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SYNTHETIC AND MODIFIED ISOFLAVONOIDS XIV. MANNICH BASES AND THEIR SALTS IN A SERIES OF SYNTHETIC ISOFLAVONE ANALOGS

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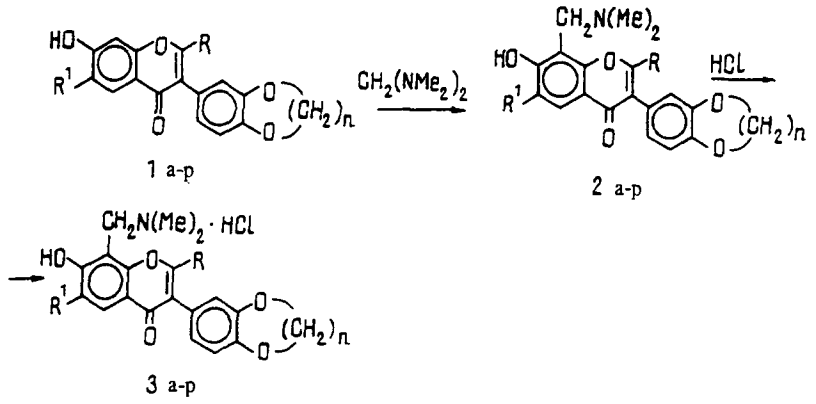
Mannich bases and their hydrochlorides have been obtained from 1,3-benzodioxolane, 1,4-benzodioxane, and 1,5-benzodioxepane analogs of pseudobaptigenin. The PMR spectra of the compounds obtained are given and are discussed.

It is known [2, 3] that Mannich bases derived from flavones and isoflavones regulate the activity of the central nervous system and the respiratory pathways. These compounds exhibit a high anticonvulsive, antiallergic, and analgesic action [4-6]. Furthermore, the Mannich bases obtained from the natural flavolignan silybin possess hepatoprotective and hypocholesteremic activity [7]. In view of this, it was of interest to synthesize compounds of this type within the series of synthetic analogs of natural isoflavones.

As a result of the interaction of 7-hydroxyisoflavones substituted in position 2 or 6 [8-11] with bisdimethylaminomethane in dioxane for 5-30 min, the corresponding Mannich bases (2a-p*) were formed (Table 1).



a: R=H, R^1=Et, n=1; b: R=H, R^1=Pr, n=1; c: R=Me, R^1=Et, n=1; d: R=Me, R^1=Pr, n=1; e: R=CF_3, R^1=Et, n=1; g: R=CF_3, R^1=Pr, n=1; h: R=R^1=H, n=2; i: R=H, R^1=Et, n=2; j: R=H, R^1=Pr, n=2; k: R=Me, R^1=H, n=2, l: R=Me, R^1=Et, n=2; m: R=Me, R^1=Pr, n=2; n: R=CF_3, R^1=H, n=2; o: R=CF_3, R^1=Et, n=2; p: R=CF_3, R^1=Pr, n=2

The PMR spectra (Table 2) of the compounds obtained showed that the dimethylaminomethyl group had entered position 8 of the chromone nucleus. In the PMR spectra of compound (2h), for example, the aromatic protons H-5 and H-6 gave signals in the form of doublets with a spin-spin coupling constant of 8 Hz. The protons of the methylene group and of the —OCH_2CH_2— grouping appeared in the form of singlets in the regions of 4.0 and 4.29 ppm, respectively. A feature of

*No compound (1f, 2f, or 3f) is mentioned in this paper — Translator.

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TABLE 1. Characteristics of Compounds (2) and (3)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
2a	87	124—125	$C_{21}H_{21}NO_5$	iso-PrOH
2b	80	141—142	$C_{22}H_{23}NO_5$	iso-PrOH
2c	88	143—144	$C_{22}H_{23}NO_5$	iso-PrOH
2d	84	105—106	$C_{23}H_{25}NO_5$	iso-PrOH/H_2O
2e	95	183—184	$C_{22}H_{20}F_3NO_5$	iso-PrOH
2g	97	159—160	$C_{23}H_{22}F_3NO_5$	iso-PrOH
2h	98	183—184	$C_{20}H_{19}NO_5$	EtOH
2i	92	147—148	$C_{22}H_{23}NO_5$	EtOH
2j	92	122—123	$C_{23}H_{25}NO_5$	iso-PrOH
2k	96	215—216	$C_{21}H_{21}NO_5$	EtOH
2l	78	181—182	$C_{23}H_{25}NO_5$	iso-PrOH
2m	91	179—180	$C_{24}H_{27}NO_5$	iso-PrOH
2n	94	206—207	$C_{21}H_{18}F_3NO_5$	iso-PrOH
2o	93	182—183	$C_{23}H_{22}F_3NO_5$	iso-PrOH
2p	93	173—174	$C_{24}H_{24}F_3NO_5$	iso-PrOH
3a	98	213—214	$C_{21}H_{22}ClNO_5$	
3b	90	200—201	$C_{22}H_{24}ClNO_5$	
3c	84	214—215	$C_{22}H_{24}ClNO_5$	
3d	64	201—202	$C_{23}H_{26}ClNO_5$	
3e	94	202—203	$C_{22}H_{21}F_3ClNO_5$	
3g	85	206—207	$C_{23}H_{23}F_3ClNO_5$	
3h	92	215—216	$C_{20}H_{20}ClNO_5$	
3i	86	220—221	$C_{22}H_{24}ClNO_5$	
3j	90	218—219	$C_{23}H_{26}ClNO_5$	
3k	99	196—197	$C_{21}H_{22}ClNO_5$	
3l	94	211—212	$C_{23}H_{26}ClNO_5$	
3m	91	224—225	$C_{24}H_{28}ClNO_5$	
3n	99	254—255	$C_{21}H_{19}F_3ClNO_5$	
3o	96	229—230	$C_{23}H_{23}F_3ClNO_5$	
3p	97	224—225	$C_{24}H_{25}F_3ClNO_5$	

the PMR spectra of the Mannich bases is that the protons of the hydroxy groups appear in the 10.4-12.4 ppm region. This shows their participation in the formation of intramolecular bonds with the nitrogen atoms of the dimethylaminomethyl groups.

In order to make the Mannich bases soluble in water, we converted them into their hydrochlorides (3a-p). The physical constants and analyses of these compounds are given in Table 1.

Thus, Mannich bases in the isoflavone series are readily accessible compounds. They are all colorless crystalline substances readily soluble in the usual organic solvents, while their hydrochlorides are soluble in water. A study of the biological activity of the hydrochlorides of the Mannich bases has revealed substances with a high anabolic activity among them.

TABLE 2. Chemical Shifts in the PMR Spectra (δ, ppm, J, Hz) of the Mannich Bases of 1,3-Benzodioxolane and 1,4-Benzodioxane Isoflavone Analogs (in $CDCl_3$)

Compound	Chromone protons					Protons of the hetero residue	
	H-2 or Me-2, s	H-5, s	R^1-6	OH-7, s	CH_2NMe_2-8, s	H-4(H-5), H-6(H-7), H-7(H-8), m	$-O(CH_2)_nO-$ n=1, 2, s
2a	7.80	7.95	2.74 q; 1.26 t	11.85	3.94; 2.42	6.94	5.93
2b	7.78	7.93	2.68 t; 1.7 m; 0.99 t	11.47	3.96; 2.4	6.93	5.94
2c	2.41	7.94	2.70 q; 1.23 t	11.59	3.95; 2.27	6.77	5.94
2d	2.26	7.90	2.68 t; 1.68 m; 0.95 t	10.53	3.96; 2.41	6.76	5.95
2e	–	7.91	2.73 q; 1.25 t	12.36	4.0; 2.45	6.72	5.97
2g	–	7.88	2.68 t; 1.69 m; 0.98 t	12.21	3.98; 2.46	6.73	5.96
2h	7.90	8.16 d, (8.0)	6.90 d, (8.0)	11.79	4.0; 2.44	7.07	4.29
2i	7.82	7.98	2.76 q; 1.30 t	12.08	3.98; 2.42	7.04	4.25
2j	7.91	8.05	2.76 t; 1.74 m; 1.01 t	11.57	4.01; 2.43	7.06	4.29
2k	2.34	8.08 d	6.88 d, (8.0)	10.40	4.03; 2.46	6.86	4.30
2l	2.28	7.88	2.69 q; 1.25 t	10.74	3.96; 2.42	6.80	4.28
2m	2.27	7.90	2.69 t; 1.68 m; 0.96 t	11.21	3.99; 2.40	6.82	4.26
2n	–	8.04 d	6.93 d, (8.0)	12.03	4.04; 2.43	6.84	4.30
2o	–	7.94	2.76 q; 1.27 t	9.74	4.06; 2.50	6.85	4.34
2p	–	7.87	2.68 t; 1.68 m; 0.96 t	11.03	4.00; 1.66	6.78	4.28

EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in chloroform—methanol (9:1). PMR spectra were measured on a Bruker WP-100 SU instrument in $CDCl_3$ relative to TMS (internal standard). The analyses of all the compounds corresponded to the calculated values.

3-Hetaryl-7-hydroxy-8-dimethylaminomethylchromones (2a-p). A mixture of 15 mmole of a 7-hydroxyisoflavone (1a-p) in 50 ml of absolute dioxane and 7.5 ml of bisdimethylaminomethane was boiled until the initial substance had completely disappeared (5-30 min). The solvent was distilled off in water-pump vacuum, and the residue was crystallizd from a suitable solvent.

Hydrochlorides of 3-Hetaryl-7-hydroxy-8-dimethylaminomethylchromones (3a-p). Dry hydrogen chloride was passed into a solution of 10 mmole of a 7-hydroxy-8-dimethylaminomethylisoflavone (2a-p) in dry chloroform. The precipitate that deposited was filtered off and was washed several times with dry chloroform.

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