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The control over the new obtaining procedeum of indomethacin[1]

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Abstract

The synthesis of the indomethacin (1H-indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl) was achieved through a new method, which reduces some stages from the previous methods. Both the structure of the finished product and the structures of the intermediaries were investigated by chromatographic methods (TLC, chromatography on column, GC-MSD) and spectroscopic methods (UV, IR, 1H-NMR, ^{13}C-NMR). The chromatographic and spectroscopic studies proved that these had a special analytical value and they serve to control synthesis and to identify the compounds in all the stages of the process. © 1998 Elsevier Science B.V.

Keywords: Synthesis of the indomethacin; Analytical control; Chromatographic methods; Spectroscopic methods

1. Introduction

The indomethacin (1H-indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl) is a substance with a strong anti-inflammatory action, and also presents weaker antipyretic and analgesic properties [1]. Several synthetic methods for indomethacin are presented in previous articles [2,3].

In this paper the synthesis of the indomethacin is achieved by a new method which reduces some stages from the previous methods [4].

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[1] Presented at the 10th Int. Symp. on Advances and Applications of Chromatography in Industry, July 1996, Bratislava, Slovak Republic.

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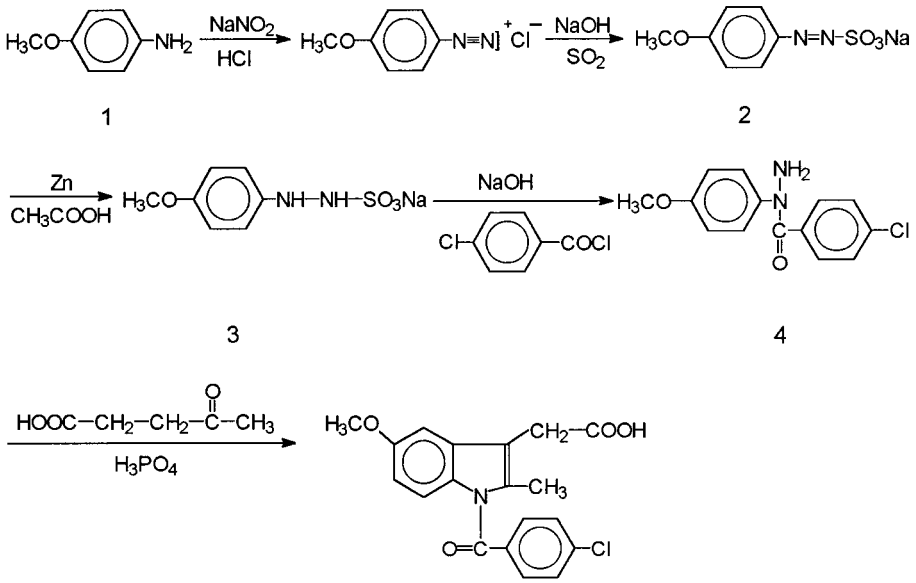


Both the structure of the final product and the structures of the intermediates have been investigated by chromatographic methods (TLC, chromatography on column, GC-MSD) and spectroscopic methods (UV, IR, ^{1}H-NMR, ^{13}C-NMR).

Using these analytical methods we tried to find out if the compound 4 and 5 was obtained in this way.

2. Experimental

2.1. Materials

Benzene, methyl-ethyl-ketone, dimethyl-formamide and methanol are commercial samples ('Reactivul' Bucharest). All solvents were of analytical grade.

2.2. Chromatography

The compounds 1 – -5: ((4-anisidine (1); 4-methoxy - benzene - Na - diazosulphonate (2); 4 - methoxy - phenil - Na - hidrazosulphonate (3); 1-(4-chlorobenzoyl)-1-(4-methoxy-phenil)-2-hydrazine (4); indomethacin (5)) were separated by TLC. We used chromatographic plates (20 × 20 cm) with silicagel F_{254} (Merck, 0.25 mm). We used the benzene/methyl-ethyl-ketone mixture (6:4, v/v) as mobile phase and the detection was made in UV light (254 nm). The solutions of the compounds were 0.01% in dimethylformamide. The plates were analysed using photodensitometry on a Shimadzu CS 9000 apparatus.

The compounds were purified by chromatography on column. We used a glass column (25 cm × 2 cm) filled with silicagel for the adsorption (Laboratory BHD Reagent 150–170 μm). The mobile phase was the same as in TLC.

For the GC-MSD analysis we used a HP5890 gas-chromatography coupled with 5972 MSD of Hewlett-Packard type mass selective detector. We used HP5MS (methyl-silicon 5%) as a stationary phase, He as a carrier gas and a temperature gradient. The processing of the data was made with HP 486/33N Soft M.S. Chem. Station computer.

2.3. Spectroscopy

The UV spectra were recorded on 10^{-5} M methanolic solutions using a Specord-UV-VIS-spectrophotometer.

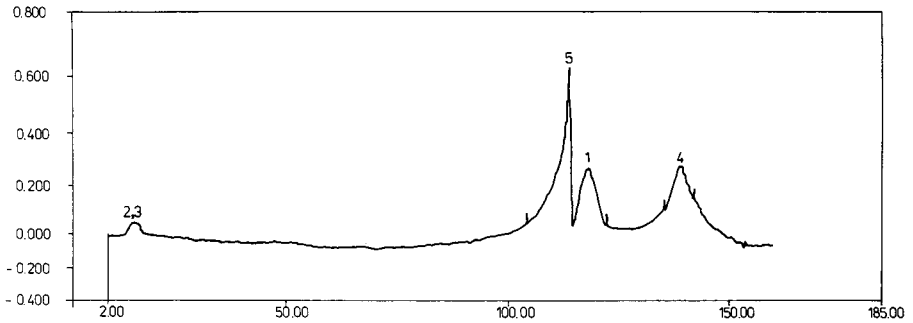


Fig. 1. The chromatogram of the compounds 1–5 mixture.

The IR spectra were made on KBr and they were recorded on Specord IRA-75-Zeiss apparatus.

The ^{1}H-NMR and ^{13}C-NMR spectra (deuterated chloroform, $CDCl_3$, as solvent and tetramethylsilan as standard) were recorded on a Varian-Gemini-300 spectrophotometer.

3. Results and discussions

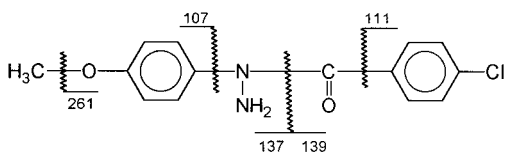
Because the acylation reaction of the compound 3 is a new stage in the synthesis process the chromatographic and spectroscopic analysis of the compound 4 was achieved. We also investigated the compound 5 because we want to be sure that this compound is obtained.

3.1. Chromatographic methods

The identification of the compounds by TLC could be achieved on the basis of the R_f values. From Fig. 1 it is noticed that a very good separation was obtained for the compounds 1,4 and 5. The separation of the compounds 2 and 3 did not succeed, but we are not interested to separate these compounds because they appeared in all previous synthesis of the indomethacin. The chromatography on column has been used for the purification of the compounds 4 and 5.

Using GC-MSD the analysis of the compound 4 which was purified by chromatography on column was achieved. From Fig. 2, it is noticed that this compound presented a component with $t_r = 25.62$ min.

Analysing the mass spectrum of this component a peak at $m/z = 276$ and a peak at $m/z = 278$ with a 3-times smaller intensity are noticed. This mass spectrum is typical of monochlorurated compounds and in this case the masses correspond to the molecular formula $C_{14}H_{13}ClN_2O_2$. The principal fragmentation of the molecule are shown in Fig. 2.



3.2. Spectroscopic methods

The main UV absorption bands of the compounds 1–5 are presented in Table 1 and in Fig. 3. The assignment of the bands is made according to [5,6].

Band 1 which is present in compound 1–5 spectra is assigned to $\pi-\pi^*$ transition from the organic conjugated systems over which the $\pi-\pi^*$ transition from the carbonyl group is superposed. Band 2 is specific only to $\pi-\pi$ transition from the aromatic system, it is present in all studied compounds. Band 3 corresponds to $n-\pi^*$ transition from the carbonyl group and it appears in the case of compounds 4 and 5. Band 4 is due to the presence of the cromophor groups and the conjugation of these with the aromatic ring. The disappearance of the bands from 338 nm due to the –N=N– group in compound 2 as a result of the

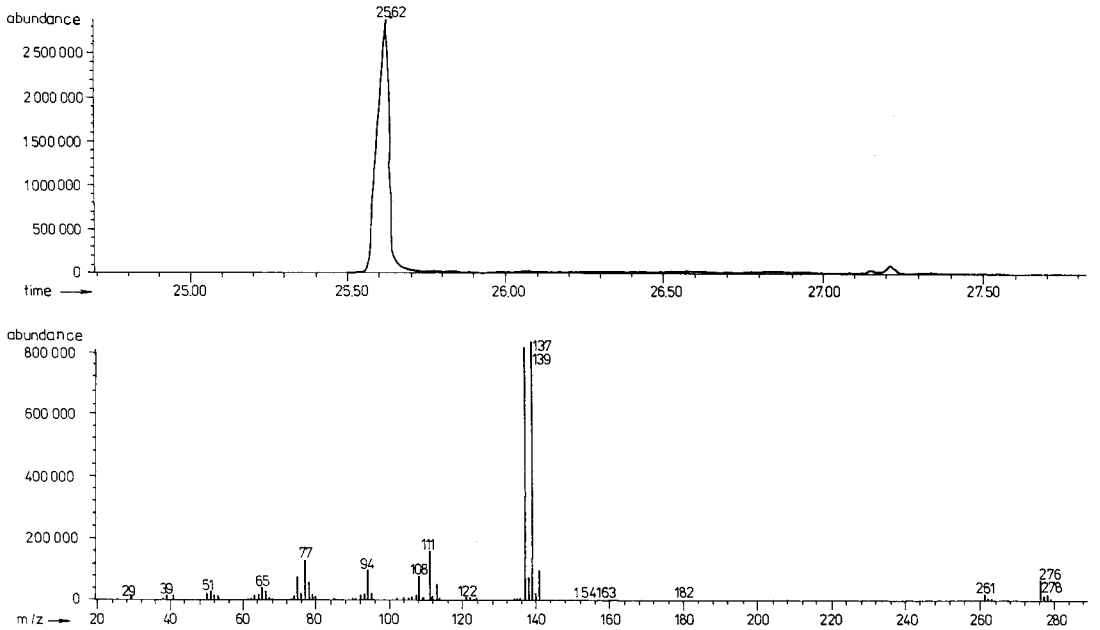


Fig. 2. The GC-MSD spectrum of the purified compound 4.

reducing reaction of this at compound 3 can be used to verify the end of the reducing reaction.

Because the last two reactions are new stages of the technological process, the IR and NMR spectra were recorded only for the compounds 4 and 5.

The results of the IR spectra are presented in Table 2.

Table 1
The absorption bands from the UV spectra

Compounds	The absorptionbands, λ (nm)			
	1	2	3	4
1	207–210	235–242	—	300–308
	208.5	238	—	304
2	206–210	234–240	—	333–344
	208	237	—	338
3	210–218	228–238	—	—
	214	233	—	—
4	208–216	227–235	260–280	—
	212	231	270	—
5	210–217	220–240	255–275	315–335
	213.5	230	265	325

The assignment of the characteristic bands was made according to [7]. Information about the structure of the organic compounds is obtained

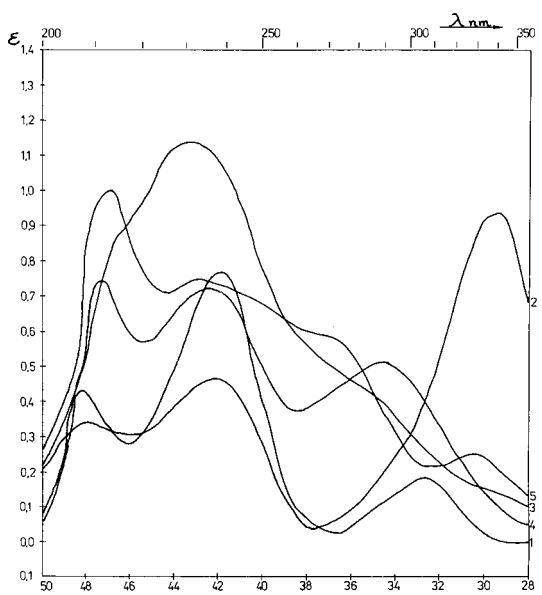


Fig. 3. The UV spectrum of the compounds 1–5.

Table 2
The values and the assignment of absorption bands from the IR spectra

The absorption bands, λ (cm^{-1})		The bands assigning
Compound 4	Compound 5	
830	830	ν (C–Cl)
1170	1170	ν (symmetric O–CH_3)
1200	1195	ν (asymmetric O–CH_3)
—	1240	ν (symmetric carboxylic C–O)
—	1250[a]	ν (asymmetric carboxylic C–O)
1420[a]	—	δ (N–H)
1460	1460	δ (O–CH_3)
1630[a]	—	δ (N–H)
1660[a]	1690[a]	ν (carbonylic C=O)
—	1718[a]	ν (carboxylic C=O)
—	2870	ν (symmetric CH_3)
—	2940	ν (asymmetric CH_3)
—	3000	ν (symmetric –CH_2–)
—	3100	ν (asymmetric –CH_2–)
3215	—	ν (symmetric N–H)
3360[a]	—	ν (asymmetric N–H)

[a]The most important absorption bands.

from the position, the intensity and the form of the absorption bands. The studied compounds present characteristic absorption in the valence vibrations region $\nu_{C\text{-}H}$ (3100–3000 cm^{-1}), in the deformation vibrations region δ_{C-H} (900–650 cm^{-1}) and in the valence vibrations region $\nu_{C\text{-}C}$ (1650–1450 cm^{-1}).

The ^{1}H-NMR signals ($CDCl_3$; δ) for the compound 4: 3.69 s (OCH_3); 4.83 s (Ar–NH_2) and 6.68–7.29 m (aromatic protons) and for the compound 5: 2.39 s (–CH_3); 3.70 s (–CH_2–); 3.83 s (OCH_3) and 6.66–7.68 m (aromatic protons), with the appropriate relative intensities [8].

The uncoupled ^{13}C-NMR spectra ($CDCl_3$; δ) for the compound 4 present ten signals: one for the C from OCH_3 at 55.47, eight on the aromatic field (4 CH: 114.6; 127.66; 128.40; 130.27 and 4 quaternary carbon: 129.0; 133.25; 136; 136.5) and one for the C from C=O at 158.6 and for the compound 5 present 17 signals: three on saturated field: C from –CH_3 at 13.37; C from –CH_2– at 31.2 and C from –OCH_3 at 55.77; 12 on aromatic field (5 CH: 102.5; 112.5; 115.83; 129.27; 131.4 and seven quaternary carbon: 129.0; 130.8; 131.1; 134.2; 136.0; 136.5; 139.6) one for the C from C=O at 156.2 and one for the C from COOH at 176.8 [8].

The experimental data suggest that after the recrystallization and the chromatographic separations we obtained pure compounds. The results are reproducible.

4. Conclusions

The chromatographic and spectroscopic studies proved that these had a special analytical value and they serve to control synthesis and to identify the compounds in all the stages of the process.

Moreover, these studies concerning compounds 4 and 5 which are obtained in this way for the first time, confirmed the proposed structures for these compounds.

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