THE OXIDATION OF 1,4-DIHYDROPYRIDINES

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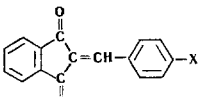
The olefinic bond of methenylbisindan-1,3-dione, 2-benzylideneindan-1,3-dione, and its derivatives is easily reduced by many 1,4-dihydropyridines. Under the conditions described, other functional groups are untouched. These β-dicarbonyl compounds are utilized to compare the effects of substituents in 1,4-dihydropyridines on their reactivity in the hydrogen transfer reaction.

The most characteristic property of 1,4-dihydropyridines is their ability to undergo oxidation to pyridines. From the earliest syntheses of dihydropyridines, they have been subjected to oxidation by the usual inorganic oxidizing agents such as the oxides of nitrogen, nitrous acid, chromic anhydride, and hydrogen peroxide, and by disproportionation [1–5]. The oxidation of 4,4-disubstituted 1,4-dihydropyridines has also been described [4, 6]. Nevertheless, not all 1,4-dihydropyridines are successfully oxidized by the oxidizing agents mentioned, for example, nitrous acid [7]. No systematic comparative investigation of the oxidation of 1,4-dihydropyridines has, however, yet been carried out. 1,4-Dihydropyridines have recently been used as model compounds for 1,4-dihydronicotinamide in a study of the transfer of hydrogen from 1,4-dihydropyridines to unsaturated organic compounds containing carbonyl, activated olefine, nitro-, and azomethine groups. However, the compounds investigated were mainly 2,6-dimethyl-3,5-bisethoxycarbonyl-1,4-dihydropyridine and some N-alkyl or N-aralkyl-1,4-dihydronicotinamides [8,9]. The same compounds were used in a study of model fermentation reactions [10–12].

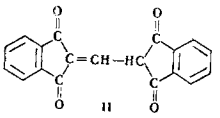
This paper presents briefly the results of a comparative investigation of the reductive properties of some 1,4-dihydropyridines towards α,β-unsaturated carbonyl compounds. On the one hand, the possibility of utilizing the reaction for the preparative reduction of α,β-unsaturated carbonyl compounds and the selectivity of the reduction was examined, and on the other hand, some comparative data were obtained on the relationship between the structure of 1,4-dihydropyridines and their hydrogenating ability. The hydrogen donors used for the preparative reduction were 2,6-dimethyl-3,5-bisethoxycarbonyl-1,4-dihydropyridine (XI), 4-phenyl-2,3(CO),6,5(CO)-dibenzoylene-1,4-dihydropyridine (VII), and 2-methyl-3-ethoxycarbonyl-4-p-nitrophenyl-6,5(CO)-benzoylene-1,4-dihydropyridine. It has been shown previously that VII reduces 2-benzylideneindan-1,3-dione (Ia) to 2-benzylindan-1,3-dione [13]. The olefinic bond of substituted 2-benzylideneindan-1,3-diones (Ib, Ic etc.) may be reduced in the same way.



a X = H, b X = NO_2, c X = Cl

The reagents were taken in equimolecular amounts. The reactions proceeded readily in boiling dioxane or acetic acid to give good yields. Reduction of 2-p-nitrobenzylideneindan-1,3-dione (Ib) gave 2-p-nitrobenzylindan-1,3-dione. The nitro group was not reduced, even with an excess of the dihydropyridine. The reaction is therefore selective for the reduction of the C=C bond in the presence of carbonyl and nitro groups, although the latter are known to be easily reduced. The activating effect of the two carbonyl groups increases the reactivity of the C=C bond to such an extent that the reduction proceeds with ease. It follows that p-nitrobenzylideneacetophenone, which possesses only one carbonyl group adjacent to the C=C bond, is almost unreduced under these conditions. In addition, it is known [8] that 2,6-dimethyl-3,5-bisethoxycarbonyl-1,4-dihydropyridine reduces nitrobenzene in poor yield on prolonged heating at 172° C, whilst benzylideneacetophenone under these conditions (i.e., at 172° C) undergoes slow reduction to benzylacetophenone.

Reduction of methenylbisindan-1,3-dione (II) gave the diindandionylmethane.



II

We decided to use the facile reduction of 2-benzylideneindan-1,3-dione (Ia), its derivatives, and methenylbisindan-1,3-dione (II) by dihydropyridines to compare the reactivities of various dihydropyridines. With brightly-colored benzoylenedihydropyridines (cf Table 1), the completion of the reaction was determined by the disappearance of the color of the dihydropyridine. 2-p-Chlorobenzylideneindan-1,3-dione (Ic), or chloranil was used as the oxidant, in excess. Some reactions were also carried out using equimolecular proportions. When the 1,4-dihydropyridines were weakly colored (cf Table 2), the reactions were carried out with the strongly colored methenylbisindan-1,3-dione (II), but in this case the dihydropyridine was taken in excess. Close comparison of the results in both tables shows that the reaction of chloranil with 2-methyl-3-ethoxycarbonyl-6,5-(CO)-benzoylene-1,4-dihydropyridine (IV) proceeds appreciably faster than with 2,6-dimethyl-3,5-bisethoxycarbonyl-1,4-dihydropyridine (XI) (according to the change in the intensity of the UV spectral absorptions). In addition, it is recorded in the literature [8] that equimolecular amounts of XI and chloranil at 25° C react completely in 15 min. The kinetics of the hydrogen-transfer reaction were not studied, and the durations of the reactions only (determined visually) are given. However, the results given in the tables show the effect of substitutents on the activity of the 1,4-dihydropyridines in the hydrogen-transfer reaction. Firstly, it will be seen that the presence of substituents in the γ-position substantially reduces (cf. IV and VIII, XI and XVII, XII and XVI), and the presence of methyl groups in the α-position apparently increases (cf. XII and XIII) the reactivity of 1,4-dihydropyridines. Secondly, the influence of various electron-accepting β-substituents is shown. The greatest activating effect in the examples given is shown by the benzoylene group. The high reactivity in this case is retained even by the γ-substituted 1,4-dihydropyridine (cf. IV and VIII in comparison with XI and XVII, or XII and XVI). In order of decreasing activating effect, the groups are: ethoxycarbonyl, acetyl, 2,3-(CO)-2,2'-dimethylbutan-4'-one-4'-ylene (cf XIV, XV, and XIX), and cyano. It should, however, be noted that these results were obtained from the reactions with benzylideneindandiones. The reactions with chloranil gave different results. Thus, in the reaction of VII, VIII, and IX with chloranil, a different relationship between the β-substituents and reactivity was observed, the order in this case being acetyl, ethoxycarbonyl, and 2,3-(CO)-benzoylene (in order of decreasing activity).

EXPERIMENTAL

2-p-Nitrobenzylindan-1,3-dione. A) **Reduction with 4-phenyl-2,3-(CO),6,5(CO)-dibenzoylene-1,4-dihydropyridine (VII).** 0.8378 g (3 mM) of 2-p-nitrobenzylideneindan-1,3-dione [14] and 1.0842 (3 mM) of VII [13] in 25 ml of acetic acid were heated under reflux for 40 min, after which time the violet color of VII had disappeared completely. The yellow precipitate was filtered off to give 1.0012 g (93%) of 4-phenyl-2,3-(CO),6,5(CO)dibenzoylenepyridine, mp 352° C. The filtrate was diluted with water, giving 0.8032 g of yellowish material which was purified by solution in 5% NaOH solution, followed by acidification with HCl. There was obtained 0.6702 g (78%) of 2-p-nitrobenzylindan-1,3-dione, mp 140–141° C (from ethanol) [15].

B) **Reduction with 2-methyl-3-ethoxycarbonyl-4-p-nitrophenyl-6,5-(CO)-benzoylene-1,4-dihydropyridine.** 0.9760 g (2.5 mM) of 2-p-nitrobenzylideneindan-1,3-dione and 0.6981 g (2.5 mM) of 4-p-nitrophenyl-6,5-(CO)-benzoylene-1,4-dihydropyridine [16] in 25 ml of acetic acid were heated under reflux for 3.5 hr, after which time the color of the dihydropyridine had almost disappeared. The reaction mixture was kept overnight, and the yellow solution evaporated to dryness in vacuo on the water bath. From the residue there was obtained 0.5488 g (78%) of 2-p-nitrobenzylindan-1,3-dione as in (A) above. The alkali-insoluble residue was 0.9352 g (96%) of 2-methyl-3-ethoxycarbonyl-4-p-nitrophenyl-6,5(CO)-benzoylenepyridine, mp 200–201° C (from ethanol) [16].

C) **Reduction with 2,6-dimethyl-3,5-bisethoxycarbonyl-1,4-dihydropyridine [17] (XI).** 0.4189 g (1.5 mM) of 2-p-nitrobenzylideneindan-1,3-dione and 0.3800 g (1.5 mM) of XI in 20 ml of dioxane were heated under reflux for 1 hr, then evaporated to dryness in vacuo. The residue was worked up as in (B) above, to give 0.3736 g (89%) of 2-p-nitrobenzylindan-1,3-dione and 0.3736 g (41%) of 2,6-dimethyl-3,5-bisethoxycarbonylpyridine, mp 70–72° C [17] (from ethanol).

2-p-Chlorobenzylindan-1,3-dione was obtained similarly from 2.6870 g (10 mM) of 2-p-chlorobenzylideneindan-1,3-dione [14] and 2.5330 g (10 mM) of XI in 30 ml of dioxane. Yield 2.2483 g (83%), mp 119–120° C [18].

Diindandionylmethane. 0.4534 g (1.5 mM) of methenylbisindan-1,3-dione [19] and 0.5421 g (1.5 mM) of VII in 20

Table 1. The Oxidation of 1,4-Dihydropyridines by 2-p-Chlorobenzylideneindandione (Ic) and Chloranil

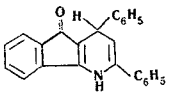
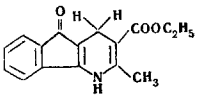
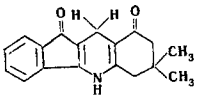
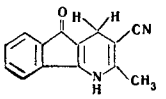
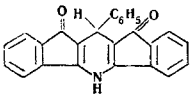
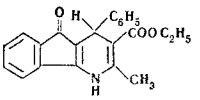
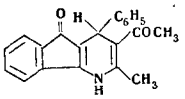
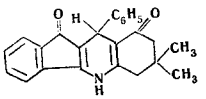
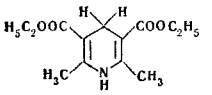
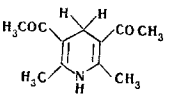
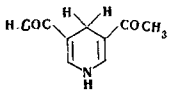
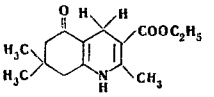
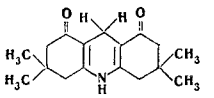
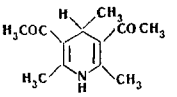
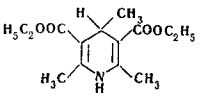
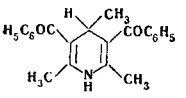
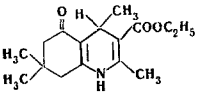
Hydrogen donor		Literature	Oxidant	Temperature, °C	Duration of reaction
Compound	Structural formula				
III		21	Ic Chloranil	20 20	5 min 5 sec
IV		22	Ic Ic Chloranil	20 118 20	10 min 10 sec 5 sec
V		22	Ic Ic Chloranil	20 118 20	2.5 hr 1 min 1 min
VI		23	Ic Chloranil	118 20	3 min 4 min
VII		13	Ic Chloranil Chloranil	118 20 118	5 min 30 min 15 sec
VIII		16	Ic Chloranil	118 20	15 min 8 min
IX		16	Ic Chloranil	118 20	30 min 3 min
X		24	Ic Chloranil	118 118	2 hr 50 sec

Table 2. The Reduction of Methenylbisindan-1, 3-dione (II) with 1, 4-Dihydropyridines

Compound	Hydrogen donor: Dihydropyridine	Literature	Temperature, ° C	Duration of reaction
XI		17	25	30 sec
XII		25	25	5 min
XIII		26	20 101	24 hr* 20 min
XIV		27	25 101	30 min** 2 min
XV		28	20 101	24 hr* 30 min
XVI		30	20 101	24 hr* 120 min*
XVII		1	20 101	24 hr* 120 min**
XVIII		29	20 101	24 hr* 100 min**
XIX		27	101	120 min**

*No color change
**Reduction incomplete

ml of acetic acid were heated under reflux for 4 hr. After this time, the red color had faded, and a yellow precipitate separated which was filtered off. Yield 0.4451 g (82.5%) of 4-phenyl-2,3(CO),6,5(CO)-dibenzoylenepyridine. The filtrate afforded 0.3679 g (81%) of diindandionylmethane, mp 202–203° C [20] (from acetic acid).

Oxidation of 1,4-dihydropyridines with chloranil or 2-p-chlorobenzylideneindan-1,3-dione (Ic) (cf Table 1). 0.02 g of the dihydropyridine was dissolved in 20 ml of acetic acid. The reactions were carried out with 5 ml of acetic acid, 0.1 g of chloranil or Ic and 2 ml of a solution of the corresponding dihydropyridine. The mixture was kept at room temperature or boiled until the color of the dihydropyridine had disappeared.

Reduction of methenylbisindan-1,3-dione (II) with 1,4-dihydropyridines (cf Table 2). 0.1 g of II was dissolved in 50 ml of hot dioxane. The reactions were carried out with 5 ml of dioxane, 0.1 g of the corresponding 1,4-dihydropyridine, and 2 ml of a cooled solution of II. The mixture was kept at room temperature or boiled until the color of II disappeared.

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