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AROMATIZATION OF ALIPHATIC COMPOUNDS—III†

ABNORMAL MICHAEL ADDITION TO DIETHYL-α-ACETYL-α'-METHYL SUCCINATE

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

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Abstract—While isobutyl vinyl ketone reacts with α-acetyl-α'-methyl succinate to give a normal Michael adduct, the Mannich base or its quaternary derivative as a source of vinylketone gives the butenolide derivative **8a**. Isobutyl cyclohexenoneacetic acid (**1b**) previously stated to be the reaction product was present only as a by-product. When α-acetyl-α'-methyl succinate is treated with acrylic acid derivatives only butenolides **8c–8f** were obtained.

In the course of experimental studies concerning the synthesis of aryl acetic acids through aromatization of 2 - cyclohexenone - acetic - acids **1**,[1] we attempted the synthesis of some of the latter compounds in which R'=CH_3. For this purpose we reacted diethyl - α - acetyl - α' - methyl succinate **2b** with some Mannich bases from different methyl ketones **3** followed by alkaline hydrolysis of the crude intermediates, according to Fig. 1.

Soon after these results were obtained, we became aware of a British Patent[4] claiming the synthesis of 4 - isobutyl - cyclohexenone acetic acid **1a** and 4 - isobutyl - α - methyl - cyclohexenone acetic acid **1b** through the reaction of 2-diethylaminoethyl-isobutyl ketone methosulphate respectively with **2a** and **2b**, followed by alkaline hydrolysis. We repeated this reaction but did not find any substantial difference in the use of the

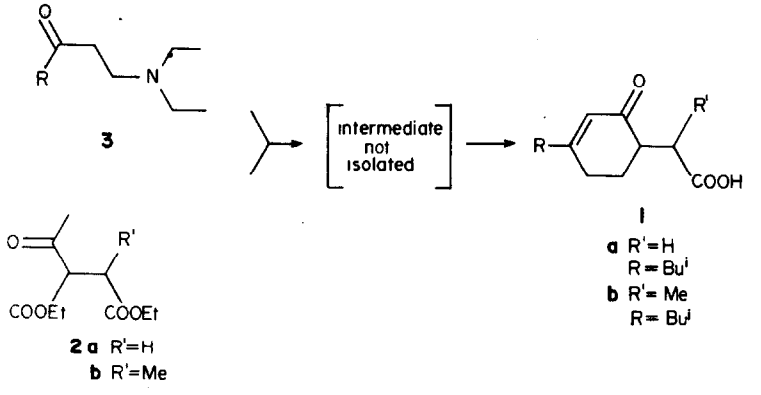
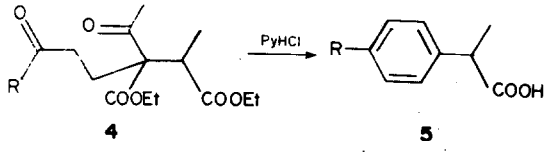


Fig. 1.

Surprisingly, the reaction, which gave good results with diethyl - α - acetyl - succinate **2a**,[2] gave crude acid materials with **2b** which did not show =C–H protons in their NMR spectra. We avoided this difficulty by reacting, at room temperature, and with catalytic amounts of the bases, **2b** and the vinyl ketones corresponding to **3**, obtaining the succinates **4**. From these latter compounds, with PyHCl, the desired aryl acetic acids **5** were obtained.[3]



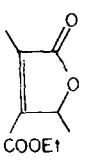
methosulphate instead of the corresponding Mannich base. Once again with **2a** we obtained **1a** and with **2b** a crude oily acid fraction that showed only a minimum amount of vinylic proton in its NMR spectrum. A white crystalline solid separated from this oil in isopropyl ether. The substance behaved as a monocarboxylic acid with an equivalent weight of 268. Esterification with ethanol gave the corresponding ethyl ester which, as proved by gas-chromatographic analysis, was present in the reaction mixture before alkaline hydrolysis. The mass spectrum of this ester showed a molecular ion at 269. From this value and from those of the elemental analysis the formula $C_{16}H_{24}O_5$ was deduced.

This formula corresponds to the sum of one molecule of isobutyl-vinyl ketone and one molecule of **2b** minus one molecule of ethanol. If the succinate **4** (R=isobutyl) is assumed to be a precursor of the unknown substance, there are several possibilities through which ethanol may be lost to give either a lactonic ring or different cyclic

†Part II see Preceding Paper.

1,3-diketones. In any case the NMR spectrum would show signals due to vinylic or to strongly acidic C–H protons. These features were completely absent in the above mentioned spectrum. Another possibility was that diethyl - α - acetyl - α' - methyl succinate **2b** lost ethanol to give a lactone before the Michael condensation.

Although **2b**, when treated with alcoholic bases, gave only scission to diethyl methylsuccinate, the lactone **6** may be regarded as an intermediate in alkaline medium. In fact, from diethyl diacetylsuccinate in alkaline medium the lactone **7** was obtained by Blood and Linstead.[5] We prepared **6** according to Bradbury and Masamune[6] and confirmed its structure by NMR.



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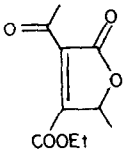
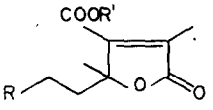


7

When treated with vinyl isobutyl ketone, **6** gave the same unknown ester we had obtained by reacting 2-diethyl-amino-ethyl isobutyl ketone methosulphate with **2b**. In light of this and its chemical and spectroscopic properties, the structure was assigned as **8a**.



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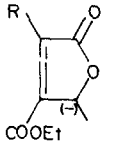
a R=Bu^{t}CO	R'=Et	**d** R=CN	R'=H
b R=Bu^{t}CO	R'=H	**e** R=COOEt	R'=Et
c R=CN	R'=Et	**f** R=COOEt	R'=H

This compound was also present before alkaline hydrolysis in the crude reaction mixture obtained from **2b** and 2 - diethylamino - ethyl - isobutylketone (**3**; R = isobutyl) according to the procedure previously described[2] as shown by GLC and NMR analyses.

The differing behaviour of **2a** and **2b** in the Michael addition is not restricted to vinyl ketone derivatives but it is also common to acrylic derivatives. While **2a** with acrylonitrile gives a normal Michael adduct,[7] **2b** gives good yields of the butenolide derivatives **8c** and **8e** with acrylonitrile or ethyl acrylate respectively. The reaction between acrylonitrile and the ethyl-t-butyl analogue of **2b**, i.e. **9** has been described by Vova *et al.*[8] According to these authors, the first product of the reaction is the succinate **10** which with pTsOH gave the lactone **11** (see Fig. 2).

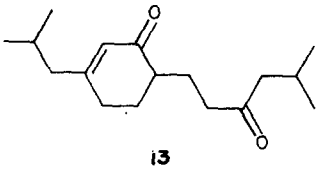
We carried out these reactions following the Chemical Abstracts indications and obtained an undistillable product from the first step of the reaction and a crude mixture, which did not show any vinylic proton in its NMR spectrum, from the second step. This latter mixture, showed both in GLC analysis and in its NMR spectrum, the presence of the butenolide **8c**.

It is important to point out that in our reactions between **2b** and acrylic derivatives, in contrast to vinyl isobutyl ketone, normal Michael adducts were never obtained, even at low temperature and using catalytic amounts of base. From a mechanistic point of view, **8** seems to be the result of a Michael addition to the anion **12** (R = Me).[9] In the resonance stabilization of the anion, hyperconjugation, which is lacking when R = H, seems to play a decisive role.



12

The differing behaviour of **2b** towards vinyl ketones and Mannich bases or acrylic derivatives, could be explained by the fact that the rate of addition of vinyl ketones to **2b** is higher than the rate of formation of **12** (R = Me). On the other hand, with Mannich bases, quaternary derivatives, or acrylates, the situation seems to be reversed and a substantial amount of **12** (R = Me) could be formed before the addition. While this mechanism accounts for the formation of **8**, it is not the only product of the reaction in the case of Mannich base derivatives. While **8c** and **8e** were obtained as single products from acrylate or acrylonitrile and **2b**, the reaction between **2b** and the quaternary derivative gave a complex mixture in which **8b** was predominant, isobutyl-cyclohexenonepropionic acid derivatives being present in smaller quantities (see Experimental). We were rather surprised to find that, although starting from samples of **2b** carefully purified from ethyl acetoacetate traces, a certain amount of the diketone **13** was always present in the crude reaction mixture. We have not, as yet, been able to explain this.



13

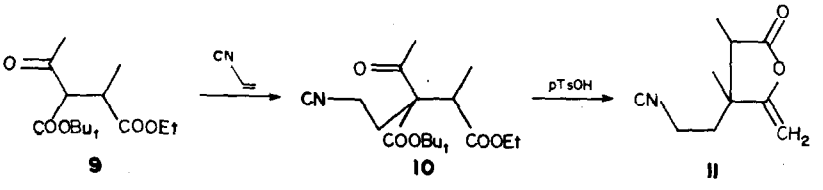
EXPERIMENTAL

For general information see preceding paper.

UV spectra were taken with a Beckmann DK_2 ratio recording spectrophotometer (for solutions in ethanol).

2,5 - Dihydro - 2,4 - dimethyl - 2(5 - methyl - 3 - oxo - hexyl) - 5 - oxo - 3 - furan - carboxylic acid **8b**

Following the described procedure,[4] dimethyl sulphate (48 ml) was added to a solution of 2-diethylaminoethyl isobutyl ketone (93.2 g) in ethanol. This solution was mixed with another



9 **10** **11**

Fig. 2.

obtained from sodium (11.5 g) in ethanol (530 ml) and diethyl - α - acetyl - α' - methyl succinate (115 g). After .30 min at room temperature and 4 hr at reflux, potassium hydroxide (49 g) in water (75 ml) was added and reflux continued for a further 8 hr. The cooled reaction mixture was poured into 1350 ml of water and the suspension obtained was extracted with dichloromethane (3 × 250 ml) (*neutral solution*). The aqueous layer was acidified and the oil which separated was taken up with dichloromethane. The crude residue (*crude acid*) (90 g) was dissolved in boiling isopropyl ether:hexane (1.2:2, 320 ml). After cooling, the solid which separated was filtered and recrystallised from hexane:ethyl acetate (1:1) to give **8b** (12 g); m.p. 79–80°. Acidmetric equivalent 268. λ_{max} 227 nm (ϵ = 11,200); ν_{max} ($CHCl_3$) 1765, 1720 cm^{-1}; δ ($CDCl_3$) 0.88 (6H, d, J 6 Hz $(CH_3)_2$–CH), 1.6 (3H, s, CH_3–), 2.22 (1H, m, CH–), 2.25 (6H, s, CH_2–), 2.32 (3H, s, CH_3–C=C), 11.33 (1H, s, OH). (Found: C, 62.3; H, 7.6. $C_{14}H_{20}O_5$ requires: C, 62.7; H, 7.5%).

Ethyl ester of **8b**, *i.e.* **8a**

Esterification of the above acid in benzene–ethanol with azeotropic removal of water gave the ethyl ester **8a**, b.p. 130° (0.1 mm/Hg); *m/e* 269 (13%), 278(2), 268(8), 252(12), 240(44), 212(16), 193(19), 184(100), 182(42), 165(16), 155(32), 137(19), 113(16), 95(10); λ_{max} 229 nm (ϵ = 10.900); ν_{max} (CCl_4) 1765, 1725 cm^{-1}; δ ($CDCl_3$) 0.88 (6H, d, J 6 Hz, $(CH_3)_2$–CH), 1.38 (3H, t, J 7 Hz, CH_3–CH_2–), 1.58 (3H, s, CH_3–), 2.15 (1H, m, CH), 2.16 (6H, s, CH_2), 2.28 (3H, s, CH_3–C=C), 4.33 (2H, q, J 7 Hz, CH_2O). Found: C, 64.9; H, 8.3. $C_{16}H_{24}O_5$ requires: C, 64.8; H, 8.2%. This ester after 30 min reflux with 2N NaOH gave **8b** (mixed m.p.) in nearly quantitative yield.

Ethyl - 2,5 - dihydro - 2,4 - dimethyl - 5 - oxo - 3 - furan - carboxylate **6**

2,5 - Dihydro - 2,4 - dimethyl - 5 - oxo - 3 - furan - carboxylic acid was prepared according to Bradburg and Massamune,[6] δ ($CDCl_3$ + DMSO) 1.52 (3H, d, J 7 Hz, CH_3–), 2.16 (3H, d, J 2 Hz CH_3–C=), 5.11 (1H, 2q, J 7 Hz, J 2 Hz, CH=), 11 (1H, s, OH) and esterified benzene–ethanol with azeotropic removal of water; δ ($CDCl_3$) 1.37 (3H, t, J 7 Hz, CH_3–CH_2), 1.42 (3H, d, J 7 Hz, CH_3), 2.18 (3H, d, J 2 Hz, CH_3–C=), 4.34 (2H, q, J 7 Hz, CH_2–O), 5.16 (1H, 2q, J 7 Hz, J 2 Hz, CH–O).

8a *from* **6** *and vinyl isobutyl ketone*

Compound **6** (5.5 g) and vinyl isobutyl ketone[10] (3.35 g) were added to a solution of sodium (70 mg) in ethanol (10 ml); the mixture was heated at 60° for 2.5 hr. After cooling, water was added and the oil which separated was extracted with ether. After removal of the solvent, the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (9:1) gave at first a mixture of several products and then the pure ester **8a** (1.2 g) which showed an NMR spectrum identical to that of the sample described above and which, after being treated at reflux for 30 min with 2N NaOH, gave **8b** (mi. m.p.).

Ethyl 2,5 - *dihydro* - 2,4 - *dimethyl* - 2 - *carbethoxyethyl* - 5 - *oxo* - 3 - *furan* - *carboxylate* **8c**

Compound **2b** (134 g) and redistilled ethyl acrylate (58 g) were added to a solution of Na (1 g) in ethanol (300 ml). The mixture was refluxed for 3 hr; the cooled solution poured into water (1 l.) and saturated with NaCl, the oil which separated being extracted with ether. After removal of the solvent, the residue was distilled twice to give 101 g of a colourless viscous oil, b.p. 150–153° (0.2 mm/Hg); λ_{max} 229 nm (ϵ = 10,500); ν_{max} (CCl_4) 1770, 1725, 1740 cm^{-1}; δ (CCl_4) 1.22 (3H, t, J 7 Hz, CH_2–CH_3), 1.4 (3H, t, J 6 Hz, CH_2–CH_3), 1.6 (3H, s, CH_3), 2.12 (3H, s, CH_3–C=), 2.17 (4H, A_2B_2 system, CH_2–CH_2), 4.15 (2H, q, J 7 Hz –CH_2–O), 4.36 (2H, q, J 6 Hz, CH_2–O). Found: C, 59.2; H, 7.2. $C_{14}H_{20}O_6$ requires: C, 59.1; H, 7.1%. The above ester (2 g) was suspended in 2N NaOH (20 ml) and the mixture was kept at reflux overnight. After cooling, the alkaline solution was filtered and acidified with 6N HCl. After standing in the cold, the white solid which separated was filtered and recrystallised from water. Compound **8f** (0.6 g) was obtained, m.p. 205–207° (dec.); λ_{max} 227.5 nm (ϵ = 12,000) ν_{max} (KBr) 1725 cm^{-1} (very broad); δ (DMSO) 1.55 (3H, s, CH_3), 2.05 (3H, s, CH_3–C=), 2.1 (4H, A_2B_2 system CH_2–CH_2), 9.55 (2H, s, 2OH). Found: C, 52.9; H, 5.3. $C_{10}H_{12}O_6$ requires: C, 52.6; H, 5.3%.

Ethyl - 2,5 - dihydro - 2,4 - dimethyl - 2 - cyanoethyl - 5 - oxo - 3 - furan - carboxylate **8c**

Compound **2b** (23 g) and acrylonitrile (5.4 g) were added to a solution of Na (0.23 g) in ethanol (60 ml). The mixture was refluxed for 45 min and the cooled solution was neutralized with glacial acetic acid, the ethanol being removed under reduced pressure. The residue was taken up with ether and the ethereal solution washed with water. After removal of the solvent, the residue was distilled to give **8c** (11.2 g), b.p. 172–175° (0.5 mm Hg); λ_{max} 229 nm (ϵ = 9500); ν_{max} (CCl_4) 2260, 1775, 1725 cm^{-1}; δ (CCl_4) 1.4 (3H, t, J 7 Hz, CH_2–CH_3), 1.6 (3H, s, CH_3), 2.2 (3H, s, CH_3–C=), 2.36 (4H, A_2B_2 system, CH_2–CH_2), 4.36 (2H, q, J 7 Hz, CH_2–O). Found: C, 59.8; H, 6.6; N, 6.1. $C_{12}H_{15}NO_4$ requires: C, 60.8; H, 6.4; N, 5.9%. The above ester (11.2 g) was suspended in 2N NaOH (50 ml) and stirred at room temperature to complete dissolution. The alkaline solution was filtered and acidified with 6N HCl. The solid which separated was filtered and crystallized from ethyl acetate to give **8d** (5 g), m.p. 154–155°; λ_{max} 227.5 nm (ϵ = 10,150); ν_{max} (KBr) 2260, 1735, 1720 cm^{-1}; δ (DMSO) 1.51 (3H, s, CH_3), 2.1 (3H, s, CH_3–C=), 2.33 (4H, A_2B_2 system CH_2–CH_2), 6.70 (1H, s, OH). Found: C, 57.4; H, 5.3; N, 6.6. $C_{10}H_{11}NO_4$ requires: C, 57.4; H, 5.3; N, 6.7%.

Study of the reaction between the methosulphate of 2 - *diethyl - amino - ethyl - isobutyl ketone and* **2b**

Acidic fraction. A gas-chromatographic analysis of a small sample of the above described "*crude acid*" (see preparation of **8b**), treated with diazomethane (p. terphenyl as internal standard) showed in the mentioned 90 g the presence of 43.2 g of **8b** and 11.3 g of **1b**.†

Neutral fraction (*diketone* **13**). The dichloromethane "*neutral solution*" above described was evaporated to dryness and the oily residue (48 g) distilled. GLC/MS analysis of the fraction boiling between 155 and 180° (0.2 mmHg) (17 g) showed besides a certain amount of ethyl ester of (Ib) and the corresponding carbethoxy derivative,‡ a third substance with M^+ 264. This fraction was suspended in 2N NaOH (100 ml) and refluxed under stirring for 4 hr. The oily residue was taken up in ether and, after removal of the solvent, distilled to give a product, b.p. 170–172° (0.2 mmHg) (8.2 g) that showed only one peak in GLC. analysis. *m/e* 264 (27%), 208(15), 190(6), 180(20), 166(50), 153(100), 138(9), 122(5), 111(24), 95(25), 83(36); δ (CCl_4) 5.68 (1H, s, CH=C); ν_{max} (CCl_4) 1670, 1713 cm^{-1}. Found: C, 77.2; H, 10.6. $C_{17}H_{28}O_2$ requires: C, 77.2; H, 10.7%.

†A sample of **1b** was obtained according to example 3 of the cited patent by spinning band distillation of a 2-diethylamino-ethyl-isobutyl ketone methosulphate and **2b** reaction mixture in which **1b** is present as a by-product.

‡A sample of this compound was prepared by saturating a solution of **4** (R = isobutyl) in dioxan with dry hydrogen chloride. After standing for 8 hr at room temperature, the mixture was evaporated and the residue distilled to give ethyl - 2 - (1 - carbethoxy - 2 - oxocyclohexenyl - 4 - isobutyl)propionate in good yields. Analytical data is in agreement with the assigned structure.

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