PYRIMIDINES

XIII. Reduction of Substituted 2-Hydroxypyrimidines to Pyrimidines*

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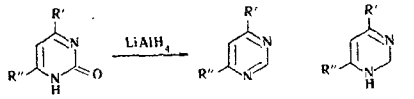
The possibility of the direct passage from 2-hydroxypyrimidines to pyrimidines by lithium aluminum hydride reduction has been established. Thus, starting from the corresponding 2-hydroxy derivatives we have obtained 4-phenylpyrimidine, 4,6-diphenylpyrimidine, and 4-phenylbenzo[h]quinazoline. With 2-hydroxy-4,6-diphenylpyrimidine as an example, it has been shown that when an excess of the reducing agent is used there is more far-reaching reduction to the corresponding dihydropyrimidine.

The most widely used method of obtaining alkyl- or aryl-substituted pyrimidines is the reductive dehalogenation of the corresponding chlorine-substituted pyrimidines, which are formed comparatively readily from hydroxypyrimidines [2]. The direct reduction of the latter to pyrimidines has scarcely been studied. It is known only that on distillation with zinc dust 2-ethyl-4-hydroxy-6-methylpyrimidine gives a very low yield of 2-ethyl-4-methylpyrimidine [3].

In our laboratory a convenient method has previously been developed for obtaining substituted 2-hydroxypyrimidines [4], and in view of this we have studied the possibility of converting them into pyrimidines. This transition consists essentially in the reduction of the grouping —NH—C(=O)—N= (since 2-hydroxypyrimidines exist in the tautomeric oxo form) to —N=CH—N=. Such a transition has not been carried out in the pyrimidine series. However, it is known that the urea grouping in a substituted 2-imidazolone has been reduced, although, it is true, with great difficulty, giving the corresponding imidazole [5]. In addition, the successful reduction of trisubstituted ureas with lithium aluminum hydride to formamidines has recently been reported [6]. These investigations gave grounds for assuming that it would be possible to reduce 2-hydroxypyrimidines to pyrimidines under suitable conditions.

As the subject of the investigation we took the readily accessible 2-hydroxy-4,6-diphenylpyrimidine (I). However, the treatment of I with lithium aluminum hydride under the conditions for the formation of formamidines [6] yielded only unchanged I. The reduction was successfully achieved by heating I with lithium aluminum hydride in dioxane. We found that when a solution of lithium aluminum hydride was added to I (inverse order of addition of the reactants), reduction took place to 4,6-diphenylpyrimidine (II) without the formation of by-products. In this, and in all the other cases, part of the starting material was recovered unchanged. Compound II was identified by comparison with an authentic sample [7].

If, however, the I was added to the lithium aluminum hydride, in addition to II a yellow product having the nature of a strong base was formed. The amount of this product rose when an excess of lithium aluminum hydride was used. In view of the conditions for obtaining this product and the absence from its IR spectrum of the absorption band of the C=O of an amide, it could be assumed that the compound obtained was 4,6-diphenyldihydropyrimidine (III). We were unable to obtain it in the analytically pure state. To characterize the product, its picrate was prepared, and the analysis of this corresponded to the figures calculated for III. To obtain additional information on the structure of III, we performed its oxidation, since it is known that dihydropyrimidines are smoothly converted into pyrimidines in this way [8]. In fact, the action of potassium permanganate on III gave II. In addition, it was established by separate experiments that the reduction of II by the action of lithium aluminum hydride gives III (very low yield). All the facts mentioned permit the assumption that we did in fact obtain III. Considering the nature of the reducing action of lithium aluminum hydride on the amide group [9], it may be assumed that the structure of the product obtained was 4,6-diphenyl-1,2-dihydropyrimidine (IIIa).



I, IV II, V IIIa

where I, II, IIIa $R' = R'' = C_6H_5$; IV, V $R' = H$, $R'' = C_6H_5$

Under the same conditions as those used for the conversion of I into II, we carried out the reduction of 2-hydroxy-4-phenylpyrimidine (IV) and 2-hydroxy-4-phenylbenzo[h]quinazoline (VI), and obtained 4-phenylpyrimidine (V) and 4-phenylbenzo[h]quinazoline, respectively. Both compounds were identified by comparison with authentic samples.

The reduction of 2-hydroxy-4,6-dimethylpyrimidine under similar conditions led to a complex mixture of products among which no 4,6-dimethylpyrimidine was detected.

EXPERIMENTAL

The identity of the compounds was confirmed by the complete agreement of the IR spectra, the absence of a depression of the melting point of mixtures with authentic samples, and by their

*For part XII, see [1].

comparative chromatographic behavior. The chromatography was carried out with silica gel of the type KSK purified from traces of iron and washed to complete neutrality (150-250 mesh for plates and less than 100 mesh for columns), and neutral alumina (activity II-III according to Brockmann). The substances were revealed on the chromatograms from their absorption in UV light.

Reduction of 2-hydroxy-4, 6-diphenylpyrimidine (I). Method A. A solution of 0.14 g (4 mmole) of lithium aluminum hydride in 5 ml of absolute ether was added dropwise with stirring to a solution* of 1 g (4 mmole) of I in 50 ml of absolute dioxane. The ether was distilled off and the reaction mixture was stirred at 100°-110° C for 5 hr and was left overnight. The solvent was eliminated in vacuum and the dry residue was stirred with ether (~75 ml) and decomposed by the successive addition of water, 15% caustic soda solution, and water [10], and after 15 min the precipitate was filtered off and was repeatedly washed with ether on the filter. The combined filtrates were dried with magnesium sulfate, the ether was distilled off, and the product was extracted with boiling petroleum ether. After the elimination of the solvent in vacuum, II was obtained. Yield 0.6 g (66%). Mp 98°-99° C (from petroleum ether). R_f 0.95 (silica gel, benzene—ethyl acetate, 4:5). According to the literature [7], mp 102°-103° C.

Method B. A solution of 5 g (20 mmole) of I in 200 ml of absolute dioxane was poured into a stirred suspension of 1.2 g (30 mmole) of lithium aluminum hydride in 50 ml of absolute ether and 100 ml of absolute dioxane. The ether was distilled off and the reaction mixture was kept at 100° C for 5 hr. During the reaction, the mixture acquired an intense yellow color. It was decomposed in a similar manner to that described above. This gave 3.5 g of a yellow mixture which was treated with boiling petroleum ether, the extract being filtered and evaporated to give 2 g (46%) of **II**. The residue (1.5 g) after the extraction of the II was chromatographed on a column of silica, being eluted with a 4 : 5 mixture of benzene and ethyl acetate. The evaporation in vacuum of the first 100 ml of eluate gave an additional 0.5 g (~10%) of II. The selection of the yellow fraction was checked by chromatography on silica gel in the methanol ammonia 40 : 1 system, R_f 0.50. This fraction was evaporated in vacuum to give 0.7 g of substance III, which did not have a sharp melting point. Readily soluble in dilute acids, alcohols, ethyl acetate, and benzene, less soluble in ether, sparingly soluble in petroleum ether. **Picrate**, mp 218°-220° C. Found, %: C 57.42, 57.57; H 3.71, 3.77; N 15.46, 15.55; Calculated for $C_{16}H_{14}N_2 \cdot C_6H_3N_3O_7$, %: C 57.00; H 3.67; N 15.15.

Reduction of 4, 6-diphenylpyrimidine (II). By method B, after the usual working up, 0.5 g (2 mmole) of II in 50 ml of absolute dioxane and 0.14 g (4 mmole) of lithium aluminum hydride in 5 ml of absolute ether gave 0.48 g of a yellow mixture. The unchanged II was extracted with petroleum ether (Soxhlet apparatus). Evaporation of the extract gave 0.45 g of II contaminated with a yellow product. The product remaining after extraction was identical with III in chromatographic behavior.

Dehydrogenation of III. A saturated solution of potassium permanganate in acetone was added to a solution of 0.05 g of unpurified III in 4 ml of acetone until the appearance of a permanent pink coloration. The filtered solution was evaporated to dryness, the residue was extracted with ether, and the ether was distilled off. This gave 0.3 g (60%) of II.

Reduction of 2-hydroxy-4-phenylpyrimidine (IV). A solution of 0.67 g (4 mmole) of **IV** [11] in 100 ml of absolute dioxane was treated with 0.14 g (4 mmole) of lithium aluminum hydride in 7 ml of absolute ether (method A). The reaction mixture was stirred at 80° C for 8 hr. and was treated in a similar manner to that described above. The mixture remaining after the ethereal treatment yielded 0.4 g of the initial **IV** (extraction with dioxane in a Soxhlet apparatus). Evaporation of the combined ethereal extracts gave 0.21 g of a mixture from which the V was isolated in the form of the picrate (0.2 g). Mp 162°-163° C. According to the literature [12], mp 163°-164° C. Yield of 4-phenylpyrimidine (V) 50% (calculated on the **IV** that had reacted).

Reduction of 2-hydroxy-4-phenylbenzo[h]quinazoline (VI). A solution of 0.08 g (2 mmole) of lithium aluminum hydride in 4 ml of absolute ether was added to a solution of 0.44 g (2 mmole) of **VI** [13] in 70 ml of absolute dioxane. The reaction mixture was kept at 100° C for 6 hr (the bright yellow color of the initial compound gradually disappeared), treated in the usual way, and extracted with ether. The ethereal extract was evaporated, and the residue (0.23 g) was chromatographed on a column of alumina, being eluted with benzene and then with a mixture of benzene and ethyl acetate (2 : 1). The collection of the fractions was controlled by chromatography on a plate of alumina in the benzene—ethyl acetate, 2 : 1, system. The fractions with R_f 0.90 were combined and evaporated in vacuum to give 0.12 g (30%) of 4-phenylbenzo[h]quinazoline. Mp 85°-87° C. According to the literature [13], mp 84.5°-86° C. **Picrate**, mp 162°-164° C. According to the literature [13], mp 161°-163° C. The residue after extraction with ether was dried and subjected to additional extraction with hot dioxane. Evaporation of the extract gave 0.81 g of unchanged **VI**.

*In view of the inadequate solubility of the hydroxypyrimidines in dioxane, hot solutions were used in all cases.

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