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# SYNTHESIS OF PYRIDINE AND QUINOLINE ANALOGS OF CHALCONE. STUDY OF THEIR STRUCTURE BY THE PMR METHOD

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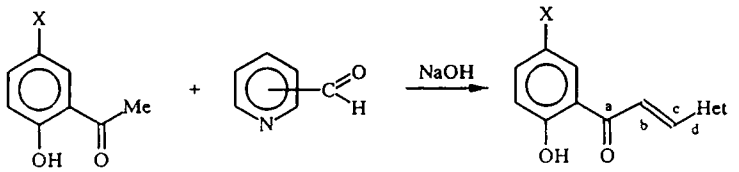
*Substituted pyridine and 2-quinoline analogs of chalcone have been synthesized. The homonuclear Overhauser effect has been used to assign the PMR signals of the olefinic protons of the indicated pyridine derivatives and to elucidate their steric orientation.*

Heterocyclic chalcone analogs constantly command interest since they act as intermediate products in the synthesis of practically important flavonoids and themselves show useful biological activity [1, 2]. Molecules of these compounds are conformationally mobile, hence, a series of works has been connected with a study of their steric structure [3-6]. Among this series, pyridine and quinoline derivatives have been little studied. Individual representatives of such chalcones were synthesized earlier [7, 8] but their stereochemistry was not studied (with the exclusion of some 3-pyridylchalcones [4]).

The corresponding novel chalcone analogs (I-IV) were synthesized from a series of 5-substituted 2-hydroxyacetophenones and 2-, 3-, or 4-formylpyridines and also 2-formylquinoline in the presence of sodium hydroxide. They contained pyridine or quinoline residues attached to the olefinic fragment:




I–IV

Ia, b Het = 4-pyridyl IIa-c Het = 3-pyridyl IIIa, b Het = 2-pyridyl
IVa-b Het = 2-quinolyl
I–III a X = $NO_2$, b X = Br, c X = F; IV a X = Cl, b X = Br

Substituents were chosen in such a way as to simplify the PMR spectra of the compounds, which is important in elucidating their conformation. The synthesized samples are yellow crystalline materials, readily crystallized from acetone or from a mixture of acetone and water. Their purity was monitored by TLC and by elemental analytical data (Table 1), and their structures confirmed from PMR spectral data (Table 2).

The spectra of the pyridine analogs of chalcone show a signal for the hydroxyl proton at lowest field (12.4-13.3 ppm). The signal is narrow when deuterochloroform is used as solvent and strongly broadened in DMSO-$D_6$. Its chemical shift points to the presence of a strong, intramolecular hydrogen bond to the carbonyl oxygen atom. The signals for the remaining aromatic protons are observed in the region 7-9 ppm and can be identified in most cases. In the same region, the olefinic signals are also observed. With analysis of the latter there always arises the question of their assignment to the protons $\alpha$- and $\beta$- to the carbonyl group. Depending on the solvent used, they have the appearance of two more or less closely spaced doublets with $^3J_{vic}$ = 17-18 Hz. For assignment of these signals in the analogous chalcones containing other heterocycles, we have previously used the method of preparing deuterated samples [9], the effect of aromatic solvent induced shifts (ASIS) [10], lanthanide shift

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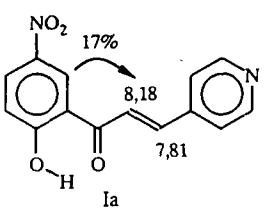
TABLE 1. Parameters for Compounds Synthesized

| Compound | mp, °C* | Found, % | | Empirical formula | Calculated, % | | Yield, % |
|---|---|---|---|---|---|---|---|
| | | N | Br | | N | Br | |
| Ia | 154...155 | 10,42 | — | $C_{14}H_{10}N_2O_4$ | 10,4 | — | 47 |
| Ib | 131...132 | 4,54 | 26,28 | $C_{14}H_{10}BrNO_2$ | 4,6 | 26,3 | 60 |
| IIa | 202...204 | 10,48 | — | $C_{14}H_{10}N_2O_4$ | 10,4 | — | 50,3 |
| IIb | 139...140 | 4,51 | 26,4 | $C_{14}H_{10}BrNO_2$ | 4,6 | 26,3 | 68 |
| IIc | 182...183 | 5,96 | — | $C_{14}H_{10}FNO_2$ | 5,76 | — | 38 |
| IIIa | 100...101 | 10,06 | — | $C_{14}H_{10}N_2O_4$ | 10,4 | — | 41,4 |
| IIIb | 145...147 | 4,5 | 26,4 | $C_{14}H_{10}BrNO_2$ | 4,6 | 26,3 | 52 |
| IVa† | 127...128 | 4,44 | — | $C_{18}H_{12}ClNO_2$ | 4,52 | — | 40 |
| IVb | 138...139 | 4,06 | 22,57 | $C_{18}H_{12}BrNO_2$ | 3,95 | 22,56 | 54,3 |

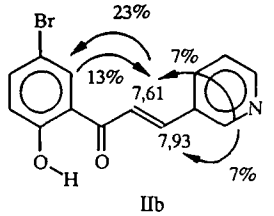
*Compounds Ia, IIc were recrystallized from acetone, IIa from methanol, and the rest from a mixture of acetone and water (3:1).

†Found, %: Cl 11.34; calculated, %: Cl 11.45.

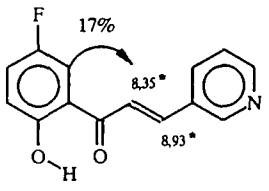
reagents (LSR) [11], or the homonuclear Overhauser effect (NOE) [12]. In the case of the compounds examined by us, it was shown that measurement of PMR spectra in deuterobenzene did not lead to an unambiguous assignment of the olefinic proton signals since they are shifted almost identically when exchanging $CDCl_3$ for $C_6D_6$ (see Table 2). This is connected with the simultaneous association of benzene with the pyridine ring and the carbonyl group. It did not prove possible to make unambiguous conclusions about the conformation of the bonds in the conjugated pyridine analogs of the chalcone from their shifts inducted by $Eu(FOD)_3$ either, nonetheless, measurement of the spectra in benzene or in the presence of that LSR proved useful in a number of cases for the separation of certain signals when carrying out the NOE experiments. The latter method proved the most informative, although some of the NOE experiments could not be carried out due to the coincidence of a number of signals. In these cases, it was necessary to analyze a combination of experimental results carried out on chalcones close in structure (starred designation of chemical shifts in the presence of $Eu(FOD)_3$).



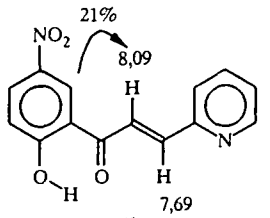

Ia



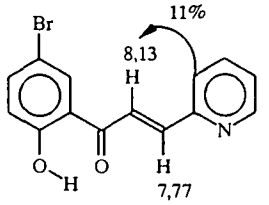

IIb




IIc




IIIa




IIIb

The NOE values on the formulae indicate the percentage increase in signal intensity. Also shown are the chemical shift values for the olefinic proton signals. The arrow indicates the direction from the irradiated proton to the proton which shows

TABLE 2. $^1$H NMR Data for the Studied Heterocyclic Analogs of Chalcones, δ, ppm

| Compound | Solvent | Protons of the phenyl fragment* | | | | Olefinic protons | | Protons of the pyridine fragment† | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2-OH s | 3-H d | 4-H d. d | 6-H d | α-H d | β-H d | 2-H | 3-H | 4-H | 5-H | 6-H |
| Ia | $CDCl_3$ | 13,24 | 7,19 | 8,41 | 8,88 | 7,91 | 7,84 | 8,78 d | 7,56 d | – | 7,56 d | 8,78 d |
| Ia | DMSO | ‡ | 7,18 | 8,33 | 8,64 | 8,01 | 7,68 | 8,68 d | 7,79 d | – | 7,79 d | 8,68 d |
| Ia | DMSO + $C_6D_6$ | ‡ | 7,26 | 8,34 | 8,92 | 8,17 | 7,80 | 8,71 d | 7,70 d | – | 7,70 d | 8,71 d |
| Ib | $CDCl_3$ | 12,47 | 6,93 | 7,58 | 7,96 | 7,83 | 7,64 | 8,72 d | 7,50 d | – | 7,50 d | 8,72 d |
| Ib+LSR | $CDCl_3$ | (1,9)** | (1,6) | (1,5) | (3,7) | (9,4) | (6,0) | (36) | (8,8) | – | (8,8) | (36) |
| IIa | DMSO | ‡ | 7,19 | 8,34 | 8,73 | 7,78 | 8,00 | 9,0 | – | 8,34 d | 7,50 t | 8,63 d. d |
| IIb | $CDCl_3$ | 12,60 | 6,94 | 7,58 | 8,02 | 7,61 | 7,92 | 8,89 s | – | 8,02 d | 7,40 t | 8,68 d. d |
| IIb | $C_6D_6$ | 13,18 | 6,68 | 7,10 | 7,62 | 6,81 | 7,55 | 8,44 s | – | 6,86 d | 6,56 t | 8,41 d. d |
| IIc | $CDCl_3$ | 12,41 | 7,2...8,1 | | 7,02 | 7,59 | 7,96 | 8,89 s | – | 8,00 d | 7,2...7,8 | 8,68 d. d |
| IIc | $C_6D_6$ | 12,90 | 6,7...8,2 | | 6,62 | 7,05 | 7,56 | 8,53 s | | 6,7...8,2 m | | 8,42 d. d |
| IIc+LSR | | (1,4) | (0,3) | | (0,3) | (5,4) | (6,9) | (31,4) | – | (11,3) | | (38,5) |
| IIIa | DMSO | ‡ | 7,18 | 8,32 | 8,55 | 8,09 | 7,69 | – | 7,88 d | 7,85 t | 7,45 d. d | 8,68 d. d |
| IIIb | $CDCl_3$ | 12,69 | 6,93 | 7,57 | 8,14 | 8,18 | 7,85 | – | 7,50 d | 7,78 t | 7,41 d. d | 8,73 d. d |
| IIIb | $C_6D_6$ | 13,19 | 6,63 | | 7,83 | 8,13 | 7,75 | – | 7,2...7,6 m | 6,92 t | 7,2...7,6 m | 8,39 d. d |
| IVa | $CDCl_3$ | 12,66 | 6,99 | | | | | 7,4...8,4 m | | | | |
| IVb | $CDCl_3$ | 12,68 | 6,93 | | | | | 7,5...8,4 m | | | | |

* $^3J$ = 8 Hz; $^4J$ = 2 Hz.

† $^3J\alpha\beta$ = 5 Hz; $^4J\alpha\gamma$ = 2 Hz; $^3J\beta\gamma$ = 8 Hz.

‡ Exact signal position could not be determined because of strong broadening.

** LIS given in brackets for an LSR:substrate ratio of 1:1.

the NOE. For IIc, the experiment was carried out in the presence of $Eu(FOD)_3$ and the signal for the phenolic 6-H proton was sufficiently removed from the olefinic proton signals. In the case of Ia, the NOE was observed for a solution in a mixture of DMSO-$D_6$ and $C_6D_6$. The clearest conformation of the molecule is revealed by the NOE for the α-olefinic proton when irradiating at the position of the phenolic 6-H proton. It follows from these data that the α-olefinic proton is found at lower field in the 2- and 4-pyridyl analogs and the β- proton in the 3-pyridyl isomers. Hence, if the pyridine ring withdraws electrons from the CH=CH bond, the signal for the α-olefinic proton is at lower field. The result agrees with conclusions in [10] regarding the effects of the electron donor ability of the heterocycle on the position in the PMR spectrum of olefinic proton signals in heterocyclic analogs of chalcone.

The observed values of the NOE also permit refinement of the structure of the conjugated chalcone chain. In fact, the only uncertainty is the orientation of the pyridine ring relative to the *d* bond of the conjugated chain since the orientation of bond *a* is determined by the presence of the strong hydrogen bond between the phenolic proton and the carbonyl oxygen atom and the orientation of the *b* bond is regulated by the high steric hindrance arising from its E-conformation. The significant NOE observed for the α-olefinic proton of the 2-pyridyl derivative when irradiating at the frequency of the phenolic 6-H proton points to a spatial proximity of these protons, i.e., confirming the Z-orientation of the *b* bond. The effects observed when irradiating at the pyridine ring proton frequency indicates that in the 2-pyridyl series of compounds the *d* bond has a Z-orientated substituent, whereas the 3- and 4- derivatives occur as a mixture of equal amounts of the corresponding Z- and E-isomers.

For a detailed interpretation of the PMR spectra of the heterocyclic analogs of the chalcones, their ability to interact with LSR is important since, in this case, considerable simplification occurs and proton signals are revealed which are hidden in complex multiplets. Hence, we studied the interaction of LSR with chalcones containing 2-, 3-, and 4-pyridyl substituents. It was found that 2-pyridyl and 2-quinolinyl derivatives are virtually unreactive towards LSR. This is evidently connected with the steric hindrance occurring towards complex formation with LSR at both alternative coordination centers in these compounds. On the other hand, the 3- and 4- pyridine isomer derivatives interact very well with LSR. The pyridine ring proton signals in the PMR spectra in the presence of $Eu(FOD)_3$ can show shifts of tens of ppm (see Table 2). Use of the LSR allowed us to carry out the NOE experiment described above on compound IIc since, without LSR, the signals form a complex multiplet in which selective saturation is impossible.

In the quinoline derivatives IVa, b, the form of the multiplet signals for the aromatic protons does not allow selective saturation of the signals and, hence, elucidation of their conformation.

Hence, the combined use of the LSR method and homonuclear NOE can lead to the assignment of the olefinic proton signals and to demonstrating quite reliably the predominant conformation of the conjugated chain in the pyridine analogs of chalcone.

## EXPERIMENTAL

PMR spectra were measured on a Bruker WP-100SY spectrometer at 100.13 MHz. NOE experiments were performed using a standard method with saturation by selective square wave pulses and variation of the irradiating frequency corresponding to the profile of the saturated signal. Monitoring of the course of the synthesis of compounds I-IV and of their purity was carried out by TLC using Silufol UV-254 plates in the system benzene–ethanol, 9:1.

**1-Aryl-3-hetaryl-2,3-propenones (I-IV).** NaOH solution (50%, 2.3 ml) was added to a heated solution of 2-hydroxyacetophenone (5 mmole) and the corresponding formylpyridine or 2-formylquinoline (5 mmole) in the minimum amount of ethanol and the mixture was stirred on a magnetic stirrer at room temperature for 5-9 h. It was then suspended in water and neutralized to pH 7 with acetic acid solution (20%), and the product was filtered and crystallized from the appropriate solvent (see Table 1). The products were Ia, b, IIa-c, IIIa, b, and IVa, b

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