SYNTHESIS, ANTI-INFLAMMATORY ACTIVITY AND METABOLISM OF ALKYL ARYL KETONES AND THEIR DERIVATIVES

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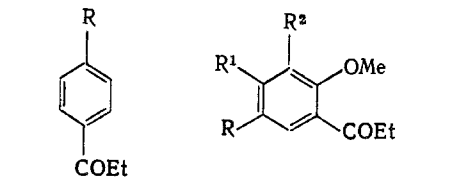
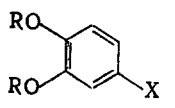
It was shown in our preceding article [2] that 5-propionyl-1,3-benzodioxolane (XVb) has anti-inflammatory activity (AIA) and is slightly toxic. Therefore, to study the relationship between the chemical structure and AIA, and also as part of our search for new drugs, we synthesized and studied alkyl aryl ketones and their derivatives, previously unknown or not investigated with respect to AIA. To clarify the question whether the alkyl aryl ketones themselves or their metabolites display AIA, we studied the metabolism of ketone XVb in the organism of a rabbit, and the AIA of its metabolites.

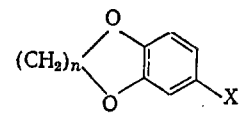


I—V

VI—X



XIb,n XIIa-c,ℓ,m XIIIb, XIVb



XVa-o, XVIb, XVIIb, XVIIIa-c, XIXb, XXb

I—V: R=H (I), Cl (II), Me (III), OH (IV), OMe (V);
VI—X: R=R¹=R²=H (VI); R=OMe, R¹=R²=H (VII); R=R²=H, R¹=OMe (VIII); R=R¹=OMe, R²=H (IX); R=H, R¹=R²=OMe (X); XI—XIV: R=H (XI), Me (XII), Et (XIII), Pr (XIV);
XV—XX: n=1 (XV), 2 (XVI), 3 (XVII), 4 (XVIII), 5 (XIX), 6 (XX);
XI—XX: X=COMe (a), COEt (b), COPr (c), COPr-i (d), COBu (e), $COCH=CH_2$ (e), COCH=CHEt (g), $COCH_2CH_2Cl$ (h), $COCH_2CH_2OMe$ (i), $COCH_2CH_2CN$ (j), $COCH_2CH_2COOH$ (k), $COCH_2CH_2NMe_2$ (ℓ), $COCH_2CH_2\overset{+}{N}Me_3 \cdot I^-$ (m), CH(OH)Et (n), CH(OMe)Et (o).

Ketones XIVb, XVe, g, XVIIb, XVIIIa-c, XIXb and XXb were synthesized by the Friedel—Crafts reaction by acylation of the corresponding aromatic compounds by acid chlorides in the presence of anhydrous $AlCl_3$ or $SnCl_4$. During the acylation of 1,3-benzo-dioxalane by 3-methoxypropionyl chloride in the presence of $SnCl_4$, ketone XVf and only traces of ketone XVi were obtained. Compounds XVi,j were synthesized by reacting chloroketone XVh with NaOMe and NaCN, respectively. Hydrolysis of ketonitrile XVj led to keto-acid XVk, while the reaction of ketone XVb with $NaBH_4$ in MeOH gave the methyl ester XVo. Alcohols XIn and XVn were synthesized by the reduction of ketones XIb and XVb, respectively, with $LiAlH_4$ in ether, while iodomethylates XIIm and XVm — by the action of MeI on amino-ketones XII*l* and XV*l*. Compounds XVf [20] and XVn [8] were previously obtained by other methods.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	mp, °C (solvent) or bp, °C (mm Hg)	UV spectrum		IR spectrum, $\nu_{C=O}$, cm^{-1}	Empirical formula
			λ_{max}, nm	lg ε		
XIn	74	143—145 (2), 1,5221*	221 282	3,82 3,50	—	$C_9H_{12}O_3$
XIIm	88	176—177 (ethanol)	224 275 305	4,37 3,95 3,88	1630	$C_{14}H_{22}INO_3$
XIVb	82	52—53 (hexane)	231 278 307	4,24 4,07 3,92	1665	$C_{15}H_{22}O_3$
XVd	64	130—132 (1), 1,5380*	228 272 307	4,40 3,82 3,87	1653	$C_{12}H_{14}O_3$
XVg	67	142—144 (3), 1,5836*	235 276 316	4,20 3,76 3,94	1635	$C_{12}H_{12}O_3$
XVi	51	68—69 (cyclohexane)	229 276 313	4,22 3,79 3,91	1640	$C_{11}H_{12}O_4$
XVj	55	91—92 (ethanol)	230 272 303	4,23 4,06 3,90	1665 2344 (C≡N)	$C_{11}H_9NO_3$
XVk	77	137—138 (water)	228 271 307	4,13 3,73 3,79	1640, 1675, 3780 (OH)	$C_{11}H_{10}O_5$
XVm	85	182—183 (ethanol)	225 280 319	3,84 3,18 3,35	1690	$C_{13}H_{18}INO_3$
XVo	81	113—114 (2), 1,5102*	235 285	3,61 3,58	—	$C_{11}H_{14}O_3$
XVIIb	73	38—39 (hexane)	226 270 297	4,24 4,06 Shoulder	1660	$C_{12}H_{14}O_3$
XVIIIa	80	157—159 (5), 1,5520*	226 274	4,17 4,02	1675	$C_{12}H_{14}O_3$
XVIIIb	75	33—34 (hexane)	226 274 292	4,04 3,95 Shoulder	1670	$C_{13}H_{16}O_3$
XVIIIc	82	147—148 (1), 1,5442*	225 271	4,10 4,00	1670	$C_{14}H_{18}O_3$
XIXb	67	140—142 (1), 1,5421*	224 271 293	4,15 4,12 Shoulder	1665	$C_{14}H_{18}O_3$
XXb	68	152—154 (1), 1,5152*	225 270 294	4,12 3,99 Shoulder	1665	$C_{15}H_{20}O_3$

Note. The n_D^{20} values are indicated by an asterisk.

The characteristics of the synthesized compounds are given in Table 1.

The structure of the synthesized compounds was confirmed by PMR spectral data (Table 2). In the IR spectra of the unsaturated ketones XVf,g, the stretching vibrations of the carbonyl group appear in a region of frequencies (1628-1635 cm^{-1}), lower than in the case of the saturated analogs XVb,e (1653-1670 cm^{-1}), while the UV absorption bands are less shifted to the long-wave side in the case of ketones XVb,e having a shorter conjugation chain, compared with unsaturated ketones XVf,g.

Compounds II [5], III [9], VI [18], VII [3], VIII [12], IX [19], X [14], XIb, XIIb [13], XIIc [21], XII*l* [2], XIIIb [6], XVa [4], XVc [10], XVd [16], XVh, *l*, and XVIb [2] were described previously. Compounds I, IV, V and XIIa are commercial products.

EXPERIMENTAL (CHEMICAL)

The UV spectra were run on a "Specord M 40" spectrophotometer (GDR) in ethanol, the IR spectra on a "Specord M 80" spectrophotometer (GDR) in mineral oil, and the PMR spectra on a "Tesla BS-487C" spectrometer (CSSR, 80 MHz), using TMS as internal standard.

TABLE 2. PMR Spectral Data (CCl_4, δ, ppm) of Compounds XIb,n, XVg,i,k,n,o, XVIIb-XXb

Compound	CH_3	$(CH_2)_n$	$CH_2C{=}$, CH_2CO	CH_3O, CH_2O, CHO	HC=, ArH, HO
XIb	1,02 t[a]	—	2,84 q[a]	—	6,76 d[b] (6-H), 7,36 dd[b,c] (5-H), 7,40 d[b] (3-H), 8,36 s (HO), 8,70 s (HO)[d]
XIn	0,85 t[a]	1,49 q[a]	—	2,38 t[a]	5,30—6,10 m (HO), 6,37—6,80 m (ArH) d
XVg	1,10 t[a]	—	2,55 q[a]	5,93 s	6,55—6,95 m (HC=), 6,70 d[b] (7-H), 7,27 d[c] (4-H), 7,40 dd[b,c] (6-H)
XVi	—	—	3,65 t[a]	3,02 t[a], 3,10 s, 6,05 s	6,73 d[b] (7-H), 7,30 d[c] (4-H), 7,40 dd[b,c] (6-H)
XVk	—	—	2,65 t[a], 3,25 t[a]	6,08 s	6,95 d[b] (7-H), 7,48 d[c] (4-H), 7,68 dd[b,c] (6-H)[f]
XVn	0,74 t[a]	1,54 q[a]	—	4,24 t[a], 5,75 s	3,25 s (HO), 6,55—6,60 m (ArH)
XVo	0,80 t[a]	1,55 q[a]	—	3,05 s, 3,75 t[a], 5,80 s	6,55—6,65 m (ArH)
XVIIb	1,10 t[a]	2,17 quart.[a]	2,78 q[a]	4,13 t[a], 4,20 t[a]	6,78 d[b] (9-H), 7,35 d[c] (6-H), 7,35 dd[b,c] (8-H)
XVIIIb	1,11 t[a]	1,58—2,16 m	2,78 q[a]	4,21 t[a], 4,43 t[a]	6,78 d[b] (10-H), 7,30—7,58 m (ArH)
XIXb	1,10 t[a]	1,60—2,00 m	2,60 q[a]	3,98—4,18 m, 4,23—4,48 m	6,78 d[b] (11-H), 7,32—7,58 m (ArH)
XXb	1,12 t[a]	1,35—1,95 m	2,83 q[a]	3,88—4,22 m	6,88 d[b] (12-H), 7,38—7,60 m (ArH)

*[a] J = 6-8 Hz. [b] J = 9 Hz. [c] J= 3-3 Hz. [d] In deuteroacetone. [e] In $CDCl_3$. [f] In deuteromethanol.

TABLE 3. Acute Toxicity and AIA of Compounds XIb,n, XIIm, XIIIb, XIVb, XVd,f,m,n, XVIIIa,b, XIXb and XXb during a Peroral Method of Administration

Compound	LD_{50}, mg/kg	Dose, mg/kg	Mean percent of inhibition of inflammation (compared with control)	
			carrageenan	bentonite
XIb	760 (660—874)	50	11,3	44,5
XIn	435 (330—574)	50	5,6	—*
XIIm**	168 (155—179)	50	68,4	66,2
XIIIb	...***	50	25,8	23,7
XIVb	...***	50	17,8	13,1
XVd	...***	50	6,1	20,0
XVf	...***	50	15,0	48,5
XVm**	231 (178—300)	50	59,4	30,9
XVn	720 (625—829)	50	24,2	37,8
XVIIIa	...***	50	22,5	22,0
XVIIIb	3143 (2632—3671)	50	31,8	36,4
XIXb	...***	50	18,5	21,6
XXb	...***	50	23,1	29,6
Acetylsalicylic acid	1000 (743—1382)	200	28,1	6,5
Lysine acetylsalicylate**	1000 (890—1130)	150	37,4	9,8
Ibuprofen	800 (647—936)	80	30,8	22,0
Voltaren	172 (108—274)	25	46,7	24,3

*Increase in edema

**Using a subcutaneous method of administration

***Not determined because of weak AIA

Note. The fluctuation limits at $p \leq 0.05$ are given in brackets.

The characteristics and yields of the synthesized compounds are given in Table 1 and 2. The results of the elemental analyses correspond to the calculated values.

1,2-Dihydroxy-4-(1-hydroxypropyl)benzene (XIn). A mixture of 3 g (18 mmoles) of ketone XIb, 2 g (53 mmoles) of $LiAlH_4$ and 150 ml of absolute ether was boiled and stirred for 6 h. Water was added, the mixture was acidified with dilute H_2SO_4, extracted with ether, and the ether was evaporated from the dry extract.

4-Propionyl-1,2-dipropoxybenzene (XIVb), 5-Acyl-1,3-benzodio-xolanes (XV e-g), 7-Propionyl-1,5-benzodioxepane (XVIIb), 8-Acyl-1,6-benzodioxocanes (XVIIIa-c), 9-Propionyl-1,7-benzodioxonane (XIXb) and 10-Propionyl-1,8-benzodioxosecane (XXb). A 5.4 g portion (40 mmoles) of anhydrous $AlCl_3$ was added at 0-5°C in the course of 30 min to a mixture of 25 ml of anhydrous CH_2Cl_2, 37 mmoles of the corresponding acid chloride, and 35 mmoles of the corresponding aromatic compound, and the mixture was stirred for 2 h at 20°C. It was then poured onto ice, acidified with HCl, and extracted with CH_2Cl_2. The extract was washed with water, dried, and the solvent was evaporated. In the case of the acylation of 1,3-benzodioxolane, 10.4 g (40 mmoles) of anhydrous $SnCl_4$ was added at –5°C, and the mixture was stirred for 15 min at 10-15°C. The yield of ketone XVf was 25%, mp 43-45°C (from ethanol).

5-(3-Methoxypropionyl)-1,3-benzodioxolane (XVi). A 5.3 g (25 mmoles) of chloroketone XVh was added at the boiling point, in the course of 15 min, to a solution of 1.7 g (75 mmoles) of Na in 30 ml of MeOH, and the mixture was boiled for 3 h. Then 300 ml of water was added, the mixture was extracted with ether, and the ether was evaporated from the dry extract.

5-(3-Cyanopriopionyl)-1,3-benzodioxolane (XVj). A 4.3 g portion (20 mmoles) of chloroketone XVh was added at 90°C in the course of 1 h, to a solution of 2 g (40 mmoles) of NaCN in 50 ml of DMSO. The mixture was heated for 3 h, and after the addition of 300 ml of water, it was extracted with benzene, and the benzene was evaporated from the dry extract.

5-(3-Carboxypropionyl)-1,3-benzodioxolane (XVk). A mixture of 1.5 g (7 mmoles) of nitrile XVj, 2.5 g (45 mmoles) of KOH and 20 ml of 50% ethanol was boiled for 4 h, then cooled and extracted with ether. The aqueous layer was acidified with HCl, extracted with CH_2Cl_2 and the solvent was evaporated from the extract.

5-(1-Hydroxypropyl)-1,3-benzodioxolane (XVn). A mixture of 4.5 g (25 mmoles) of ketone XVb, 1 g (26 mmoles) of $LiAlH_4$ and 100 ml of absolute ether was boiled for 30 min, and alcohol XVn was isolated in a similar way as compound XIn. Yield, 4.1 g (90%), bp 127-128°C (2 mm Hg).

5-(1-Methoxypropyl)-1,3-benzodioxolane (XVo). A 1.1 g portion (30 mmoles) of $NaBH_4$ was added at 10°C to a solution of 5.4 g (30 mmoles) of ketone XVb in 50 ml of MeOH. The mixture was stirred for 30 min at 20°C, and 300 ml of water was added. The mixture was acidified with dilute H_2SO_4, extracted with benzene, and the benzene was evaporated from the dry extract.

Iodomethylates XIIm and XVm. A solution of 25 mmoles of aminoketones XII*l* or XV*l* and 10.7 g (75 mmoles) of MeI in 50 ml of benzene was allowed to stand for 2 days at 20°C, and the iodomethylate precipitate was filtered off.

EXPERIMENTAL (PHARMACOLOGICAL)

The iodomethylates XIIm and XVm were introduced subcutaneously in the form of a 1% aqueous solution, while the remaining compounds (insoluble in water) were introduced perorally in the form of a suspension in 1% solution of carboxymethylcellulose with the addition of Tween-80. Nonpedigree white mice, each weighing 18-25 g, white rats each weighing 150-230 g, and chinchilla breed of rabbits of both sexes each weighing 2.5-3.5 kg were used in the tests.

The acute toxicity for mice was determined by the modified Litchfield and Wilcoxon method [1]. The AIA was studied using a model of carrageenan [22] and bentonite-induced [15] edema on a rat paw. Table 3 shows the mean arithmetic values of percent decrease in the edema (compared with control) 1, 2, 3, and 5 h after the introduction of the compounds studied.

The metabolism of ketone XVb was studied on rabbits by examining an ethereal extract of urine collected in the course of 2 days (until no more metabolites were eliminated) after a single oral administration of the compound (XVb) in a dose of 200 mg/kg (1/10 LD_{50} for mice), incubated with β-glucuronidase-arylsulfase at 37°C and at pH 5 for 24 h [11], and then acidified with HCl to pH 1. Using the TLC method on Silufol plates (CSSR), four compounds which were not natural metabolites were identified. Given are the R_f values in an acetone–hexane, 1:2, system

(development with iodine vapor): 0.24 (XIb), 0.91 (XVn) — the main metabolites, 0.51 (XIn) — traces, and (XVb) — a small amount. The alcohol XVn and the phenolic compound XIb were separated by treating the above ether extract with a 5 N solution of NaOH, and were additionally identified from the PMR spectra (see Table 2).

It was found that compounds I-X, XIIa,c, XVa,c,e,g,i,k,o, XVIIb, XVIIIc as well as XVh, XVIb [2] do not have AIA. Ketones XIb, XIIIb, XIVb, XVd,f, XVIIIa, XIXb and XXb are moderately active like XIIb [2] while ketone XVIIIb in its convenient combination of high AIA with low toxicity is similar to ketone XVb [2], and is superior to several preparations used in medical practice (see Table 3). Of the alkyl aryl ketones XIIa-c, XVa-e and XVIIIa-c, compounds XIIb, XVb and XVIIIb are the most active, which corresponds to the results obtained in the investigation of the AIA of 5-acyl-2-methylcoumarans [2]. Introduction of a double bond (XVf) or β-carboxy (methoxy, chlorine) substituent (XVh,i,k) into the ethyl radical, of ketone XVb leads to decrease or disappearance of AIA. Nevertheless, the β-diemthylamino derivatives XIII*l* and XV*l* are highly active [2], while the quaternization of their nitrogen atom preserves the AIA, and only their toxicity increases (XIIm, XVm). Hence, the presence of a free electron pair on the nitrogen atom is not obligatory for the manifestation of the AIA by β-amino-ketones. The corresponding α-, and γ-aminoketones, i.e., derivatives of methyl- and propyl aryl ketones, respectively, are inactive [2]. For the manifestation of the AIA by ethyl aryl ketones, alkoxy- or hydroxy substituents must be present in their aromatic ring, which have a fairly high electron-donor capacity with respect to the aromatic ring and toward the carbonyl group, as indicated by the value of the bathochromic shift of the middle wave band of UV absorption (the electron transfer bands) [17] of these compounds. For ketones XIb-XIVb and XVb, XVIIIb, most active among ketones IV-X, XIb-XIVb, and their corresponding cyclic analogs XVb and XXb this band has λ_{max} in the 274-278 nm region, while in the less active analogs or inactive ketones (IV-X, XVIb, XVIIb, XIXb and XXb) the λ_{max} is in a region lower than 274 nm, which in ketones VI-X, XVIb, XVIIb, XIXb and XXb is due to a decrease in the electron-donor capacity of the oxygen atoms with respect to the aromatic ring, because of the rotation of the alkoxy substituents around the C_{Ar}—O bond [7].

Ethyl aryl ketones themselves have an AIA, since ketone XVb, which undergoes reduction or O-dealkylation in the rabbit organism, forms slightly toxic metabolites XIb,n and XVn, which do not exhibit high AIA (see Table 3).

Our investigations thus indicate the prospects of finding new anti-inflammatory agents among ethyl aryl ketones which contain electron donor substituents in the aromatic ring.

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SYNTHESIS, PROPERTIES AND BIOLOGICAL ACTIVITY OF 2-[N-(1^1-ADAMANTYL)-IMINO]-4-R^1-5-p-R-PHENYL-2,3-DIHYDRO-3-FURANONES AND THEIR HYDROLYSIS PRODUCTS

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As is known, adamantane derivatives have a wide biological activity spectrum. Introduction of the adamantyl radical into a molecule frequently leads to modification of the biological activity, usually with its increase [5].

It has shown earlier that N-substituted 2-imino-5-aryl-2,3-dihydro-3-furanones are hydrolyzed under mild conditions to give N-substituted amides of aroylpyruvic acids [3]. Compounds were discovered among the amides of aroylpyruvic acids having anti-inflammatory activity [1].

In order to find biologically active compounds in the series of N-substituted 2-iminofuranones and their transformation products, we synthesized 2-[N-(1^1-adamantyl)imino]-4-R^1-5-p-R-phenyl-2,3,-dihydro-3-furanones (IIIa-f) and hydrolyzed them to N-(1^1-adamantyl)-amides of 4-p-R-benzoylpyruvic acids (IVa-d).

Furanones IIIa-f were obtained by the reaction of equimolar amounts of 5-p-R-phenyl-4-R^1-2,3-dihydro-2,3-furandiones (Ia-f) with adamantyl isocyanide (II) in a benzene-octane (1:1) mixture at 85-90°C (R^1 = H) or in boiling xylene at 140°C (R^1 = Br). The synthesized furanones IIIa-f are yellow crystalline compounds, which are readily soluble in $CHCl_3$, DMFA, and DMSO.

There appears an intense absorption in the 1705-1690 cm^{-1} region in the IR spectra of the synthesized compounds, which is due to the superposition of the stretching vibrations of the C=O and C=N bonds. The absorption in the 1595-1580 cm^{-1} region belongs to the stretching vibrations of the carbon-carbon double bonds of the heterocyclic ring and the substituent at the 5 position. In the PMR spectra there are signals of 15 adamantyl protons in the 1.85-1.91 ppm region, a singlet of the methine proton at the 4-position of the heterocyclic ring in the 5.98-6.15 ppm (for compounds IIIa-d), a quadruplet (for compounds IIIb-d,f) or a multiplet (for compounds IIIa,e) of aromatic protons in the 7.18-7.63 ppm region.

The furanones IIIa-f obtained undergo hydrolysis in an aqueous dioxane medium in the presence of equimolecular amounts of HCl. Hydrolysis of the 4-bromo-substituted furanones IIIe,f resulted in ω-chloro-p-R-acetophenones (Va,b) and 1-adamantylamine hydrobromide (VI), which are described in the literature. Hydrolysis of furanones IIIa-d unsubstituted at the 4-position resulted in N-(1^1-adamantyl)amides or 4-p-R-benzoylpyruvic acids (IVa-d), which occur in the enol form with an intramolecular hydrogen bond like the N-aryl analogs [2].

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