Tetrahedron Letters No.9, pp. 799–802, 1967. Pergamon Press Ltd. Printed in Great Britain.

SYNTHESIS OF ESTRONE INTERMEDIATES

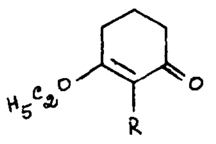
C. S. Menon and S. V. Sunthankar
University Department of Chemical Technology, Bombay
(India)

(Received 20 December 1966)

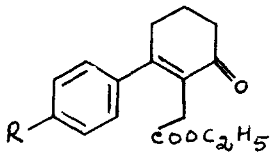
In connection with the study of reactions of organometallic compounds with conjugated enolethers, it was of interest to investigate whether reaction products of organometallic compounds with enol ethers of dihydroresorcinol could be utilised for the synthesis of steroidal intermediates. In this note we report our preliminary results.

For the synthesis two enol ethers were used, (a) enol ether of dihydroresorcinol I, (Ia, R = H) and (b) ethyl-3-ethoxy-1-oxocyclohex-3-ene-2-acetate I (Ib, R = $CH_2COOC_2H_5$).

In the first case phenylmagnesium bromide and p-anisyl magnesium bromide were reacted with ethyl enol ether of dihydroresorcinol to obtain the corresponding 3-aryl-Δ^2-cyclohexanones. These were then alkylated with ethyl bromoacetate using pot-t-amyloxide as the base in benzene solution to get II. (IIa, R = H; IIb, R = OCH_3).



Ia, R = H
b, R = $CH_2.COOC_2H_5$

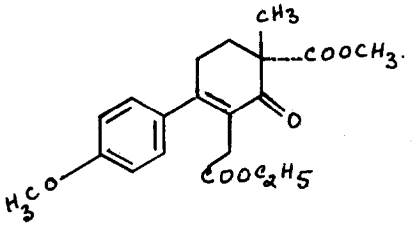


IIa, R = H
b, R = OCH_3

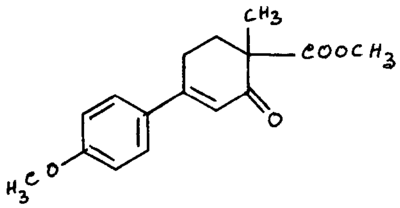
The compound (IIa) was hydrolysed to the acid and identified as its 2,4-dinitrophenylhydrazone derivative. m.p. 245°. (Found C, 59.0, H, 4.2, N, 13.2, $C_{20}H_{18}N_4O_6$ requires, C, 58.53; H, 4.39; N, 13.66%). (Turner[1] reports m.p. 239°). The compound (IIb) was hydrolysed to the acid which melted after crystallisation from benzene-pet:ether (60-80°) mixture at 135°. (Found C, 68.7; H, 6.1; $C_{15}H_{16}O_4$ requires C, 69.23; H, 6.15%). λ^{alc}_{max} 226 mμ. (log e 4.04), λ_{max} 289 mμ (log e 4.12), λ_{min} 252 mμ (log e 3.70). (m.p. reported by Banerjee[2] et al., 136°; Johnson[3] et al., 135-37°, Turner[1] 137-38° and Guha[4] et al., 137°).

The preparation of enol ether (Ib) was accomplished by the following steps:- Dihydroresorcinol was first alkylated with ethyl bromoacetate using pot-ethoxide in the usual way and the resulting compound was then converted to the ethyl enol ether (Ib) by treatment with ethyl orthoformate and absolute alcohol in the presence of a few drops of concentrated hydrochloric acid. This enol ether was reacted with phenylmagnesium bromide and p-anisylmagnesium bromide to obtain (IIa and IIb) in one step. The keto-esters were hydrolysed to the corresponding acids and identified by analysis and mixed melting point with the respective compounds obtained earlier.

In order to obtain the keto diester (III), the key steroid intermediate in one step from the keto ester (IIb), Temple Robinson's[5] method of introducing carbomethoxy group and methyl group was applied. As a preliminary experiment first 3-p-anisyl-Δ^2-cyclohexenone was converted to 6-p-anisyl-3-methyl-3-carbomethoxycyclohexanone (IV).



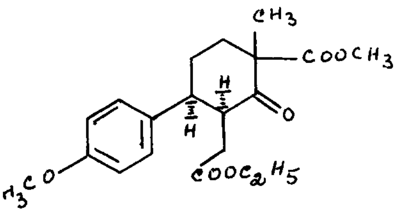
III



IV

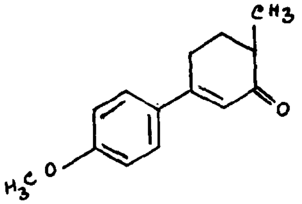
(Found: C, 69.8; H, 7.1. $C_{16}H_{18}O_4$ requires C, 70.06; H, 6.92%). λ^{alc}_{max} 232 mμ (log e 3.77), λ_{max} 315 mμ (log e 4.10), λ_{max} 257 mμ (log e 3.21).

The same conditions were followed to convert (IIb) to ethyl-6-p-anisyl-2-oxo-3-methyl-3-carbomethoxy-cyclohex-6-ene-1-acetate. However, the product was obtained as a thick glassy liquid which analysed for the saturated compound (V). (Found, C, 66.7; H, 7.5. $C_{20}H_{26}O_6$ requires C, 66.30; H, 7.18%). λ^{alc}_{max} 274 mμ (log e 3.24), λ_{max} 285 mμ (log e 3.17), ,λ_{min} 260 mμ (log e 3.26) and I.R. spectrum showed absence of 6.04 μ band characteristic of α-β-unsaturated ketone. This could not be obtained in a crystalline form probably being a mixture of isomers; if so we are not yet clear as to the reduction of the expected compound under the reaction conditions used.



V

As an alternative approach, it was, therefore, thought to alkylate the compound (IV) and then to reduce it to the compound (V). However, the alkylation with ethyl bromoacetate using pot-t-amyloxide as the base at 0-5° resulted into two compounds, a solid, 6-p-anisyl-3-methylcyclohexenone (VI), m.p. 75-76°. (Found C, 78.1; H, 7.5. $C_{14}H_{16}O_2$ requires C, 77.76; H, 7.41%). (Novello[6] et al., reported m.p. 77.5-78.5°) and a liquid which analysed for ethyl-5-p-anisyl-2-methyl-cyclohex-1,5-diene-1-acetate. (Found C, 75.5; H, 7.4; $C_{18}H_{22}O_3$ requires, C, 75.53; H, 7.69%).



VI

Further work is in progress.

REFERENCES:

1. D. L. Turner, J. Amer. Chem. Soc., **73**, 1284 (1951).
2. D. K. Banerjee and K. M. Sivanandaiah, J. Ind. Chem. Soc. **38**, 652 (1961).
3. W. S. Johnson, R. G. Christansen and R. E. Ireland, J. Amer. Chem. Soc., **79**, 1995 (1957).
4. M. Guha, U. Rakshit and D. Nasipuri, J. Ind. Chem. Soc., **37**, 267 (1960).
5. M. J. Temple Robinson, Tetrahedron, **1**, 49 (1957).
6. F. C. Novello, M. E. Christy and J. M. Sprague, J. Amer. Chem. Soc., **75**, 1330 (1953).