. Adams *et al.*, *J. Am. Chem. Soc.* **65**, 552 (1943).