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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF ACYL SUBSTITUTED BENZODIOXA HETEROCYCLES AND O-DIALKOXYBENZENES

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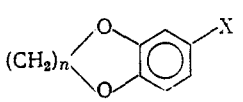
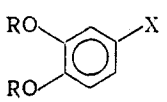
Among aroyl and cinnamoyl substituted 1,4-benzodioxanes and 1,5-benzodioxepanes, compounds having antiinflammatory activity are found [3, 4]. Therefore, with the purpose of studying the relationship between chemical structure and biological activity, and also of searching for new medicines, we have synthesized and investigated the hitherto unknown benzodioxa heterocycles (I-IV) and their acylic analogs, the o-dialkoxybenzenes (V, VI).



I—IV



V, VI

n = 3 (I), 4 (II), 5 (III), 6 (IV); R = Et (V), Pr (VI); X = H (Ia-VIa), COC_6H_4Br-o (Ib), COC_6H_4Br-p (Ic), COC_6H_4Cl-o (Id), COC_6H_4Cl-p (Ie), COC_6H_4F-o (If), COC_6H_4F-p (Ig), COC_6H_4OH-p (Ih), COC_6H_4OMe-p (Ii), $COC_6H_4NO_2$-p (Ij), $COC_6H_4NH_2 \cdot HCl$-p (Ik), $COC_6H_4(CH_2)_3CH_3$-p (Il), CO-α-naphthyl (Im), CO-β-naphthyl (In), CO-α-furyl (Io), CO-α-thienyl (Ip), COPh (IIq-VIq), COCH=CHPh (IIr-VIr).

Ketones Ib-g, i, j, and l-p, IIq-VIq, and IIr-VIr were synthesized by Friedel-Crafts acylation of benzodioxa heterocycles Ia-IVa with anhydrides in the presence of waterfree $AlCl_3$ or $SnCl_4$. Hydroxy derivative (Ih) was prepared by diazotization of aminoketone (Ik), which was prepared by reduction of nitroketone (Ij).

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In the IR spectra of ketones Ib-d, f, g, i, k, and l the valence vibration bands of the carbonyl group are found in the region 1640-1655 cm^{-1} and those of ketones Ie, j, and n are shifted to 1635 cm^{-1}. The same band of β-naphthyl derivative In is found at a lower frequency (1635 cm^{-1}) than that of the α-isomer Im (1675 cm^{-1}), and the absorption bands in the UV spectra are shifted more to the longer wave side in the α-isomer Im [λ_{max} (lg ε): 221(4.72), 283(4.05), 309(3.98) nm] than in the β-isomer In [λ_{max} (lg ε): 218(4.65), 255(4.39), 288(4.15) nm]. Thiophene derivative Ip is characterized by a lower frequency of the carbonyl vibration (1610 cm^{-1}) and a larger bathochromic shift of the UV absorption bands [λ_{max} (lg ε): 274(shoulder), 305(4.15) nm,] as compared with furan analog Io [1630 cm^{-1} and 235(4.13), 297(4.43) nm]. The carbonyl vibrations of benzoyl derivatives IIq-VIq are found at higher frequencies (1660-1675 cm^{-1}) than those of the corresponding cinnamoyl derivatives IIr-VIr (1645-1660 cm^{-1}), and the long-wave absorption bands in the UV spectra are shifted more to the long-wave side and are more intensive in the case of the cinnamoyl derivatives [λ_{max} 322-348 nm (lg ε about 4.4)] than in the case of benzoyl derivatives IIq-VIq [λ_{max} 280-318 nm (lg ε 3.9-4.0)]. The UV absorption bands are thereby shifted more to the long-wave side in the case of compounds Vq and VIq, and Vr and VIr, and in case of compounds IIq-IVq and IIr-IVr they are shifted to the short-wave side with increasing the number of methylene groups in their heterocyclic rings, which may be caused by a lower electron-donating capacity of the oxygen atoms relative to the aromatic ring due to rotation of the alkoxy substituent around C_{Ar}-O bond [2].

The structures of the novel compounds prepared were confirmed by data from the PMR spectra, in which the OCH_2 group manifests itself as two triplets (δ, 4.1-4.2 and 4.2-4.3 ppm) in case of ketones Ib-p and IIq, r, or two multiplets (δ, 3.9-4.2 and 4.2-4.5 ppm) in case of ketones IIIq, r, and IVq, r.

The starting benzodioxa heterocycles Ia-IVa are described in [7].

EXPERIMENTAL (CHEMICAL)

UV spectra were taken from ethanol solutions on a specord UV-VIS spectrometer (GDR), and IR spectra on a Specord 751R spectrometer in paraffin oil. PMR spectra were recorded on a Tesla BS-487C spectrometer (Czechoslovakia) in CCl_4 with TMS as internal standard.

Found and calculated values of elemental analyses were in agreement.

7-Acyl-1,5-benzodioxepanes (Ib-g, i, j, l-p), 8-Acyl-1,6-benzodioxocanes (IIq, r), 9-Acyl-1,7-benzodioxonanes (IIIq, r), 10-Acyl-1,8-benzodioxecanes (IVq, r), 4-Acyl-1,2-diethoxybenzines (Vq, r), and 4-Acyl-1,2-dipropoxybenzenes) (VIq, r). At 0-5°C, 55 mmole of waterfree $AlCl_3$ (for the synthesis of ketones Io, p: waterfree $SnCl_4$) is added to a mixture of 70 ml of dry CH_2Cl_2, 55 mmole of the appropriate acid chloride, and 50 mmole of compound Ia-VIa, the mixture is stirred at 20°C for 3 h, poured out on ice, and acidified with HCl. The organic layer is separated, extracted with water, dried, and the solvent is evaporated. In the following are listed: the compound, empirical formula, yield (%), mp (°C), crystallization solvent, bp (°C) /1 mm Hg: Ib, $C_{16}H_{13}BrO_3$, 57, –, –, 210-211; Ic, $C_{16}H_{13}BrO_3$, 82, 78-79.5, ethanol, –; Id, $C_{16}H_{13}ClO_3$, 82, –, –, 200-201; Ie, $C_{16}H_{13}ClO_3$, 90, 73-74, ethanol, –; If, $C_{16}H_{13}FO_3$, 86, 48-49, ethanol, –; Ig, $C_{16}H_{13}FO_3$, 92, 80-81, ethanol, –; Ii, $C_{17}H_{16}O_4$, 82, 61-63, ethanol, –; Ij, $C_{16}H_{13}NO_5$, 83, 168-168.5, ethanol–CH_2Cl_2, –: Il, $C_{20}H_{22}O_3$, 81, –, –, 210-211; Im, $C_{20}H_{16}O_3$, 48, 74-75, absolute ethanol, –; In, $C_{20}H_{16}O_3$, 56, 92-92.5, absolute ethanol, –; Io, $C_{14}H_{12}O_4$, 33, 65-65.5, ethanol, –; Ip, $C_{14}H_{12}O_3S$, 35, 78-78.5, ethanol, –; IIq, $C_{17}H_{16}O_3$, 83, –, –, 177-178; IIr, $C_{19}H_{18}O_3$, 55, 67-68.5, ethanol, –; IIIq, $C_{18}H_{18}O_3$, 52, –, –, 185-186, IIIr, $C_{20}H_{20}O_3$, 80, 117-118, ethanol, –; IVq, $C_{19}H_{20}O_3$, 44, –, –, 191-193; IVr, $C_{21}H_{22}O_3$, 66, 75-76.5, ethanol, –; Vq, $C_{17}H_{18}O_3$, 87, 115-115.5, ethanol, –; Vr, $C_{19}H_{20}O_3$, 75, 80-81, ethanol, –; VIq, $C_{19}H_{22}O_3$, 91, 85-86, ethanol, –; VIr, $C_{21}H_{24}O_3$, 65, 54-55, absolute ethanol, –.

Hydrochloride of 7-(p-Aminobenzoyl)-1,5-benzodioxepane (Ik). One tenth ml (1 mmole) of concentrated HCl is added to a refluxing mixture of 150 ml of 80% ethanol, 8 g (29 mmole) of nitro derivative Ij, 9 g (161 mmole) of iron powder, and 0.5 g (7.5 mmole) of copper powder. The mixture is refluxed with stirring for 6 h, filtered, the filtrate is cooled, acidified with HCl, and concentrated. The residue is made alkaline with KOH, extracted with benzene, the extract is concentrated, the residue is dissolved in ethanol, acidified with HCl, the ethanol is evaporated under vacuum and the residue is crystallized from an ethanol–acetone mixture. Yield 6.7 g (75%) of Ik, $C_{16}H_{15}NO_3HCl$, mp 150-152.5°C.

7-(p-Hydroxybenzoyl)-1,5-benzodioxepane (Ih). A solution of 1 g (15 mmole) of $NaNO_2$ in 30 ml of water is added at 0-5°C to a solution of 3.5 ml (65 mmole) of concentrated H_2SO_4 and 3.5 g (13 mmole) of the free amine of Ik in 250 ml of water. The mixture is added over 15 min to 500 ml of boiling water, boiling is continued for 15 min, the mixture is cooled, extracted with CH_2Cl_2, and the extract is concentrated. The residue is chromatographed over Al_2O_3 with ether–hexane 3:1 as the eluent. The solvent is evaporated and the residue is crystallized from a benzene–cyclohexane mixture to yield 1.4 g (40%) of Ih, $C_{16}H_{14}O_3$, mp 137-139°C.

EXPERIMENTAL (PHARMACOLOGICAL)

The acute toxicity in white mice was determined by the Litchfield–Wilcoxon method as modified by Roth [1]. The antiinflammatory activity was studied by means of the models of experimental carrageenan [6] and bentonite [5] edemas of the foot of white rats. All the compounds were administered perorally as suspensions in a 1% carboxymethylcellulose solution to which Tween-80 had been added. We used mongrel mice weighing 18-25 g and rats of both sexes weighing 150-230 g.

It has been shown that acyl substituted 1,5-benzodioxepanes Ic, d, h, i, k, n, and o-dialkoxybenzenes Vr and VIq have high antiinflammatory activity and low toxicity and because of the advantageous combination of these properties surpass a series of preparations that find use in medicinal practice [4]. Below we list the compounds and the mean arithmetical values of the percentage decrease of the edemas induced by carrageenan and bentonite measured at 1, 2, 3, and 5 h after administering the compounds under investigation at a dose of 50 mg/kg: Ic, 20.6, 41.7; Id, 36.8, 18.3; Ih, 15.8, 59.1; Ii, 21.0, 41.0; Ik, 38.7, 20.5; In, 26.6, 29.8; Vr, 35.1, 40.3; VIq, 25.3, 26.0. The LD_{50} (in mg/kg) are 1500-1600 for compounds Ik, n, 2100-2900 for compounds Ic, d, i, Vr, and VIq, and > 3000 for compound Ih. Halogenobenzoyl substituted 1,5-benzodioxepanes Ic, e-h do not much differ with respect to antiinflammatory activity from their 1,4-benzodioxane analogs [3], but β-naphthoyl-1,5-benzodioxepane In is more active than the α-naphthoyl, α-furoyl, and α-thenoyl analogs (Im, o, p). Cinnamoyl substituted o-diethoxybenzene Vr is the most active compound of the cinnamoyl derivatives. That chalcone Vr is close to 7-cinnamoyl-1,5-benzodioxepane with respect to antiinflammatory activity and acute toxicity [4].

Our investigations point to possibilities in the search for new antiinflammatory agents among acyl substituted 1,5-benzodioxepanes and o-dialkoxybenzenes.

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