REDUCTION OF 1,2,3,4-TETRAHYDRO- TO 1,2,3, 4,4a,9b-HEXAHYDROBENZOFURO[3,2-c]PYRIDINES

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UDC 542.942.7:547.728.2'83

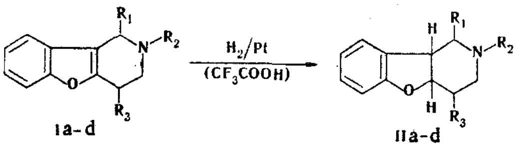
1,2,3,4,4a,9b-Hexahydrobenzofuro[3,2-c]pyridines (HFP) have not been examined in contrast to their nitrogen analogs, 1,2,3,4,4a,9b-hexahydro-γ-carbolines, which include substances with marked pharmacological activity (e.g., 3,6-dimethyl-1,2,3,4,4a,9b-γ-carboline is a psychotropic [1] and antialcoholism [2] agent). The combination of the 2,3-dihydrobenzofuran and piperidine fragments in HFP's could reveal some structural analogy with morphine and with analgesics of the aminoalkyl-2,3-dihydrobenzofuran series [3, 4]. Equally, there are certain structural differences between HFP's and known narcotic analgesics, which suggests that new features could appear in the pharmacological spectrum of HFP's, such as antimorphine activity. In this context the synthesis of HFP's as a new system and the examination of various properties is of some relevance.

For the preparation of HFP's we examined the reduction of 1,2,3,4-tetrahydrobenzofuran[3,2-c]pyridines (Ia)-(Id) [5, 6], which, we might mention, are themselves pharmacologically active compounds [7]. An attempt to reduce compounds (Ia)-(Id) with zinc amalgam in hydrochloric acid under the conditions widely used for the reduction of indoles and indolenines was unsuccessful. Nor did the efficient method using alkali-metal borohydrides for the reduction of indoles [8] and 1,2,3,4-tetrahydro-γ-carbolines [9] give any better results. In both cases we recovered the starting compounds (up to 90%) and detected slight resinification.

The catalytic hydrogenation of benzofurans often proceeds nonspecifically and its results depend on the nature of the substituents in the benzofuran compound, the type of catalyst, and the reaction conditions (see, e.g., the brief review [10]). The simplest representatives of the indole and benzofuran systems are known to be readily converted to indolines [11] and 2,3-dihydrobenzofurans [10] by ionic hydrogenation. Consequently, we turned to this method and tried several systems for the ionic hydrogenation of compounds (Ia)-(Id).

We found the usual system for ionic hydrogenation, $(C_2H_5)_3SiH-CF_3COOH$, to be inactive in the series of compounds (Ia)-(Id). Nor did the more efficient $(C_2H_5)_3SiH-CF_3COOH-(C_2H_5)_2O \cdot BF_3$ system [12] bring success. The increased stability toward ionic hydrogenation of compounds of the type of (Ia)-(Id) is obviously due to the electron-accepting effect of the protonated amino group. This has also been detected in the ionic hydrogenation of 2-(ω-diethylaminoalkyl)thiophenes by the $CF_3COOH-HSiEt_3$ system, where hydrogenation of the thiophene ring takes place only when the electron-accepting group is separated from the ring by at least three methylene units [13]. The ionic hydrogenation systems $CF_3COOH-L_2PtX_2-H_2$, $CF_3COOH-RuX_3-H_2$, and $CF_3COOH-Pt/C-H_2$ [14, 15] were also inactive at 40°C under a hydrogen pressure of 1-75 atm. However, use of the $CF_3COOH-PtO_2-H_2$ system at room temperature and normal pressure resulted in the hydrogenation of compounds (Ia)-(Id). The reaction did not end at the stage of reduction of the double bond; hydrogenation of the benzene ring took place simultaneously. By selecting the optimum reaction time we were able to prepare compounds (IIa)-(IId) in satisfactory yield. We monitored the course of hydrogenation by GLC.

Thus we have developed a simple method for the reduction of the double bond in compounds (Ia)-(Id) with the $CF_3COOH-PtO_2-H_2$ system, although in this case the ionic mechanism cannot be considered substantiated.



Ia IIa $R_1=R_2=R_3=H$; Ib, IIb $R_1=R_3=H$, $R_2=CH_3$; Ic, IIc $R_1=R_2=H$, $R_3=CH_3$;
Id, IId $R_1=R_2=R_3=CH_3$

Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow 125315. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1178-1180, September, 1979. Original article submitted November 23, 1978.

0009-3122/79/1509-0957$07.50

TABLE 1. Hydrochlorides of 1,2,3,4,4a, 9b-Hexahydrobenzofuro[3, 2-c]pyridines (IIa)-(IId)

Compound	Amt. of hydrogen absorbed, mole	mp, °C	Found, %				Formula	Calculated, %				Yield, %
			C	H	N	Cl		C	H	N	Cl	
IIa · HCl[a]	0,02	184—186	62,2	6,6	6,9	16,9	$C_{11}H_{13}NO \cdot HCl$	62,4	6,7	6,6	16,8	63
IIb · HCl[b]	0,023	242,5—243	64,2	7,2	6,4	15,7	$C_{12}H_{15}NO \cdot HCl$	63,9	7,1	6,2	15,7	68
IIc · HCl[c]	0,027	260—263	61,3	7,5	6,3	15,0	$C_{12}H_{15}NO \cdot HCl \cdot 0,5\,H_2O$	61,4	7,3	6,0	15,1	30
IId · HCl[d]	0,015	247—247,5	66,2	8,2	5,6	13,8	$C_{14}H_{19}NO \cdot HCl$	66,2	8,0	5,5	14,0	60

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[a] Analysis by GLC revealed that crude (IIa) hydrochloride was contaminated by the starting compound. It was treated with the minimum amount of water, precipitating compound (Ia) (0.15 g), which was separated. The mother liquor was made alkaline with potassium hydroxide solution and extracted with ether; the ethereal extract was dried over magnesium sulfate and (IIa) was precipitated with alcoholic hydrogen chloride. [b] Hydrochloride of (IIb) was precipitated from ethereal solution with alcoholic hydrogen chloride at pH 3 and recrystallized from isopropyl alcohol. [c] Hydrochloride of (IIc) was precipitated from ethereal solution by addition of alcoholic hydrogen chloride until the appearance of a precipitate, filtered off after 24 h (20°C), and recrystallized from isopropyl alcohol. [d] Hydrochloride (IId) was derived by addition to the ehthereal solution of alcoholic hydrogen chloride at pH 3 followed by fractional crystallization from isopropyl alcohol.

We verified the structures of compounds (IIa)-(IId) by elemental analysis, PMR spectroscopy, and molecular weight determination [mass spectrometrically for (IIa) and (IId) as examples]. Thus in the PMR spectra (in CCl_4) bases (IIa) and (IIb) have the 4a-H proton as a multiplet at 4.5 and 4.7 ppm respectively; in compound (IId) it appears as a triplet at 4.1 ppm with similar values of J_{44a} and J_{4a9b} (8 Hz). In CD_3OD solution the hydrochlorides of these compounds show a downfield shift of the 4a-H proton to 5 ppm. Compounds (IIa)-(IId) were isolated in the pure form and were stereochemically homogeneous (probably with the cis ring junction), which we established by GLC and PMR spectroscopy, which revealed that the single set of proton signals for each group (for example the 4a-H, NCH_3, or $C-CH_3$) persisted when the solvent was varied. The trans-configuration relative to the $C_{(1)}$ and $C_{(4)}$ substituents has previously been established for the starting compound (Id) [16].

We screened compounds (IIa)-(IId) as hydrochlorides for analgesic activity. Tests were carried out on rats; all compounds were administered intravenously. A painful reaction was induced by electrical stimulation of the skin of the tail. Hydrochloride of (Id) in a dose of 25 mg/kg doubled the pain sensitivity threshold; the duration of the analgesic effect was 40-60 min. Hydrochloride of (IIc) in a dose of 25 mg/kg caused a clear reduction in the pain sensitivity threshold and shortened morphine-induced analgesia but was considerably inferior to nalorphine in antimorphine activity.

EXPERIMENTAL

Molecular weights were measured with an MAT-112 spectrometer, ionizing energy 70 eV, ion source temperature 200°C; GLC analysis was carried out on a 1 KhM-8D chromatograph, SE-30 column (l = 25 m, d = 2 mm), carrier gas nitrogen, temperature 150-180°C. The PMR spectra were recorded on a Varian T-60.

Hydrochlorides of 1,2,3,4,4a,9b-Hexahydrobenzofuro[3,2-c]pyridines (IIa)-(IId). Hydrochloride of (I) (0.014 mole) was hydrogenated over a Pt catalyst (from 0.3 g PtO_2) in trifluoroacetic acid (25 ml). The catalyst was removed by filtration and the solvent was distilled off. The residue was dissolved in water. The solution was made alkaline with ~20% potassium hydroxide solution or ~10% ammonia solution to pH 10 and the base was extracted with ether. The ethereal solution was dried over magnesium sulfate and hydrochlorides (IIa)-(IId) were precipitated with hydrogen chloride. Their properties are summarized in Table 1.

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SYNTHESIS OF FUNCTIONALLY SUBSTITUTED COUMARINS*

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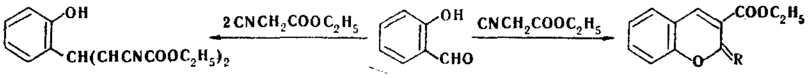
UDC 547.814.07:542.953

We have found that the interaction of salicylaldehyde with ethyl cyanoacetate in the presence of sodium ethoxide or potassium carbonate at room temperature for 40–48 h forms a mixture of 3-ethoxycarbonylcoumarin (I) and 2-imino-3-ethoxycarbonylcoumarin (II) in 5 and 35% yield (with sodium ethoxide) or 4 and 32% yield (with potassium carbonate), respectively.



III

I, II

I R=O; II R=NH

Increase in the amount of ethyl cyanoacetate caused the yield of (II) to rise. When a twofold excess of ethyl cyanoacetate was used, we obtained only (II) in almost quantitative yield (~93%).

Treatment of the reaction mixture with dilute hydrochloric acid (1:1) (25°C, 18 h) gave a single reaction product, 3-ethoxycarbonylcoumarin in 80% yield.

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*Communication 42; for Communication 41 see [1].

Erevan State University, Erevan 375049. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1181–1182, September, 1979. Original article submitted July 12, 1978; revision submitted January 11, 1979.

0009-3122/79/1509-0959$07.50