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DIOXANE ANALOGS OF FLAVYLIUM SALTS

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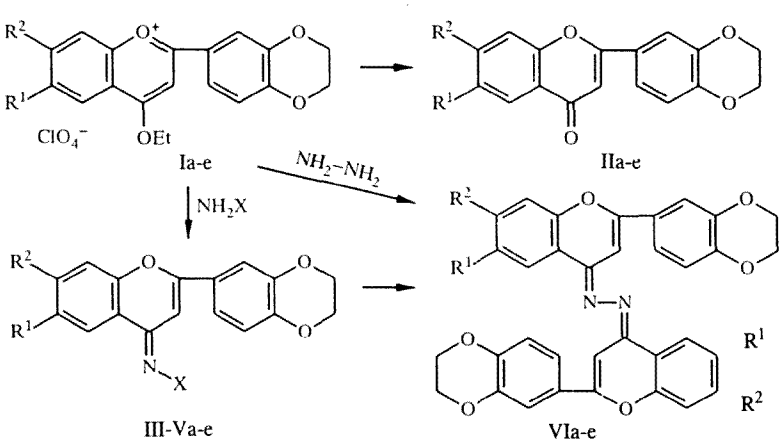
The synthesis of benzodioxane derivatives of 1-benzopyrilium salts is reported and their reaction with nucleophiles is investigated.

Despite their broad spectrum of biological activity in living organisms and reasonable abundance in the form of anthocyanins in many plant forms, flavylium (2-phenyl-1-benzopyrilium) salts have been insufficiently investigated. In fact, 1-benzopyrilium salts, in contrast to their 2-benzo analogs, are significantly different in properties to monocyclic pyrilium salts. In this respect, there is particular interest in oxygen containing hetero analogs. Because benzodioxane and its analogs have been known since the last century and there is information about their high biological activity [1] there is naturally an interest in benzodioxane analogs of 1-benzopyrilium salts. Dioxane analogs of flavylium salts I have not generally been synthesized before.

Benzopyrilium salts can be prepared from chalcones or, avoiding the chalcone separation stage, directly from acetophenone, aldehydes, and ethyl o-formate [2, 3]. Both methods when used to prepare benzodioxane analogs of 1-benzopyrilium salts have a number of disadvantages, viz. 2-(1,4-benzodioxane-6-yl)-4-ethoxychromylium perchlorates I prepared from chalcones are difficult to separate and contain many impurities. With several modifications for obtaining benzodioxane analogs of the 1-benzopyrilium salts we use the procedure from 2-hydroxy-acetophenones.

IR spectral data supported formation of the 2-(1,4-benzodioxan-6-yl)-4-ethoxychromylium perchlorates Ia-e showing absorption bands corresponding to symmetric and asymmetric stretching of the pyrilium ring at 1590-1510 cm^{-1} and perchlorate anion absorption at 1080-1100 cm^{-1}.

Scheme 1



I—VIa $R^1 = H, R^2 = H$; b $R^1 = H, R^2 = CH_3$, c $R^1 = H, R^2 = OCH_3$, d $R^1 = F, R^2 = H$; e $R^1 = CH_3, R^2 = H$; III X = OH; IV X = Ph; V X = NHPh

Further support came from their PMR spectral signals which showed an ethoxy group at 1.58 and 4.9 ppm and a singlet for the dioxane ring methylene protons at 4.5 ppm. The 5-H and 3-H proton signals in the chromone ring showed a characteristic low field shift when compared with the same proton signals in the corresponding flavones. The 1-benzopyrilium salts obtained react extremely readily with nucleophiles (see Scheme 1). Thus 2-(1,4-benzodioxan-6-yl)-4-ethoxychromylium perchlorates react

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TABLE 1. Physicochemical Parameters for I-VI

Compound	Empirical formula	Mp, °C	PMR spectral parameters (δ, ppm, J, Hz)	Yield, %
Ia	$C_{19}H_{17}ClO_8$	175...176	7,75 (1H, s, 3-H); 8,3 (1H, d, 5-H), J = 9	54
Ib	$C_{20}H_{19}ClO_8$	232...233	7,73 (1H, s, 3-H); 8,3 (1H, d, 5-H), J = 8; 2,74 (3H, s, 5-CH_3)	38
Ic	$C_{20}H_{19}ClO_9$	223...225	7,66 (1H, s, 3-H); 8,32 (1H, d, 5-H), J = 9,5; 4,53 (3H, s, 7-OCH_3)	44
Id	$C_{19}H_{16}FClO_8$	211...213	7,81 (1H, s, 3-H); 8,13 (1H, d, 5-H), J = 4	57
Ie	$C_{20}H_{19}ClO_8$	241...243	7,75 (1H, s, 3-H); 8,21 (1H, d, 5-H); 2,67 (1H, s, 6-CH_3)	68
IIIa	$C_{17}H_{13}NO_4$	223...224	7,25 (1H, s, 3-H); 7,85 (1H, d, 5-H), J = 7; 10,6 (1H, s, OH—N)	80
IIId	$C_{17}H_{12}FNO_4$	239...240	7,26 (1H, s, 3-H); 7,6 (1H, d.d, 5-H), J_O = 10, J_M = 3; 11 (1H, s, OH—N)	82
IVa	$C_{23}H_{17}NO_3$	252...253	7,2 (1H, s, 3-H); 8,7 (1H, d, 5-H), J = 8	82
IVb	$C_{24}H_{19}NO_3$	258...259,5	7,15 (1H, s, 3-H); 8,57 (1H, d, 5-H), J = 8,5	81
IVd	$C_{23}H_{16}NO_3$	181...182	7,23 (1H, s, 3-H); 8,52 (1H, d.d, 5-H), J_O = 9, J_M = 3	83
Va	$C_{23}H_{18}N_2O_3$	212...214	7,47 (1H, s, 3-H); 8,3 (1H, d, 5-H), J = 8	99
Vb	$C_{24}H_{20}N_2O_3$	213...214,5	7,5 (1H, s, 3-H); 8,24 (1H, d, 5-H), J = 8; 2,49 (3H, s, 7-CH_3)	97
Ve	$C_{24}H_{20}N_2O_3$	216...218	7,61 (1H, s, 3-H); 8,11 (1H, s, 5-H); 2,43 (3H, s, 6-CH_3)	99
VId	$C_{34}H_{22}F_2N_2O_6$	>350	Not conflicting with the proposed structure	70

*PMR spectrum of Ia-e recorded in CF_3COOD, remainder in DMSO-D_6.

even with traces of moisture in the deuterated DMSO used for recording the PMR spectra and are fully converted to the corresponding flavones IIa-e if the DMSO solution is refluxed for just two minutes. Compounds IIa-e are also formed by treating 1-benzopyrilium salts Ia-e with solutions of aqueous ammonia or caustic alkali with piperidine. Their physicochemical parameters agreed completely with those of flavones synthesized by other methods [4]. As is seen, the behavior of the benzodioxane analogs of the 1-benzopyrilium salts with the above named nucleophiles does not differ from that of 1-benzopyrilium salts with other substituents, i.e. the benzodioxane substituent does not have a significant effect on these reactions.

It has been reported [5, 6] that the final stage of reaction of 1-benzopyrilium salts with N− containing nucleophiles involves recyclization products, i.e. with fission of the pyrone ring. Ia-e react somewhat differently with such nucleophiles. Aniline, phenylhydrazine, and hydroxylamine give the corresponding 4-phenyliminochromones IVa-d, 4-phenylhydrazones Va, b, e, and oximes IIIa, d. All of these compounds gave a negative reaction with an alcoholic solution of ferric chloride and were insoluble in 2N solutions of caustic alkali or sodium carbonate. This points to the absence of recyclization products containing a hydroxyl group and hence preservation of the pyrone ring. The IR spectra of these derivatives show a C=N stretching vibration at 1610-1640 cm^{-1}. In their PMR spectra, the 5-H proton signal is shifted to low field of that in the flavone due to the effect of the unshared electron pair on the nitrogen atom (see Table 1).

Treatment of the 4-ethoxychromylium salts with hydrazine gives the chromone azines. Their structure was supported by the absence in their IR spectra of absorption bands for hydroxyl group and the presence of C=N stretching bands (1615-1630 cm^{-1}) and also by elemental analytical data. The PMR spectra were not in conflict with this.

EXPERIMENTAL

IR spectra were recorded on a Pye Unicam SP-300 instrument for KBr tablets. PMR spectra were taken on a Bruker WP-100 Fourier instrument with TMS as internal standard. Monitoring of the reaction and of the purity of the synthesized com-

pounds was performed by TLC on Silufol UV-254 plates in the solvents benzene–ethanol (9:1) and chloroform–methanol (85:15).

Elemental analytical data for C and H for the newly synthesized compounds were in agreement with that calculated.

2-(1,4-Benzodioxan-6-yl)-4-ethoxychromylium Perchlorates (Ia-e). 1,4-Benzodioxan-6-carboxaldehyde (0.98 g, 6 mmole) was added to a solution of the corresponding o-hydroxyacetophenone (0.27 g, 2 mmole) in ethyl orthoformate (8.3 ml, 2 mmole). After the components had dissolved, perchloric acid (70%, 0.11 ml, 2 mmole) was added and the reaction mixture held at room temperature for 24-50 h. The precipitate was filtered off, washed with ethanol, and recrystallized from acetic acid.

2-(1,4-Benzodioxan-6-yl)-4-chromone Oxime (IIIa,d). A mixture of the chromylium perchlorate (1a, d, 6 mmole) and hydroxylamine hydrochloride (1.25 g, 18 mmole) in dry pyridine (12 ml) was heated at 110-115°C for about 12 h. The mixture was poured into water and the precipitate filtered, washed with water, and recrystallized from acetic acid.

2-(1,4-Benzodioxan-6-yl)-4-phenylimine Chromones (IVa, b, d). Chromylium perchlorate I (0.41 g, 1 mmole) and aniline (0.19 ml, 2 mmole) in acetic acid (15 ml) were refluxed for 2 h. After cooling, the product was precipitated with ether and recrystallized from acetic acid (preliminary refluxing in 2-propanol).

2-(1,4-Benzodioxan-6-yl) Chromone Phenylhydrazones (Va, b, e). A mixture of chromylium perchlorate I (0.41 g, 1 mmole) and phenylhydrazine (0.2 ml, 2 mmole) in acetic acid (15 ml) was refluxed for 2 h. After cooling the product was separated using ether. The precipitate was filtered, refluxed in 2-propanol to remove impurities, and recrystallized from acetic acid.

Chromone Azine VId. A mixture of perchlorate Id (0.82 g, 2 mmole) and hydrazine hydrate (0.2 ml, 4 mmole) in acetic acid (15 ml) was refluxed for 40-50 h (monitored by TLC). After cooling, the precipitate was filtered and recrystallized from DMF.

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