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1957

SovietRxiv

Abstract

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CHEMISTRY

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THE ACTION OF VINYLMAGNESIUM BROMIDE ON 6-METHOXYTETRALONE-1 AND THE ENOL ETHERS OF DIHYDRORESORCINOL AND METHYLDIHYDRORESORCINOL

PREPARATION OF INTERMEDIATES FOR THE TOTAL SYNTHESIS OF STEROID COMPOUNDS

Earlier work in our laboratory showed that, starting from vinyl alcohols, it is possible to proceed to the synthesis of various polycyclic compounds either by the method of diene condensation (1,2), or by the method of condensation of allyl-type bromides with cyclic 1,3-diketones and subsequent cyclization (3):

[reaction scheme]

Vinyl alcohols, as a rule, were obtained by selective hydrogenation of acetylene alcohols, which in turn were prepared by condensation of ketones with acetylene under various conditions. In some cases, as, for example, for 1-vinyl-6-methoxytetralol-1 (II), such a synthetic route involved considerable difficulties (4). It was therefore of interest to test a method for preparing vinyl alcohols according to Grignard, using vinylmagnesium bromide, which, as Normant (5) showed, is readily formed in the usual way in a tetrahydrofuran medium.

We have established that the reaction of vinylmagnesium bromide with cyclohexanone in tetrahydrofuran solution gives 60% vinylcyclohexanol and a considerable amount of cyclohexanone condensation products, from which cyclohexylidenecyclohexanone was isolated (as the semicarbazone).

The reaction of vinylmagnesium bromide with 6-methoxytetralone (I) proceeds more smoothly and leads to 1-vinyl-6-methoxytetralol-1 (II) in almost quantitative yield. On heating carbinol II in the vacuum of a water-jet pump at a temperature above 120°, partial dehydration occurs, which is greatly accelerated by the addition of various dehydrating agents and even ordinary sand. Thus it was possible to obtain, in 47% yield, pure 1-vinyl-6-methoxy-3,4-dihydronaphthalene (III)—an important intermediate in the synthesis of steroid compounds related to estrone (4).

reaction scheme: formation of adducts IV and V from diene III with maleic anhydride and quinone

Figure 1: reaction scheme: formation of adducts IV and V from diene III with maleic anhydride and quinone

reaction scheme: conversion of VI to VII and VIII

Figure 2: reaction scheme: conversion of VI to VII and VIII

$$\mathrm{I} \xrightarrow{\mathrm{CH_2{=}CHMgBr}} \mathrm{II} \xrightarrow{-\mathrm{H_2O}} \mathrm{III}$$

The diene III obtained readily undergoes diene condensations, rapidly polymerizes, and becomes strongly resinified on distillation even under high va-

in vacuo. Therefore, the indicated diene condensations are more expediently carried out without isolating diene III in pure form (avoiding its distillation), or directly with carbinol II, which can dehydrate under the conditions of diene synthesis. Thus, condensations of diene III with maleic anhydride and quinone were carried out, and the corresponding adducts (IV) and (V) were obtained in good yields:

Upon reduction of adduct (V) with zinc in acetic acid, a tetracyclic diketone of the cis series (VI) was obtained; when passed through alkaline alumina, it isomerizes (at C_{14}) to the trans isomer (VII).

Under the catalytic action of acids on the trans-diketone VII, inversion of the other asymmetric center also occurs, as well as migration of the double bond into the position between the rings, as a result of which the isomeric tetracyclic ketone of the cis series (VIII) is formed. The same diketone VIII is obtained by heating diketone VI with acetic acid.

We have previously shown [6] that the reaction of methyldihydroresorcinol enol acetate with methylmagnesium iodide gives 2,3-dimethyl-Δ^2-cyclohexenone-1 in 41% yield.

The reaction of vinylmagnesium bromide with ethers of the enol forms of dihydroresorcinol and methyldihydroresorcinol (IX) and (X) proceeds in an entirely analogous manner. As a result of this reaction, the corresponding dienones (XI) and (XII) are obtained in 70% yield; these are important intermediates for the total synthesis of steroid compounds [7,8].

IX $R = H; \quad R' = C_2H_5$

reaction scheme: IX/X to XI/XII via vinylmagnesium bromide

Figure 3: reaction scheme: IX/X to XI/XII via vinylmagnesium bromide

X $R = CH_3$; $R' = iso\text{-}C_4H_9$

XI $R = H$

XII $R = CH_3$

In separate experiments with vinylmagnesium bromide, we successfully replaced tetrahydrofuran by α-methyltetrahydrofuran. Attempts to use certain other cyclic ethers, namely 2,2-dimethyltetrahydropyran, dioxane, and 2,2,5,5-tetramethyltetrahydrofuran, were unsuccessful.

Experimental Part

Preparation of 1-vinyl-6-methoxytetralol-1 (II). To 6 g of magnesium turnings, activated with traces of iodine, in 50 ml of anhydrous tetrahydrofuran, with stirring and heating to 30°, a solution of 33 g of freshly prepared vinyl bromide in 30 ml of tetrahydrofuran was added under a nitrogen atmosphere. After approximately 1/5 of the solution had been added, the reaction began after 10–15 min, and the flask was cooled with ice water; one-

simultaneously adding the bromide solution and maintaining the temperature at 40–45°, which took about 20 min. The mixture was then boiled for half an hour, cooled to −20°, diluted with 70 ml of abs. ether, and a solution of 12 g of 6-methoxytetralone (I) (m.p. 78°) in a mixture of 10 ml of tetrahydrofuran and 70 ml of ether was added at a temperature of about −15°. The mixture was stirred for 3 hours at this temperature and left overnight. The following day the suspension that had formed was heated to gentle boiling for 2 hours, cooled, and poured into a mixture of 32 g of ammonium chloride and 200 g of ice. The ether layer was separated, the aqueous layer was extracted twice with ether, and the combined ether extracts were dried with sodium sulfate, filtered, and the solvents were distilled off (toward the end in vacuo). The residue gave a light-yellow oil (14 g) with n_D^{18}1.5622, representing nearly pure 1-vinyl-6-methoxytetralol-1 (II). Distillation in vacuo (the material foams strongly) gave 12 g (86%) of carbinol II with b.p. 116–117° at 0.5 mm; n_D^{20}1.5635; d_4^{20}1.0112.

$C_{13}H_{16}O_2$. Found, %: C 76.6; 76.7; H 7.85; 8.0
Calculated, %: C 76.4; H 7.9

Dehydration of 1-vinyl-6-methoxytetralol-1 (III). A mixture of 4.7 g of undistilled carbinol II and 1.5 g of ordinary sand was heated at 120° in a vacuum of 6–7 mm. Dehydration began immediately and ended after 6–8 min, as was evident from the decrease in foaming and cessation of water evolution. The refraction of the reaction mixture rose to 1.6050. Distillation gave 2.0 g (47%) of diene III with b.p. 102–106° at 1.5 mm; n_D^{20}1.5935 (4).

On mixing diene III with a benzene solution of maleic anhydride with heating, adduct IV is formed, yield 70%, m.p. 202–203° (9). In lower yield adduct IV is formed by boiling carbinol II with maleic anhydride in xylene solution.

Condensation of 1-vinyl-6-methoxy-3,4-dihydronaphthalene (III) with quinone. To a solution of undistilled diene III (obtained from 2.5 g of carbinol II) in 20 ml of glacial acetic acid, 1.2 g of quinone was added with stirring under nitrogen. Already after 5 min crystals of the adduct began to precipitate. After 1 hour the crystals were filtered off and washed with cold methanol. Obtained were 1.8 g (47%, calculated on carbinol II, and 52%, calculated on quinone) of 3-methoxy-$\Delta^{9,16}$-isooestrochrysadienedione-15,17a (V)* with m.p. 156–159°. The pure diketone has m.p. 165–166° (from methanol) (9).

$C_{19}H_{18}O_3$. Found, %: C 77.3; 77.2; H 6.2; 6.1
Calculated, %: C 77.5; H 6.2

With distilled diene the yield is 86%.

Reduction of adduct V. To a solution of 1.15 g of adduct V in 115 ml of acetic acid, 0.85 g of zinc dust was introduced with stirring under nitrogen. The mixture was stirred for 17 min at 20–22°, filtered, the precipitate was washed with hot benzene, and the filtrate was evaporated in vacuo. Obtained were 806 mg (70%) of 3-methoxy-Δ^9-isooestrotriazadienedione-15,17a (VI) with m.p. 192–193° (from ethyl acetate).

$C_{19}H_{20}O_3$. Found, %: C 76.8; 76.7; H 6.65; 6.9
Calculated, %: C 77.0; H 6.8

Isomerization of cis-diketone VI under the influence of alkali and acid. A solution of 273 mg of diketone VI in dioxane was poured into a column containing 25 ml of alkaline alumina (containing 2% caustic potash), slightly moistened with petroleum ether. After being kept for 40 min under nitrogen, the product was washed out with dioxane. The solution was evaporated in vacuo, and the residue was crystallized from methanol. Obtained were 138 mg (50%) 3-methoxy-Δ^9-estrahizenedione-15,17a (VII) with m.p. 168–170°. The pure diketone melts at 174–175° (from methanol).

Found, %: C 76.7; 76.9; H 6.8; 6.8
$C_{19}H_{20}O_3$. Calculated, %: C 77.0; H 6.8

A solution of 100 mg of the cis-diketone VI in 10 ml of acetic acid was boiled in a nitrogen atmosphere for 3 hours. After removal of the solvent in vacuo and crystallization from methanol, 21 mg of 3-methoxy-$\Delta^{8(9)}$-isoestrahizenedione-15,17a (VIII) was obtained, with m.p. 151–152°. The pure diketone melts at 154–155° (from methanol).

Found, %: C 76.9; 76.8; H 6.75; 6.7
$C_{19}H_{20}O_3$. Calculated, %: C 77.0; H 6.8

* Nomenclature of polycyclic compounds according to I. N. Nazarov (10).

Isomerization of trans-diketone VII. A solution of 45 mg of trans-diketone VII in 15 ml of benzene was boiled in the presence of 7.5 mg of *p*-toluenesulfonic acid in a nitrogen atmosphere for 4 hours. After neutralization with bicarbonate and the usual work-up, 19 mg (42%) of the above-described cis-diketone VIII was obtained, with m.p. 150-151°, which gave no depression with the preceding sample.

Preparation of 3-vinyl-Δ^2-cyclohexenone (XI). To magnesium bromovinyl, prepared from 7 g of magnesium and 32 g of vinyl bromide in 70 ml of tetrahydrofuran and cooled to $-15°$, there was added, with stirring, a solution of 15 g of 3-ethoxy-Δ^2-cyclohexenone (IX) (b.p. 80° at 1.5 mm; n_D^{18} 1.5060) in 20 ml of tetrahydrofuran, in such a way that the temperature did not rise above $-10°$. The mixture was left overnight in ice, and on the following day was heated for half an hour at 50-60° and the tetrahydrofuran (75 ml) was distilled off under a weak vacuum. The semisolid residue was diluted with 100 ml of ether, treated with 50 g of ice, and then with dilute hydrochloric acid at 5°. The product was extracted with ether; the extract was washed successively with solutions of sodium thiosulfate, soda, water, and dried over magnesium sulfate. Distillation gave 9 g (70%) of 3-vinyl-Δ^2-cyclohexenone (XI) as a colorless liquid with b.p. 82-83° at 4 mm; n_D^{17} 1.5488.

Found, %: C 78.9; 78.6; H 8.2; 8.2
$C_8H_{10}O$. Calculated, %: C 78.65; H 8.25

The dinitrophenylhydrazone melts at 169-170° (from alcohol-dioxane). Dienone XI, on storage, by the third day turns into a glassy mass.

Preparation of 2-methyl-3-vinyl-Δ^2-cyclohexenone (XII). By an analogous method, from magnesium bromovinyl (prepared from 7 g of magnesium and 31 g of vinyl bromide) and 20 g of 2-methyl-3-isobutoxy-Δ^2-cyclohexenone (b.p. 103-105° at 0.5 mm; n_D^{19} 1.5015), 10.7 g of 2-methyl-3-vinyl-Δ^2-cyclohexenone (XII) was obtained as a slightly yellowish liquid, polymerizing on storage, with b.p. 67-68.5° at 2 mm; n_D^{20} 1.5512; d_4^{20} 0.996, which agrees with the literature data (7). On cooling, the dienone crystallizes and melts at $-14°$. The dinitrophenylhydrazone melts at 178-180° from alcohol-dioxane.

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Received
21 II 1957

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