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4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone, the intermediary product of the carbonyl condensation reaction between 1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone and benzaldehyde, rearranges in the presence of an equivalent quantity of sodium hydride into 4-benzyl-1-phenyl-3(2*H*)-isoquinolinone. As the possibility of the migration of the hydrogen at C-1 in the form of a proton or a hydrogen atom (radical reaction) was excluded, the mechanism of the rearrangement could be depicted as an intermolecular hydride anion migration. In case of the 1-(4-pyridyl)- and 1-(3-pyridyl)-1,4-dihydro-3(2*H*)-isoquinolinones, however, the rearrangement can be carried out also in polyphosphoric acid and in this case a proton loss-proton gain mechanism was proved.

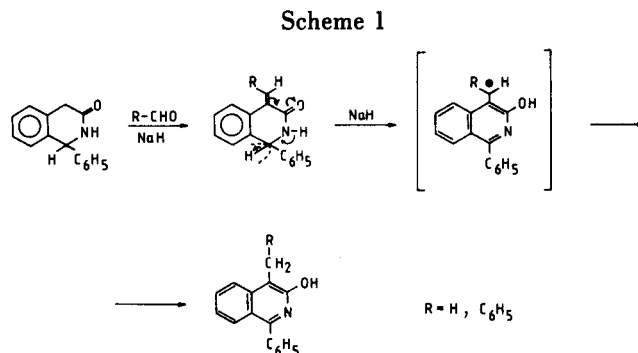
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While investigating the increased reactivity of the methylene group at position 4 in 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones synthesized first by us [1] we have established that in the presence of a strong base, for example sodium hydride, a carbonyl condensation reaction takes place between these compounds and aromatic aldehydes [2].

When interrupting the reaction at the appropriate point of time, we succeeded in isolating the intermediary 4-benzylidene-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone [3] that rapidly rearranges under basic conditions into 4-benzyl-1-phenyl-3(2*H*)-isoquinolinone. Similar reaction was carried out with 1-(4-pyridyl)- and 1-(3-pyridyl)-1,4-dihydro-3(2*H*)-isoquinolinones under acidic conditions, in polyphosphoric acid [4].

On investigating the mechanism of the reaction by means of labelled compounds we proved that it is the hydrogen at C-1 which migrates into the α -position of the benzylidene group and that this migration is of intermolecular character [5]. On the basis of these experiments the following mechanism was suggested (Scheme 1):

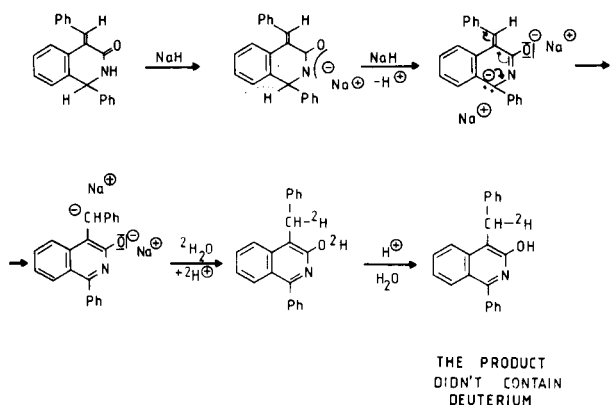
In order to clarify the details of the proposed mechanism, the rearrangement of 4-benzylidene-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone was investigated in the presence of a base into 4-benzyl-1-phenyl-3(2*H*)-isoquinolinone. It was established that the reaction could not be effected by a catalytic amount of sodium hydride; the consumption of the starting compound could be detected by tlc only after having added to its benzene solution an



equivalent quantity of sodium hydride and having heated the solution at 50° for 6 hours. The rearrangement can be effected also by sodium ethoxide in ethanolic solution.

The next question to be answered was whether the hydrogen at C-1 was split off during this rearrangement in the form of a proton, a hydride anion or perhaps as a radical. The splitting off as a proton in a medium containing sodium hydride is rather improbable. As the previously proved intermolecular character of the process similarly contradicts this possibility, the splitting off of a hydride anion seemed to be the most likely. Nevertheless it was necessary to prove experimentally that the hydrogen at C-1 could not split off as a proton. Therefore, after having performed the reaction, when working up the reaction mixture, deuterium oxide was used instead of water (Scheme 2).

Scheme 2

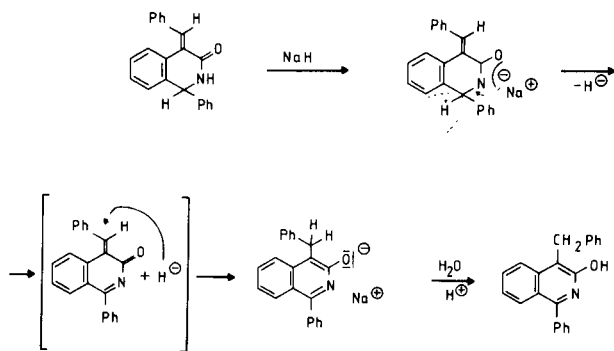


Scheme 2 shows the rearrangement as a proton migration process (proton loss and proton incorporation). The observation by nmr spectroscopy, that deuterium incorporation did not take place into the α -position of the benzyl group, proved that the migration of the C-1 hydrogen as a proton could be excluded.

Further the reaction in the presence of a catalytic amount of dibenzoyl peroxide and hydroquinone, respectively, was studied, but these radical reaction accelerating and inhibiting compounds did not influence the rate and the yield of the reaction.

On the basis of these results we can now outline a mechanism shown in Scheme 3.

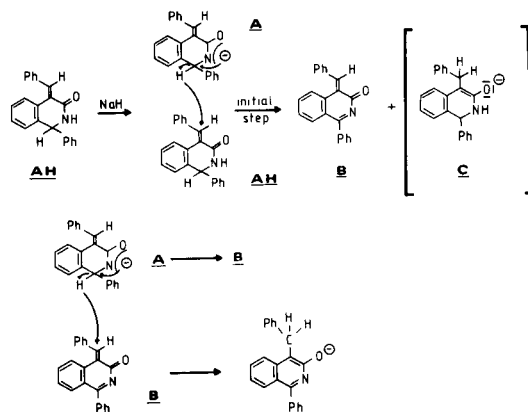
Scheme 3



The migration of the C-1 hydrogen may take place in the form of a hydride anion. In the first step a salt is formed from the 4-benzylideneisoquinolinone derivative. In this delocalised carbanion, as a result of the electron displacement into the direction of C-1, the hydrogen at C-1 is split off as a hydride anion and the latter attacks intermolecularly on the β -carbon atom of the intermediate molecule which can be regarded as an α,β -unsaturated carboxylic acid derivative.

Scheme 4 shows the details of this mechanism. The hydride ion, split off from the C-1 position of the A ion

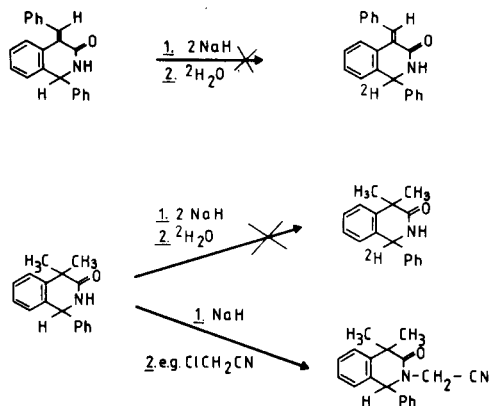
Scheme 4



formed in the salt producing step, attacks the unchanged starting compound (AH). In this step the **B** neutral molecule and the **C** ion are formed. Molecule **B** reacts then with another **A** ion to give the end product of the rearrangement (in the form of a salt), and molecule **B** is regenerated. This regenerated **B** molecule can again react with a new **A** molecule and thus the reaction takes place step by step. In our opinion this mechanism gives a satisfactory explanation of the intermolecular character of the rearrangement.

As this reaction is not quantitative, we also investigated whether the sodium hydride could not split off a hydrogen directly from C-1, reducing the yield in this way (Scheme 5). In these experiments the starting 4-benzylidene derivative was allowed to react with 2 equivalents of sodium

Scheme 5



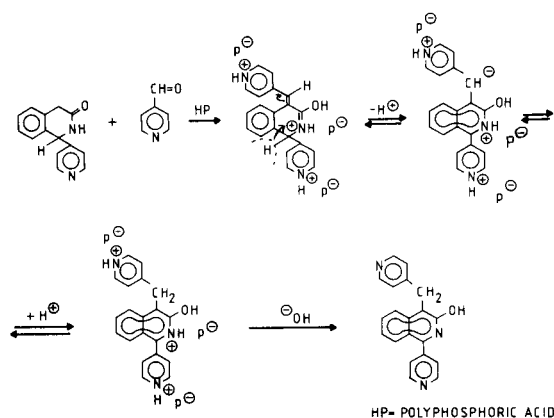
hydride at room temperature to prevent the rearrangement reaction. After a time the mixture was treated with deuterium oxide and the isolated product was analyzed. Its nmr and mass spectra showed that deuterium incorporation into the position C-1 did not take place. In the next experiment, in which the 4,4-dimethyl derivative was treated with sodium hydride at 100°, we obtained similar results. These results are in good agreement with those found in the reaction of the 4,4-dimethylisoquinolinone

derivative with chloroacetonitrile in the presence of sodium hydride: only substituent at the ring nitrogen could be detected (Scheme 5). (The resulting *N*-cyanomethyl derivative could be converted with hydroxylamine to give the corresponding amide oxime in high yields.)

These results gave convincing evidence that sodium hydride did not attack against C-1 even when used in excess or under vigorous conditions.

As mentioned earlier, contrary to the reaction of 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinone with aromatic aldehydes, the same carbonyl condensation reaction between 1-pyridylisoquinolinone and pyridinecarboxaldehydes takes place also in acidic medium, in polyphosphoric acid (PPA). In this case we may assume that in such a strong protonating medium as PPA, the C-1 hydrogen can split off as a proton, especially in view of the two strong electron-attracting

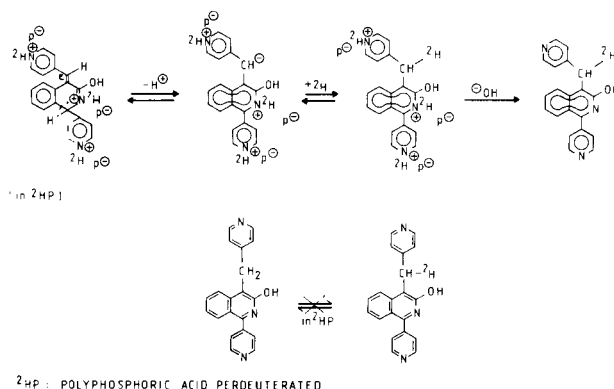
Scheme 6



groups in its vicinity. The carbanion formed through electron displacement adds a proton from PPA and, after rendering the mixture alkaline, the end product is obtained (Scheme 6).

This assumption was proved also by the method of tracing with deuterium. Perdeuterated polyphosphoric acid was prepared from phosphorus pentoxide and deuterium oxide and the reaction was carried out in this medium. When our assumption about the proton loss and proton gain from the PPA is correct, then the reaction of pyridylisoquinolinone with pyridinecarboxaldehyde must yield the end product containing deuterium in the α -position of the 4-picolinyl group. As the nmr spectrum of the product showed, in the methylene group at C-4 one of the hydrogens was indeed quantitatively replaced by deuterium. To check this result we investigated, whether there was not a spontaneous hydrogen-deuterium exchange in the strong acidic medium. We experienced that under similar reaction conditions deuterium incorporation was not detectable (Scheme 7).

Scheme 7



The deuterium incorporation experiments described earlier were undertaken also with the isolated and pure 4-(3-picolinylidene)-derivative with the same results: one of the hydrogens in the methylene group of the C-4 picolinyl group was replaced by deuterium.

On the basis of these experiments we may state that the rearrangement reactions of 1-pyridyl-4-picolinylideneisoquinolinones take place in acidic medium with a proton loss-proton gain mechanism. It must be finally mentioned that this rearrangement - similarly to the phenyl-substituted compounds - takes place also in the presence of a base, but then presumably with the hydride ion mechanism outlined earlier.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. The ir spectra were recorded in potassium bromide pellets (Perkin Elmer Model 457). The ^1H nmr spectra were determined using a JEOL FX-100 spectrometer and chemical shifts δ are given in ppm units relative to internal tetramethylsilane standard. Mass spectra were run on a Varian Mat Spectrometer at 70 eV. Tlc was performed in Kieselgel 60F₂₅₄ (Alurolle, Merck) layer using benzene:ethyl acetate (1:1 v/v), chloroform:acetone (9:1 v/v), benzene:methanol:chloroform (7:3:2 v/v), ethanol:ethyl acetate (1:1 v/v) and ethyl acetate:acetone:water (2.5:2.5:0.25 v/v) developing mixtures.

Preparation of 4-Benzyl-1-phenyl-3(2*H*)-isoquinolinone in the Presence of Catalytic and Equivalent Amounts of Sodium Hydride.

4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (3.11 g, 0.01 mole) was dissolved in anhydrous benzene (60 ml) with stirring at 50°, then sodium hydride (0.048 g, 0.001 mole) was added in the form of an 50% oily dispersion in a stream of nitrogen gas. The mixture was stirred at 50° for 5 hours, and a minimum extent of conversion was established by means of tlc; the reaction mixture contained, besides the product, mainly the starting 4-benzylidene derivative. Now sodium hydride (0.48 g, 0.01 mole) in the above form was added again and the mixture was stirred at 50°, taking samples in every hour which were tested by tlc. It was found that after stirring for 6 hours, the sample contained predominantly the product. Water (50 ml) and 2*N* hydrochloric acid (5 ml) were then added and the mixture was extracted with chloroform. The extract was evaporated to dryness and the residual oil rubbed with ether. The resulting solid was filtered off and dried (1.9 g, 61.2%), mp 230-232°, lit [2] mp 233-235°. The ir spectrum agreed with that of substance prepared in another reaction series [2].

Investigation on the Incorporation of Deuterium in the Reaction of 4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone.

The 4-benzylidene derivative (1 g, 0.00322 mole) was dissolved in anhydrous benzene (20 ml) under stirring at 50°, then sodium hydride (0.18 g, 0.0036 mole) was added in the form of an 50% oily dispersion in a stream of nitrogen gas. The mixture was stirred at 50° for 6 hours, evaporated to dryness and deuterium oxide (5 ml) was added to it in a stream of nitrogen gas. The oily mixture formed was acidified with 2*N* hydrochloric acid and extracted with chloroform; the extract was dried over sodium sulphate then evaporated to dryness and rubbed with ether to give the product (0.6 g, 60%), mp 230°, lit [2] mp 233-235°; nmr (deuteriochloroform): δ 6.95-7.75 (12H, m, ArH), 7.76 (1H, d, ArH), 7.82 (1H, d, ArH) to CH₂ at site 4, 4.30 (2H, s), that is, no incorporation of deuterium occurred.

Preparation of 4-Benzyl-1-phenyl-3(2*H*)-isoquinolinone in the Presence of Hydroquinone.

4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (1 g, 0.00322 mole) was dissolved in anhydrous benzene (20 ml), with stirring at 50°, then sodium hydride (0.18 g, 0.0036 mole) was added in the form of an 50% oily dispersion in a stream of nitrogen gas. Hydroquinone (0.1 g) was added and stirring was continued at 50° for 6 hours. The mixture was poured into water, acidified with 2*N* hydrochloric acid and extracted with chloroform. The chloroform phase was dried over sodium sulphate, evaporated to dryness and the residue was rubbed with ether (0.6 g, 60%), mp 229-230°, lit [2] mp 233-235°. The tlc and ir data also agree with those of the product prepared earlier [2].

Preparation of 4-Benzyl-1-phenyl-3(2*H*)-isoquinolinone in the Presence of Dibenzoyl Peroxide.

The amounts of reagents and the conditions used were identical with those employed in the reaction effected in the presence of hydroquinone but instead of the latter, dibenzoyl peroxide (0.1 g) was added to the mixture. The reaction mixture was processed as given above, and the product (0.7 g, 70%), was in all respects identical with those prepared earlier.

Studies on the C-1 (H → ²H) Exchange in 4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone.

4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (1 g, 0.00322 mole) was dissolved in anhydrous dimethylformamide (10 ml), then sodium hydride (0.31 g, 0.0064 mole) was added to it in the form of an 50% dispersion with stirring in a stream of nitrogen gas. The mixture was stirred at room temperature until the evolution of hydrogen ceased (10 minutes) and deuterium oxide (11 ml) was added to it dropwise. When the intense foaming stopped, the solid was filtered off, washed with water and dried, then it was rubbed with a mixture of ether and gasoline (5:1) to obtain a solid (0.4 g), mp 168-175°; according to the tlc tests, the literature [3] mp 192-193° of the 4-benzylidene derivative is lowered by the presence of 4-benzyl-1-phenyl-3(2*H*)-isoquinolinone (the latter amounts to 5% according to the mass spectrum); nmr (deuteriochloroform): calculating for the intensity of the =CH signal [3], the intensity of H-1 did not change as compared to that in the starting material; incorporation of deuterium to C-1 did not occur; *m/z*: 313 (3.6, M+2), 312 (25.0, M+1), 311 (M⁺, 100%), 310 (54, M-1). In view of the mole bunch distribution of the sample, also considering the natural isotope content, the deuterium content can be maximum 3%, which is insignificant. The amount of the isomerized 3(2*H*)-isoquinolinone is maximum 5%, on the basis of the intensity of the M-1 and M-77 peaks.

Studies on the C-1 (H → ²H) Exchange in 4,4-Dimethyl-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone.

4,4-Dimethyl-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (1 g, 0.004 mole) was dissolved in anhydrous dimethylformamide (10 ml), and sodium hydride (0.384 g, 0.008 mole) was added in the form of an 50% oily dispersion, with stirring, in a stream of nitrogen gas. The mixture was stirred at 100° in a stream of nitrogen gas for 1 hour, deuterium oxide (6

ml) was added and the mixture was poured into water (50 ml) and acidified with 2*N* hydrochloric acid. The product (0.8 g), mp 143-145°, in spite of its lower melting point, had tlc and ir data identical with those given in the literature [6] and, after crystallization from benzene it showed the mp of the pure substance, lit [6] 172°; nmr (deuteriochloroform): δ 5.63 (1H, s, H_{ar}-1), 6.43 (1H, s, NH), 1.52 (3H, s, Me), 1.63 (3H, s, Me), 6.74 (1H, d, J = 8 Hz, ArH), 6.95-7.49 (8H, m, ArH). On the basis of the signal 6.74 (1H, d, ArH) no deuterium was incorporated at C-1.

2-Cyanomethyl-4,4-dimethyl-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone.

4,4-Dimethyl-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (1.1 g, 0.0044 mole) was dissolved in anhydrous dimethylsulfoxide (10 ml), and sodium hydride (0.38 g, 0.008 mole) was added in the form of an 50% oily dispersion, with stirring, in a stream of nitrogen gas. Stirring was continued for 30 minutes. A solution of chloroacetonitrile (0.51 ml, 0.604 g, 0.008 mole) in dimethylsulfoxide (5 ml) was added dropwise while keeping the temperature of the mixture below 20° by cooling in ice-water. The dropwise addition took 30 minutes; the mixture was then stirred at exactly 20° for 3 hours, poured into water, acidified with 2*N* hydrochloric acid and extracted with chloroform. The extract was evaporated to dryness in vacuum and the residual oil rubbed with water. The resulting solid was subjected to chromatographic separation on a column packed with aluminium oxide using chloroform eluent. The fractions collected according to tlc tests were evaporated to dryness and the residue was rubbed with ether. The product was crystallised from ethanol (0.65 g, 51%), mp 138-139°; ir: 1640 cm⁻¹ (C=O), 2220 cm⁻¹ (C≡N).

Anal. Calcd. for C₁₉H₁₈N₂O: C, 78.60; H, 6.25; N, 9.65. Found: C, 78.72; H, 6.50; N, 9.63.

(1-Phenyl-4,4-dimethyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide Oxime.

2-Cyanomethyl-4,4-dimethyl-1-phenyl-1,4-dihydro-3(2*H*)-isoquinolinone (4.05 g, 0.014 mole) was dissolved in ethanol (50 ml) and a solution of hydroxylamine hydrochloride (0.97 g, 0.014 mole) in water (10 ml) was added dropwise. [From the hydroxylamine hydrochloride the base was liberated previously by the addition of sodium hydrogen carbonate (1.18 g, 0.014 mole)]. The reaction mixture was refluxed for 3 hours, then refrigerated overnight. The solid product was filtered off, washed with water, dried and recrystallized from ethanol (4.1 g, 61%), mp 180-182°; ir: 1660 (C=O), 1600 (C=N), 3370, 3480 cm⁻¹ (NH₂); nmr (deuteriochloroform): δ 1.68 (6H, s, Me), 3.17 (1H, d, J_{gem} = 14.6 Hz, NCH₂), 4.76 (1H, d, OH), 5.12 (2H, s, NH₂), 5.70 (1H, s, H-1), 6.8-7.4 (9H, m, ArH).

Anal. Calcd. for C₁₉H₂₁N₃O₂: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.55; H, 6.91; N, 13.03.

Hydrochloride.

This compound had mp 215-217° dec.

Anal. Calcd. for C₁₉H₂₂ClN₃O₂: C, 63.42; H, 6.16; N, 11.68; Cl, 9.88. Found: C, 63.24; H, 6.16; N, 11.64; Cl, 9.85.

Preparation of 4-(4-Picolinyl)-1-(4-pyridyl)-3(2*H*)-isoquinolinone Labeled with Deuterium in Perdeuterated Polyphosphoric Acid (PPA).

Phosphorus pentoxide (13.1 g) was slowly added to deuterium oxide (4.5 ml), with stirring, in a stream of nitrogen gas, then the reaction mixture was kept at 100° for 8 hours to obtain perdeuterated polyphosphoric acid of a composition 1:1 (1:1 PPA-*d*). Into this cold PPA-*d*, 1-(4-pyridyl)-1,4-dihydro-3(2*H*)-isoquinolinone (0.8 g, 0.00357 mole) was added; after stirring for 5 minutes, 4-pyridinecarboxaldehyde (0.34 ml, 0.38 g, 0.00357 mole) was added. The mixture was stirred at 120-125° for 6 hours, it was poured into water (200 ml) and made alkaline with concentrated ammonium hydroxide to pH 8. The product which separated was filtered off, washed with water, dried and recrystallized from dimethyl formamide (0.5 g, 45%), mp 227°, lit [4] mp 231-232°. The ir and tlc data agreed with those of the product prepared by us earlier [4], in non-deuterated 1:1 PPA; nmr (deuteriochloroform): δ for the unlabelled compound [4] 7.32 (1H, t, ArH), 7.54 (1H, d, ArH), 7.80 (1 + 1H, d, ArH), 8.40, 8.74 (2H-2H, d, pyridine α), 7.08 7.50 (2H-2H, d, pyridine β), 4.30 (2H, s,

CH₂). According to the integrated nmr spectrum of the compound prepared in 1:1 PPA-*d*, one ²H was incorporated in the CH₂ group.

Studies on the Spontaneous 4-CH₂ (H → ²H) Exchange in 4-(4-Picolinyl)-1-(4-pyridyl)-3(2*H*)-isoquinolinone.

Into PPA-*d* (1:1) prepared from deuterium oxide (4.5 ml) and phosphorus pentoxide (13.1 g) in the above manner, unlabelled 4-(4-picolinyl)-1-(4-pyridyl)-3(2*H*)-isoquinolinone (1.12 g, 0.00357 mole), synthesized by us earlier [4], was added. The reaction mixture was stirred at 120° for 6 hours, poured into water (200 ml), and made alkaline with concentrated ammonium hydroxide to pH 8. The product (1.05 g) was filtered off, and dried; crystallized from dimethylformamide to obtain the starting material unchanged as shown by the ir and tlc results, mp 227°, lit [4] mp 231-232°; nmr (deuteriochloroform): the signal at 4.30 (s, CH₂) had the original intensity of 2H, *i.e.* no incorporation of ²H took place.

Preparation of 4-(3-Picolinyl)-1-(3-pyridyl)-3(2*H*)-isoquinolinone Labelled with Deuterium in Perdeuterated PPA.

Fresh 1:1 PPA-*d* was prepared from deuterium oxide (2.25 ml) and phosphorus pentoxide (6.55 g) as described above, and 4-(3-picolinylidene)-1-(3-pyridyl)-1,4-dihydro-3(2*H*)-isoquinolinone (0.1 g, 0.00032 mole) was added to it. The mixture was stirred at 140° for 16 hours. It was then poured into water (50 ml) and made alkaline with concentrated ammonium hydroxide to pH 8. The opaque solution was extracted with chloroform, the organic phase was dried over sodium sulphate then evaporated to dryness and the residue was rubbed with ether (0.05 g, 50%), mp 222-224° lit [4] mp 229-230°. The ir and tlc results agreed with those obtained for the product prepared by us earlier [4] in non-deuterated fresh polyphosphoric acid; nmr (deuteriochloroform): δ for the unlabelled compound [4] 6.95-7.60 (5H, m, ArH), 7.80 (1 + 1H, d, ArH), 8.34 (1H, dd, pyridine α), 8.59 (1H, dd, pyridine α), 9.15 (1H, dd, pyridine α), 8.65 (1H,

dd, pyridine α), 7.93 (1H, d, pyridine γ), 4.37 (2H, s, CH₂). According to the integrated nmr spectrum of the compound prepared in fresh (1:1) PPA-*d*; one ²H was incorporated in the CH₂ group in nearly 100%.

Preparation of 4-(3-Picolinyl)-1-(3-pyridyl)-3(2*H*)-isoquinolinone in the Presence of a Base.

4-(3-Picolinylidene)-1-(3-pyridyl)-1,4-dihydro-3(2*H*)-isoquinolinone (0.45 g, 0.00143 mole) was dissolved in ethanol (25 ml) and a solution of sodium ethoxide (0.0658 g, 0.00286 mole) in ethanol (20 ml) was added dropwise. The solution was refluxed for 2 hours. It was then evaporated to dryness, the residue dissolved in 2*N* hydrochloric acid and the product was precipitated with a 1:1 mixture of concentrated ammonium hydroxide and water. The solid was filtered off, washed with water and dried to give the product (0.25 g, 56%), mp 229-230°, lit [4] mp 229-230°. The ir and tlc data agreed with those obtained for the product prepared by us earlier [4] in PPA and in the presence of sodium hydride.

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