CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES

14.* ISOXAZOLE ANALOGS OF ISOFLAVONES

N. V. Gorbulenko, S. A. Kirpa, and V. P. Khilya

Isoxazole analogs of isoflavones have been synthesized by the cyclization of α-(3-isoxazolyl)-2-hydroxyacetophenones. Their alkylation, acylation, and electrophilic substitution reactions, and reactions with binucleophiles have been studied. 3-(3-Isoxazolyl)-7-methoxychromones are rearranged selectively into 2-aminochromone derivatives by the action of hydroxylamine as a result of a double recyclization and are recyclized into pyrazole derivatives by hydrazine. Preparations with hypolipidemic, anabolic, hypoglycemic, and antiarrhythmic action are found among the derivatives of 3-(3-isoxazolyl)chromones.

The introduction of an azoheterocycle into the nucleus of a chromone leads essentially to a new type of organic compound, the azaheterylchromones, that are not encountered in nature. The 3-azaheterylchromones are of practical interest since compounds are found among them which possess antisclerotic, hypoglycemic, and anti-inflammatory activity [2]. While investigating the azole derivatives of chromone and studying the connection between structure and biological activity we returned to the synthesis of the isoxazole analogous of isoflavone.

Literature data on the synthesis of compounds of this class are sparse. 3-Isoxazolinyl- and 3-isoxazolylchromones [3] are obtained by the cycloaddition of olefinic dipolarophiles to chromone-3-carbonitrile oxide. 3-Isoxazolidinylchromones are formed by treating 3-formylchromone with phenyl- and methylhydroxylamine hydrochlorides and subsequent reaction with alkenes [4]. 3-Isoxazolyl-chromones are obtained as intermediates in the synthesis of benzo[b]xanthones [5] by the reaction of 3,5-dimethyl-isoxazole with esters of 2-hydroxybenzoic acid.

The substituted α-(3-isoxazolyl)-2-hydroxyacetophenones (I)-(VI) served as key compounds for the synthesis of the isoxazole analogs in this work. They were obtained by the condensation of 3-cyanomethylisoxazole with resorcinol and alkylresorcinols under modified conditions of the Gash reaction where boron trifluoride etherate is used as solvent and also fulfills the role of catalyst. Maximum yields of the desired ketones (I)-(VI) were achieved when carrying out the reaction at 50-60°C (Table 1).

It is possible to form isomeric ketones in the reaction of 3-cyanomethylisoxazole with resorcinol, orcinol, and 4-alkylresorcinols. However, it was found that only one of them was obtained from resorcinol, which is probably explained by the significantly different reactivities of positions 2 and 4 of the diphenol. The PMR spectrum of ketone (I) (DMSO-d_6) indicates an unsymmetrical position for the hydroxyl groups in the phenolic portion of the ketone. The aromatic protons form an ABX spin system with $J_{5,6}$ = 8 Hz and $J_{3,5}$ = 2 Hz which correspond to the coupling constants of protons in the ortho and meta positions. The signal for the 6-H proton was 1.4 ppm distant from the other two aromatic protons due to the deshielding effect of the carbonyl group and the coordinated positive inductive effect of the two OH groups. The signals of the latter were observed as singlets at 12.08 (2-OH) and 10.68 (4-OH) ppm. The proton of the 2-OH group forms an intramolecular hydrogen bond with the carbonyl group and the proton of the 4-OH group participates in an intermolecular hydrogen bond with the solvent. The protons of the methylene unit appear as a singlet at 4.5 ppm, but the protons of the isoxazole ring give doublets with coupling constant 1.5 Hz.

According to chromatographic data the two isomeric ketones (II) and (IIA) were formed when using orcinol in the condensation. In orcinol the more reactive 4 position is sterically hindered. The ketone (II) was isolated in the pure state and its structure was confirmed by the PMR spectrum. Distinct signals were detected for the protons of the 2-OH and 4-OH

*For Communication 13, see [1].

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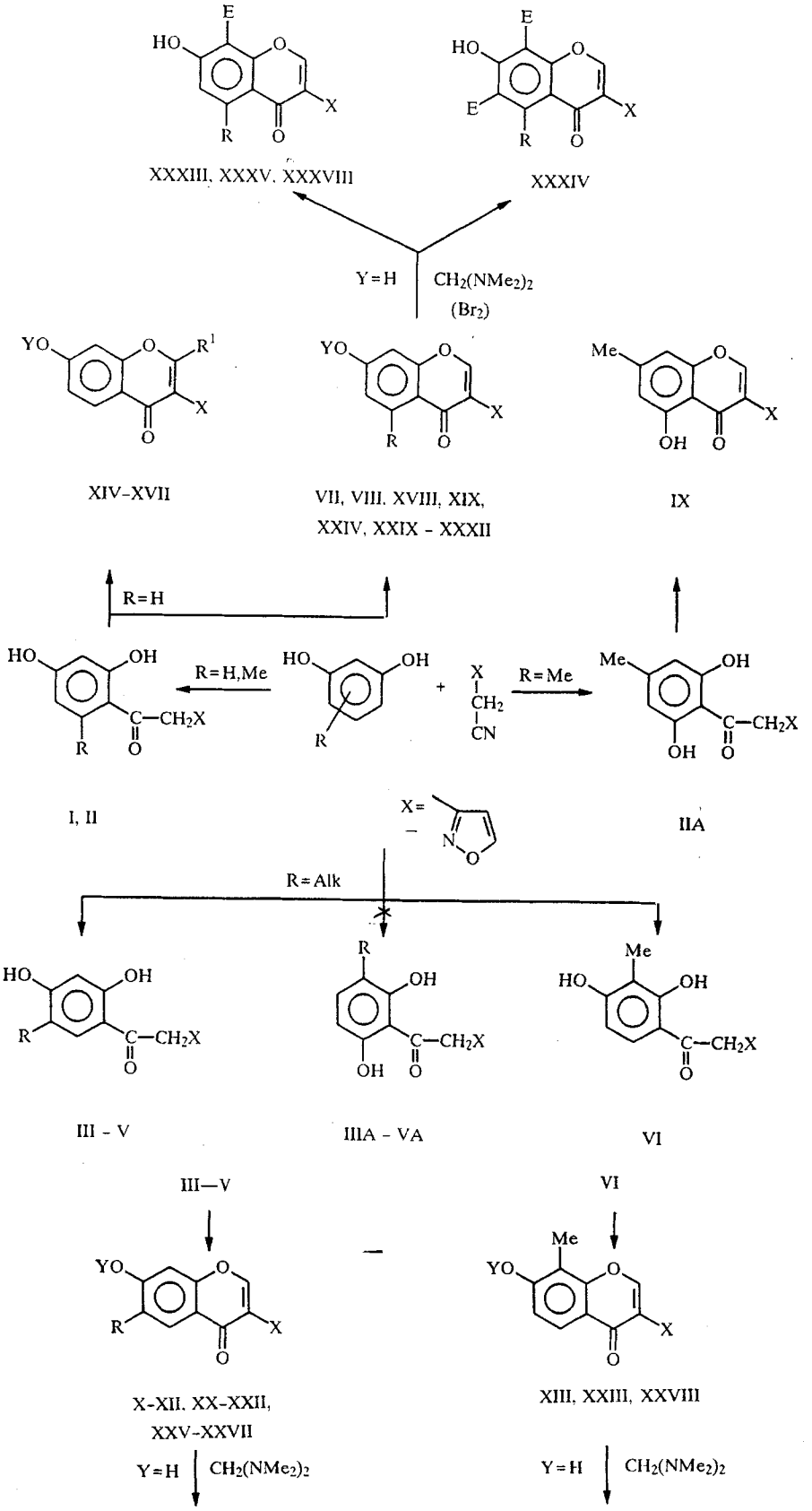
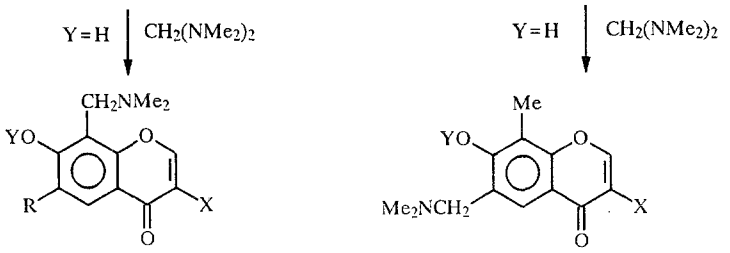
groups, and for the 3-H and 5-H aromatic protons in the PMR spectrum (see Table 1). In the case of structure (IIA) the aromatic protons of the phenolic portion of the molecule and the hydroxyl group protons should be displayed as two proton singlets.

Scheme 1





XXXVI, XXXVII XXXIX

I R = H; II, III, XXXVI R = Me; IV R = Et; V, XXXVII R = Pr; VII R = Y = H; VIII, X R = Me, Y = H; XI R = Et, Y = H; XII R = Pr, Y = H; XIII Y = H; XIV Y = H, R^1 = Me; XV Y = H, R^1 = CF_3; XVI Y = H, R^1 = = COOEt; XVII Y = COMe, R^1 = Me; XVIII R = H, Y = COMe; XIX, XX R = Me, Y = COMe; XXI R = = Et, Y = COMe; XXII R = Pr, Y = COMe; XXIII Y = COMe; XXIV R = H, Y = Me; XXV R = Y = Me: XXVI R = Et, Y = Me; XXVII R = Pr, Y = Me; XXVIII Y = Me; XXIX R = H, Y = Et; XXX R = H, Y = = CH_2COOEt; XXXI R = H, Y = CH_2Ph; XXXII R = H, Y = $CH_2C_6H_4Br$-*p*; XXXIII, XXXIV R = H, E = = Br; XXV R = H, E = CH_2NMe_2; XXXVIII R = Me, E = CH_2NMe_2

The formation of two isomeric compounds (III)-(V) and (IIIA)-(VA) might be expected from the reaction of 3-cyanomethylisoxazole with 4-alkylresorcinols. The TLC data showed that one isomer was formed in practice in these reactions. The choice between the structures was made on the basis of PMR spectra. There were peaks for protons of the hydroxyl groups at 10.7-10.9 and 12.1-12.2 ppm and singlets for the protons of the phenolic portion of the molecule at 6.4-6.5 and 7.7-7.8 ppm which confirm structures (III)-(V). It might be expected that the aromatic protons of the phenolic fragment of the molecule of the possible isomers (IIIA)-(VA) would be displayed as doublets of an AB system and the signals of the hydroxyl groups, alternately forming intramolecular hydrogen bonds with the carbonyl oxygen, would merge into one peak.

The structure of the ketone (VI), the condensation product of 3-cyanomethylisoxazole and 2-methylresorcinol, was not in doubt. In its PMR spectrum the aromatic protons of the phenolic fragment of the molecule are displayed as doublets with coupling constant 8.5 Hz. The proton of the 2-OH phenolic hydroxyl group, which forms an intermolecular hydrogen bond of chelate type, absorbs at low field (12.7 ppm).

The isoxazole analogs of the natural isoflavones (VII)-(XIII), in which there are no substituents at the 2 position of the pyrone ring, are formed readily by heating the ketones (I)-(VI) with ethyl orthoformate in the presence of a catalytic quantity of piperidine. The reaction of ketone (I) with acetic anhydride, trifluoroacetic anhydride, or ethoxalyl chloride in the presence of organic bases under mild conditions leads to the formation of 2-methyl-, 2-trifluoromethyl-, and 2-ethoxycarbonyl-7-hydroxychromones (XIV)-(XVI) respectively.

Unlike the initial ketones the isoxazole analogs of isoflavones did not give a positive reaction with an alcoholic solution of ferric chloride, which indicates the absence from their molecules of hydroxyl groups capable of forming chelates. In the PMR spectra (Table 2) of the 3-(3-isoxazolyl)chromones the two-proton singlet of the methylene group and the low-field peak of the phenolic proton disappeared and a sharp solitary singlet for the 2-H proton appeared at 8.5-8.7 ppm for compounds (VII)-(XIII). In addition, a characteristic sign of the chromone ring is the presence of a peak at 7.8-8.0 ppm belonging to the 5-H aromatic proton, which brings into question the deshielding effect of the neighboring carbonyl group. The data indicated confirm the formation of a 3-(3-isoxazolyl)-chromone system.

The isoflavone analogs (VII), (VIII), and (X)-(XIV) were readily acetylated in the phenolic fragment and formed the acetyl derivatives (XVII)-(XXIII). The corresponding alkoxy derivatives (XXIV)-(XXXII) were formed by treating the 7-hydroxychromones (VII) and (X)-(XIII) with methylating agents in acetone solution in the presence of potassium carbonate. The structures of the acetoxy and alkoxy derivatives were confirmed by PMR spectra.

The electrophilic substitution of the isoxazole analogs of isoflavones was studied using bromination and aminomethylation as examples. On bromination a mono (XXXIII) or a dibrominated derivative (XXXIV) was obtained depending on the conditions. On brief boiling of the chromone (VII) with one equivalent of bromine in acetic acid, the bromine enters at position 8 of the chromone as follows from the PMR data. On more extended boiling a second atom of bromine enters at position 6. The reaction of the chromones (VII), (VIII), (X), (XII), and (XIII) with bis(dimethylamino)methane in dioxan leads on heating to the formation of the Mannich bases (XXXV)-(XXXIX). The dimethylamino group enters into position 8 of the chromone ring or, if that is occupied, into position 6.

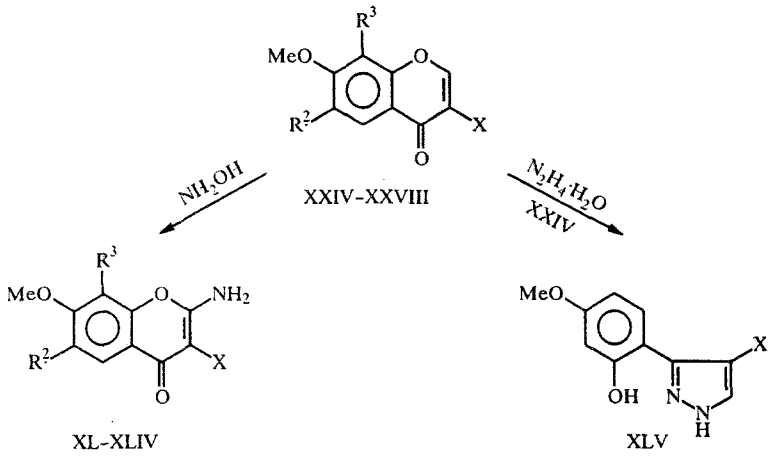
The behavior of the 3-(3-isoxazolyl)chromones towards nucleophilic reagents was studied using the reaction with hydroxylamine or hydrazine hydrate as examples.

TABLE 1. Characteristics of the α-(3-Isoxazolyl)-2,4-dihydroxyacetophenones (I)-(VI)

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm (coupling constant, Hz)*								Yield, %
			Phenyl protons						isoxazole protons		
			2-OH, s	3-R	4-OH, s	5-R	6-R	CH_2, s	4-H (d 2.0)	5-H (d 2.0)	
I	$C_{11}H_9NO_4$	121...123	12,08	6,40 (d,2,0)	10,68	6,43 (d,d,8,0; 2,0)	7,84 (d,8,0)	4,53	6,54	8,78	64
II	$C_{12}H_{11}NO_4$	177...178	10,21	6,16 (d,2,0)	9,74	6,24 (d,2,0)	2,14, s	4,29	6,40	8,78	63
III	$C_{12}H_{11}NO_4$	152...153	12,16	6,44, s	10,78	2,14, s	7,82, s	4,56	6,61	8,93	83
IV	$C_{13}H_{13}NO_4$	147...148	12,09	6,43, s	10,70	1,18 (t,7,0); 2,59 (q, 7,0)	7,74, s	4,54	6,58	8,83	86
V	$C_{14}H_{15}NO_4$	137...138	12,04	6,48, s	10,71	0,96 (t, 7,0); 1,82 (m; 2,63 (t,7,0)	7,81, s	4,65	6,64	8,90	78
VI	$C_{12}H_{11}NO_4$	144...146	12,67	2,02, s	10,66	6,53 (d,8,5)	7,81 (d,8,5)	4,56	6,56	8,88	70

*Spectra were measured in DMSO-d_6.

Scheme 2



XXIV, XL $R^2 = R^3 = H$; XXV, XLI $R^2 = Me$, $R^3 = H$; XXVI, XLII $R^2 = Et$, $R^3 = H$; XXVII, XLIII $R^2 = Pr$, $R^3 = H$; XXVIII, XLIV $R^2 = H$, $R^3 = Me$

It has been established [6, 7] that isoflavones do not give the normal carbonyl reaction with hydroxylamine. The oximation reaction proceeds with fission of the pyrone ring and subsequent cyclization of the intermediates into derivatives of the isomeric isoxazoles or 4-hydroxycoumarins [8]. In our previous studies on the reaction of isoflavone [9] and 3-heterylchromone [10-13] derivatives with hydroxylamine in dry pyridine, it was shown that the course of the reaction depends on the substituent in position 2 of the chromone ring. Isoxazoles were formed from the 2-methyl-, 2-trifluoromethylisoflavone and 2-methyl-3-heterylchromone derivatives in the majority of cases. A multicomponent mixture of products of various structure is formed in the reaction of hydroxylamine with isoflavone and 3-heterylchromone derivatives having no substituent at position 2. The quantity and nature of the products is determined by the character of the substituent at position 4′ of the isoflavone derivatives or the heterocyclic nucleus in 3-heterylchromones [2, 9]. In view of these data we expected a multicomponent mixture to be formed from the reaction of 3-(3-isoxazolyl)-7-methoxy-chromones (XXIV)-(XXVIII) with

Scheme 3

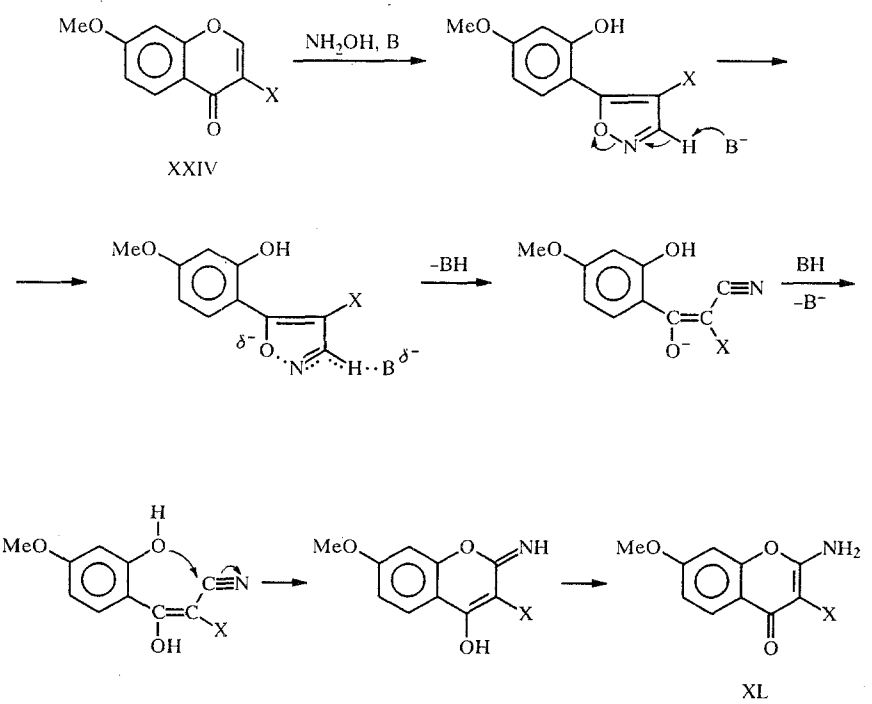


TABLE 2. Characteristics of 3-(3-Isoxazolyl)chromones (VII)-(XLIV)

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm (coupling constant, Hz)							Yield, %
			chromone ring protons					isoxazole protons		
			2-R,	5-R	6-R	7-R	8-R	4-H (d 2,0)	5-H (d 2,0)	
VII	$C_{12}H_7NO_4$	258	8,69	7,95 (d 8,0)	6,95 (d.d.8,0; 2,0)	10,85 s	6,86 (d,2,0)	7,06	8,96	70
VIII	$C_{13}H_9NO_4$	263...264 decomp.	8,57	2,80 s	6,70 s	10,68 s	6,70 s	7,04	8,95	71
IX	$C_{13}H_9NO_4$	187...188	8,53	12,10 s	6,67 (d,2,0)	2,52 s	6,76 (d,2,0)	7,09	8,45	53
X	$C_{13}H_9NO_4$	254...255 decomp.	8,79	7,87 s	2,29 s	11,09 s	6,97s	7,13	9,08	92
XI	$C_{14}H_{11}NO_4$	234...235	8,67	7,78 s	1,21 (t,7,0); 2,67 (q,7,0)	10,88 s	6,89 s	7,05	8,95	82
XII	$C_{15}H_{13}NO_4$	226...227	8,72	7,83 s	0,98 (t,7,0); 1,89 m 2,77 (t,7,0)	10,88 s	6,98 s	7,12	9,00	98
XIII	$C_{13}H_9NO_4$	250...251 decomp.	8,72	7,76 (d, 8,0)	6,98 (d, 8,0)	10,68 s	2,29 s	7,05	8,93	98
XIV	$C_{13}H_9NO_4$	265...266 decomp.	2,44	7,85 (d,8,0)	6,95 (d.d.8,0; 2,0)	10,78 s	6,80 (d,2,0)	6,80	8,95	67
XV	$C_{13}H_6F_3NO_4$	240...241	—	7,89 (d,9,0)	7,00 (d.d,9,0; 2,5)	11,15 s	6,89 (d,2,5)	6,74	9,00	54
XVI	$C_{15}H_{11}NO_6$	199...200	**	7,87 (d,9,0)	6,98 (d.d,9,0; 2,0)	11,07 s	6,88 (d,2,0)	6,76	8,95	58
XVII	$C_{14}H_9NO_5$	169...170	2,64	8,20 (d,8,0)	7,13 (d.d,8,0; 2,0)	2,38 s	7,27 (d,2,0)	6,84	8,46	72
XVIII	$C_{14}H_9NO_5$	167...168	8,58	8,21 (d,8,0)	7,20 (d.d,8,0; 2,0)	2,44 s	7,27 (d,2,0)	7,14	8,42	98
XIX	$C_{15}H_{11}NO_5$	160...161	8,40	2,92 s	7,08s	2,39 s	7,08s	6,90	8,40	81
XX	$C_{15}H_{11}NO_5$	193...194	8,62	8,10 s	2,33s	2,41 s	7,26s	7,16	8,47	78
XXI	$C_{14}H_{14}NO_5$	147...148	8,59	8,12 s	1,27 (t,7,0); 2,68 (q,7,0)	2,39 s	7,24s	7,15	8,45	96
XXII	$C_{17}H_{15}NO_5$	145...146	8,61	8,13 s	1,02 (t,7,0); 1,8 m; 2,76 (t,7,0)	2,47 s	7,32s	7,21	8,45	64
XXIII	$C_{15}H_{11}NO_5$	216...217	8,73	8,17 (d,8,5)	7,16 (d, 8,5)	2,41 s	2,35 s	7,18	8,50	92
XXIV	$C_{13}H_9NO_4$	161...162	8,50	8,09 (d,8,0)	6,97 (d.d,8,0; 2,0)	3,87 s	6,85 (d,2,0)	7,14	8,41	72
XXV	$C_{14}H_{11}NO_4$	191...192	9,41	8,36 s	2,58s	4,28 s	7,43s	7,20	8,78	78
XXVI	$C_{15}H_{13}NO_4$	179...180	8,63	8,07 s	1,31 (t,7,0); 2,83 (q, 7,0)	4,08 s	6,91s	7,28	8,53	87
XXVII	$C_{16}H_{15}NO_4$	175...176	8,62	8,05 s	1,03 (t,7,0); 1,93 m; 2,83 (t,7,0)	4,07 s	6,92s	7,28	8,51	80
XXVIII	$C_{14}H_{11}NO_4$	192...193	8,66	8,14 (d,8,5)	7,01 (d,8,5)	3,99s	2,38s	7,21	8,51	85
XXIX	$C_{14}H_{11}NO_4$	135	8,60	8,18 (d,9,0)	7,01 (d.d,9,0; 2,5)	1,49 (t, 7,0); 4,15 (q, 7,0)	6,89 (d, 2,5)	7,21	8,48	68
XXX	$C_{16}H_{13}NO_6$	159...160	8,58	8,19 (d,8,0)	7,06 (d.d,8,0; 2,0)	4,72 s; 4.35q, 7,0); 1,35 (t,7,0)	6,89 (d, 2,0)	7,34	8,48	58

TABLE 2 (continued)

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm (coupling constant, Hz)							Yield, %
			chromone ring protons					isoxazole protons		
			2-R,	5-R	6-R	7-R	8-R	4-H (d 2.0)	5-H (d 2.0)	
XXXI	$C_{19}H_{13}NO_4$	157...158	8,67	8,29 (d, 8,0)	7,24 (d.d, 8,0; 2,0)	5,27 s; 7,51 s	7,12 (d, 2,0)	7,35	8,55	88
XXXII	$C_{19}H_{12}BrNO_4$	185...186	8,86	7,91 (d, 8,0)	7,10 (d.d, 8,0; 2,0)	5,30 s; 7,46 s	7,04 (d, 2,0)	7,20	8,68	80
XXXIII	$C_{12}H_6BrNO_4$	269...270 (decomp.)	8,85	7,93 (d, 8,5)	7,22 (d, 8,5)	11,65 s	—	7,04	8,98	78
XXXIV	$C_{12}H_5Br_2NO_4$	241...242 (decomp.)	8,98	8,19 s	—	10,46 br.s	—	7,04	9,05	57
XXXV	$C_{15}H_{14}N_2O_4$	188...189	8,53	8,07 (d, 8,0)	6,90 (d, 8,0)	11,00 s	4,03 s; 2,45 s	7,18	8,45	85
XXXVI	$C_{16}H_{16}N_2O_4$	157...158	8,58	7,98 s	2,36 s	11,22 s	4,05 s; 2,46 s	7,22	8,51	84
XXXVII	$C_{18}H_{20}N_2O_4$	157...158	8,58	7,98 s	1,02 (t, 7,0); 1,77 m; 2,76 (t, 7,0)	12,35 s	4,03 s; 2,45 s	7,22	8,53	87
XXXVIII	$C_{16}H_{16}N_2O_4$	155...156	8,44	2,83 s	6,69 s	10,10 s	3,99 s; 2,44 s	7,16	8,51	72
XXXIX	$C_{16}H_{16}N_2O_4$	217...218	8,61	7,77 s	3,82 s; 2,41 s	11,48 s	2,37 s	7,18	8,45	74
XL	$C_{13}H_{10}N_2O_4$	248...249	8,66	7,96 (d, 8,0)	7,02 (d.d, 8,0; 2,0)	3,96 s	6,93 (d, 2,0)	7,62	8,88	78
XLI	$C_{14}H_{12}N_2O_4$	274...275 (decomp.)	8,56	7,74 s	2,21 s	3,91 s	6,81 s	7,60	8,87	85
XLII	$C_{15}H_{14}N_2O_4$	227...228	8,53	7,70 s	1,20 t, 7,0)' 2,63 (q, 7,0)	3,91 s	6,82 s	7,58	8,81	87
XLIII	$C_{16}H_{16}N_2O_4$	212...213	8,61	7,81 s	0,96 (t, 7,0); 1,68 m, 2,70 (t, 7,0)	4,05 s	6,92 s	7,73	8,93	80
XLIV	$C_{14}H_{12}N_2O_4$	300...301 (decomp.)	8,23	7,82 (d, 8,0)	6,98 (d, 8,0)	3,90 s	2,28 s	7,50	8,63	88

*PMR spectra of compounds (VII), (VIII), (X)-(XVI), (XXXII)-(XXXIV), (XL)-(XLIV) were measured in DMSO-d_6, of compound (XXV) in CF_3COOD, and of the remainder in $CDCl_3$.

**1.13 (t, 7.0); 4.23 (q. 7.0).

hydroxylamine in dry pyridine. However, the reaction occurred with high selectivity and proceeded exclusively to 2-amino-3-(3-isoxazolyl)chromones (XL)-(XLIV) in high yield.

The preparation of these compounds may be the result of sequential recyclization and isomerization proceeding under the influence of hydroxylamine and the organic base.

The structures of the 2-amino-3-isoxazolylchromones (XL)-(XLIV) were confirmed by data of IR, UV, and ^{1}H, ^{13}C, and ^{15}N NMR spectra. The following data indicate the formation of the 2-aminochromones. The compounds obtained do not give the characteristic reaction with ferric chloride. They do not dissolve in 2 N sodium hydroxide solution. The UV absorption spectra of compounds (XL)-(XLIV) are similar to the absorption curves of the corresponding initial chromones (XXIV)-(XXVIII). The position of the peak for the 5-H proton of the chromone ring in the PMR spectra is at 7.7-8.0 ppm (for an isoxazole structure the peak of this proton should fall at higher field). A two-proton singlet (2-NH_2) is present at 8.2-8.7 ppm and disappears on adding heavy water. Absorption bands are present in the IR spectra at 3160-3180, 3270-3330, and 1640-1660 cm^{-1} assigned to the stretching vibrations of the primary amino group and the carbonyl group of the pyrone ring. Signals are observed in the carbon spectra of compounds (XL)-(XLIV) at 157-158 (2-C), 85-87 (3-C), and 172-173 (4-C) ppm corresponding to a 2-aminopyrone ring. In addition the chemical shift (92.2-93.0 ppm relative to NH_3) and the shape of the signals for the nitrogen atom of the 2-NH_2 group in the ^{15}N NMR spectrum are compatible with a 2-aminochromone structure for these compounds. The peak for the nitrogen atom of the amino group was a triplet with $J_{^{15}N,^{1}H} = 90.33$ Hz.

The 7-methoxychromone (XXIV) recyclized readily into the 2-hydroxyphenylpyrazole (XLV) under the influence of hydrazine hydrate. This compound dissolves readily in 5% alkali solution and forms a blue-green chelate with alcoholic ferric chloride solution. This indicates the presence of a free phenolic hydroxyl group in the ortho position to nitrogen in the pyrazole ring. The pyrazole structure for compound (XLV) is indicated by the singlets for the 2-OH and NH groups and also by the shift of 0.9 ppm for the 6-H proton signal towards high field compared with the position of the peak for the 5-H proton in the initial methoxychromone (XXIV).

Pharmacological investigations of the 3-(3-isoxazolyl)chromone derivatives enabled the range of their biological activity to be determined and revealed preparations with antiarrhythmic hypolipidemic, anabolic, and hypoglycemic activity.

EXPERIMENTAL

The purity of the compounds obtained and the course of reactions were checked by TLC on Silufol UV-254 plates. Eluents used were mixtures of benzene and ethanol, chloroform and methanol (9:1), and ethyl acetate for Mannich bases. The NMR spectra for ^{1}H and ^{13}C nuclei were taken on ZKR-60, Bruker WP 100 SY, and Bruker CXP 200 instruments relative to TMS (internal standard), and for ^{15}N nuclei on the Bruker CXP 200 instrument relative to nitromethane (external standard). The IR spectra were determined in KBr disks on a Pye Unicam SP-3-300 and the UV spectra on a Specord UV-Vis spectrometer in alcohol.

Data of elemental analysis for new compounds for N and Br corresponded with calculated values.

2-Hydroxy-α-(3-isoxazolyl)acetophenones (I)-(VI). A stream of dry hydrogen chloride was passed into a solution of 3-cyanomethylisoxazole (0.22 mole) and the appropriate resorcinol (0.24 mole) in boron trifluoride etherate (80 ml) for 10-12 h with stirring and heating to 50°C. The reaction mixture was poured into hot water (0.5 liter) and boiled for 30 min. The precipitated oil solidified on standing. Compounds (I), (II), and (VI) were crystallized from alcohol and (III)-(V) from aqueous alcohol.

7-Hydroxy-3-(3-isoxazolyl)chromones (VII), (VIII), (X)-(XIII). A mixture of the appropriate ketone (I)-(VI) (75 mmole) in ethyl orthoformate (50 ml), pyridine (50 ml), and piperidine (2 ml) was heated for 4 h at 120-130°C. The crystals which precipitated on cooling were filtered off and washed on the filter with cold water. All the compounds were crystallized from alcohol.

5-Hydroxy-3-(3-isoxazolyl)-7-methylchromone (IX) was obtained similarly to the previous chromone by cyclization of the mixture of isomers (II) and (IIA) and was purified by subsequent fractional crystallization from alcohol.

7-Acetoxy-3-(3-isoxazolyl)-2-methylchromone (XVII). A mixture of ketone (I) (4.38 g: 20 mmole), acetic anhydride (11.4 ml: 112 mmole), and triethylamine (1.7 ml: 118 mmole) was heated for 2 h at 110-120°C. The reaction mixture was poured into cold water (250 ml). The solid was filtered off, washed with cold water, and crystallized from benzene.

7-Hydroxy-3-(3-isoxazolyl)-2-methylchromone (XIV). A solution of compound (XVII) (1.45 g: 6 mmole) in alcohol (50 ml) and concentrated hydrochloric acid (0.5 ml) was boiled for 2 h, then diluted with water. The precipitated solid was filtered off and crystallized from aqueous alcohol.

7-Hydroxy-3-(3-isoxazolyl)-2-trifluoromethylchromone (XV). Trifluoroacetic anhydride (2.8 ml: 20 mmole) was added dropwise with cooling to a solution of the ketone (I) (2.19 g: 10 mmole) in the minimum volume of pyridine. After 48 h at room temperature the reaction mixture was poured into water (100 ml). The precipitated solid was filtered off and crystallized from alcohol.

2-Ethoxycarbonyl-7-hydroxy-3-(3-isoxazolyl)chromone (XVI) was obtained analogously to compound (XV) from ketone (I) (10 mmole) and ethoxalyl chloride (20 mmole) and was purified by crystallization from alcohol.

7-Acetoxy-3-(3-isoxazolyl)chromones (XVIII)-(XXIII). Acetic anhydride (5 mmole) was added to a solution of the appropriate 7-hydroxychromone (1 mmole) in the minimum quantity of pyridine and the reaction mixture was left for a day at room temperature. The precipitated solid was filtered off, washed with cold alcohol, and crystallized from benzene.

7-Alkoxy-3-(3-isoxazolyl)chromones (XXIV)-(XXXII). A solution of either dimethyl sulfate (11 mmole), benzyl bromide (20 mmole), or ethyl iodide (15 mmole) (p-bromobenzyl bromide, ethyl bromoacetate) was added dropwise to a hot mixture of the appropriate 7-hydroxychromone (10 mmole) and potassium carbonate (30 mmole) in absolute acetone and boiled for 3-4 h. The hot solution was filtered from the inorganic precipitate, the solvent distilled off, and the desired products were crystallized from alcohol.

8-Bromo-7-hydroxy-3-(3-isoxazolyl)chromone (XXXIII). Bromine (0.8 g: 5 mmole) in glacial acetic acid (10 ml) was added gradually to a solution of chromone (VII) in glacial acetic acid (15 ml) with stirring and heating to 70-80°C. Heating was continued for 4 h. After cooling, the product was filtered off, washed with water and with cold alcohol, and crystallized from alcohol.

6,8-Dibromo-7-hydroxy-3-(3-isoxazolyl)chromone (XXXIV). A solution of bromine (1.6 g: 10 mmole) in glacial acetic acid (10 ml) was added dropwise to a solution of chromone (VII) (1.15 g: 5 mmole) in glacial acetic acid (15 ml) with stirring and heating. The mixture was boiled for 10 h. After cooling, the solid was filtered off and crystallized from alcohol.

(6R)-8-Dimethylaminomethyl-7-hydroxy-3-(3-isoxazolyl)chromones (XXXV)-(XXXVII), 8-Dimethylaminomethyl-7-hydroxy-3-(3-isoxazolyl)-5-methylchromone (XXXVIII), 6-Dimethylaminomethyl-7-hydroxy-3-(3-isoxazolyl)-8-methylchromone (XXXIX). A mixture of the appropriate chromone (5 mmole) and bisdimethylaminomethane (2.5 ml) in dioxan (25 ml) was boiled for 3 h. The dioxan and the excess of amine were distilled off under reduced pressure. All the products were crystallized from alcohol.

6(8)-Alkyl-2-amino-3-(3-isoxazolyl)-7-methoxychromones (XL)-(XLIV). A mixture of the appropriate 7-methoxychromone (XXIV)-(XXVIII) (10 mmole) and hydroxylamine hydrochloride (30 mmole) in dry pyridine was heated at 110-120°C for 1-3 h. The solid, which precipitated on cooling, was filtered off, washed on the filter with water, and crystallized from alcohol.

3-(2-Hydroxy-4-methoxyphenyl)-4-(3-isoxazolyl)pyrazole [(XLV), $C_{13}H_{11}N_3O_3$]. A 2 N solution (12 ml) of hydrazine hydrate in alcohol was added to a solution of chromone (XXIV) (0.49 g: 2 mmole) in alcohol (15 ml) and the reaction mixture boiled for 5-10 min. A yellow color formed which disappeared at the end of the reaction. After diluting the solution with water the solid was filtered off and crystallized from alcohol. Colorless crystals of mp 119-120°C were obtained. PMR spectrum (DMSO-d_6): protons of the phenolic portion at 9.72 (2-OH), 6.58 (3-H), 3.76 (4-OCH_3), 6.47 (5-H), 7.22 (6-H) ppm; protons of the pyrazole at 9.72 (N−H), 7.97 (5-H) ppm; protons of the isoxazole at 6.31 (4-H), 8.70 (5-H) ppm. Yield was 0.49 g (91%).

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