Translated from *Uspekhi Khimii* **58** 812–838 (1989) U.D.C. 547.814.1

Advances in the chemistry of isochroman

E A Markaryan, A G Samodurova
Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan

ABSTRACT. Data on the synthesis and chemical and biological properties of isochroman and its derivatives dating from 1923 (the start of research into this field) until 1985 inclusive are examined and described systematically.

The bibliography includes 235 references.

Contents

I. Introduction 479
II. Methods of synthesis of isochroman and its derivatives 479
III. Chemical properties of isochroman and its derivatives 485
IV. Biological activity of isochroman derivatives 489

I. Introduction

The synthesis of the oxygen-containing heterocyclic isochroman {3,4-dihydro-1*H*-benzo[*c*]pyran} system has been known for a long time but intensive research undertaken to investigate the chemistry of this heterocycle and to seek biologically active compounds (BAC) in the isochroman series date back to the 1970s. The increasing number of publications and patent data during the last 10–15 years indicate the undoubted value of the isochroman ring as the structural basis of a large number of BAC.

The isochroman ring enters into the composition of many substances of natural origin: compounds obtained by the cultivation of micro-organisms,[1] the antibiotic isochroman quinone,[2,3] various metabolites,[4–15] compounds isolated from Oidiodendron rhodogenum,[16] and other substances of plant origin.[17–23] Some of the compounds indicated[1] are of practical value (for example, in the treatment of ulcers and oedemas).

Isochroman derivatives are structural analogues of biogenic amines and derivatives of tetrahydroisoquinoline. In particular, 1-alkylaminoisochromans can be regarded as cyclic analogues of arylalkanolamines incorporating the phenylethylamine fragment in a rigidly fixed structure, which is of definite interest, since it can promote a more specific interaction with a bioreceptor.[24] The analogy between the isochroman and tetrahydroisoquinoline derivatives is determined not only by their structures but also by their interconversions. A series of studies devoted to the conversion of tetrahydroisoquinoline derivatives into isochroman derivatives[25–32] and conversely [33–34] have been published.

Isochroman derivatives, in particular isochromanones, serve in their turn as synthons in the synthesis of nitrogen-containing bicyclic and polycyclic compounds: galanthamine,[35] phthalazones,[36] yohimbine and its derivatives,[37,38] the seleno-analogue of yohimbine,[39] heterocyclic steroids,[40,41] and other compounds.[42–44] Furthermore, isochroman derivatives can be used also for the synthesis of iridoids,[45] analogues of prostaglandin,[46] indole derivatives,[47] tricyclic systems,[48] and dibenzotropolone.[49] Compounds resembling the last one, especially its derivatives involving the carbonyl group, have a pronounced biological activity, which is accounted for by their structural relation with a natural alkaloid–colchicine.

Despite the very considerable interest in isochroman derivatives, they have been scarcely surveyed in the literature (with the exception of a brief review[50]).

The present review surveys the methods of synthesis and the chemical and biological properties of isochroman and its derivative, mainly of synthetic origin, with different positions of the substituents in the benzene and dihydropyran rings. It does not include isochromanone derivatives, which, in view of the extensive nature of the data available, can be the subject of a separate review.

II. Methods of synthesis of isochroman and its derivatives

There are many features in common between the methods of synthesis of isochroman and its derivatives, but, depending on the position of the substituents and the need to employ different starting materials, there are also specific features in the synthetic approach. It is therefore useful to subdivide isochroman derivatives into the following groups: (a) with substituents in the dihydropyran ring; (b) with substituents in the aromatic ring; (c) with substituents in both the dihydropyran and benzene rings.

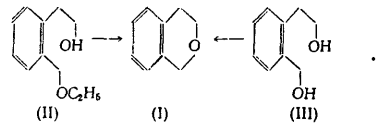
1. Methods of synthesis of isochroman

Isochroman (I) was first synthesised in 1923[51] by heating 2-(2-ethoxymethylphenyl)ethanol (II) with a fourfold excess of fuming hydrobromic acid for 32 h at 100 °C. The homoxylylene dibromide formed simultaneously can be converted into compound (I) by heating with water or a dilute solution of potassium carbamate. The initial alcohol (II) can be obtained by a multistage synthesis. This method is merely of historical interest.

One of the ways of obtaining isochroman involves the cyclisation of 2-(2-hyroxymethylphenyl)ethanol (III), which was obtained from homophthalic anhydride.[52,53] Cyclisation at 45 °C in the presence of potassium bisulphate[52] or on treatment with a mixture of hydrobromic and acetic acids[53] leads to isochroman in 50% yield. In the second case, homoxylylene dibromide is formed together with isochroman.

The most effective method, which ensures an almost quantitative yield of compound (I), involves the direct distillation of the diol (III) at 70 °C and a pressure of 3 mmHg in the presence of catalytic amounts of concentrated sulphuric acid.[54] Isochroman has been synthesised in

80% yield by the reaction of 2-phenylethanol with formaldehyde in the presence of concentrated sulphuric acid:[55]



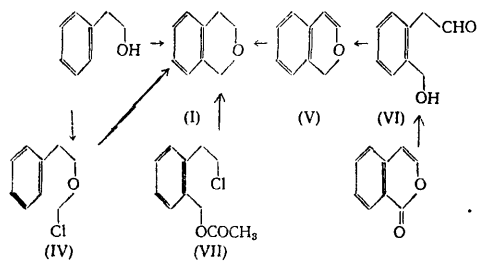
Methods of synthesis of compound (I) based on the chlorometallation of 2-phenylethanol with subsequent cyclisation were developed subsequently. Such a method was first described in 1935.[56,57] Treatment of 2-phenylethanol with paraformaldehyde and hydrogen chloride results in the formation of the chloromethyl derivative, which is then converted into isochroman in 50% yield on treatment with inorganic acids, preferably at 100 °C. Compound (I) with m.p. +3 °C was thus obtained. In 1954, the method was improved and the yield of isochroman reached 90%.[58] The intermediate chlorometallation product was cyclised in this case when the temperature of the reaction mixture rose spontaneously to 45–50 °C without the addition of concentrated hydrochloric acid. Consequently the decrease in the cyclisation temperature leads to an appreciable increase in the yield of compound (I).

Up to 1956, it was assumed that the chlorometallation of 2-phenylethanol results in the formation of 2-(2-chloromethylphenyl)ethanol which subsequently cyclises to isochroman. However, detailed study of the chemistry of this reaction showed[59] that the first stage of the reaction involves the formation of chloromethyl 2-phenylethyl ether (IV), which then cyclises to isochroman. By carrying out the reaction in the temperature range –5–0 °C, it is possible to isolate the intermediate (IV) in 76% yield. The cyclisation product (isochroman) was obtained in 67% yield by heating the ether (IV) with hydrochloric acid at 20–40 °C. The yield of compound (I) increases appreciably (by 30%) when the intermediate (IV) is refluxed in carbon disulphide in the presence of aluminium trichloride.[59] The ether (IV) has been cyclised[60,61] in the presence of alkali or without it, a high yield of compound (I) being ensured in both cases (the yield is 10% higher in the former case than in the latter).

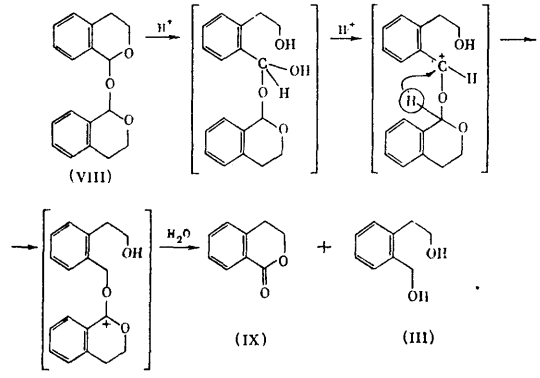
From the standpoint of increasing the yield (to 95%), the synthesis of isochroman from 2-phenylethanol and formaldehyde in the presence of a mixture of hydrochloric acid and phosphorus trichloride also merits attention.[62]

The preparation of isochroman by hydrogenating isochromen (V) in acetic acid in the presence of 10% palladium on charcoal has been described.[63] Isochromen was synthesised from isocoumarin via the hydroxyaldehyde (VI).

Isochroman can be obtained in 70% yield from the acetyl derivative (VII) by treatment with alcoholic alkali:[64]



Isochroman has been isolated after cleaving di-1-isochromanyl ether (VIII) in the presence of sulphuric acid.[65] The ether then disproportionates to the diol (III) and 1-isochromanone (IX):

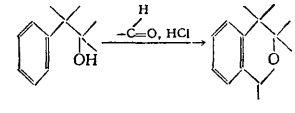


2-(2-Hydroxymethylphenyl)ethanol formed under the reaction conditions readily cyclises to isochroman.

Thus the most effective procedures for the synthesis of isochroman are the methods[58,62] involving the cyclisation of chloromethyl 2-phenylethyl ether in the temperature range 45–50 °C.

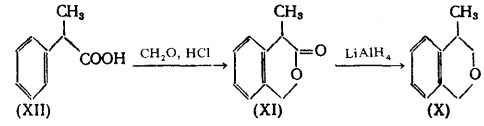
2. Derivatives of isochromans with substituents in the dihydropyran ring

There are several methods of synthesis of isochroman derivatives containing one or several substituents in the 1-, 3-, and 4-positions. One of them is the chloroalkylation of 2-phenylalkanol, analogous to the chloromethylation described in the previous Section:



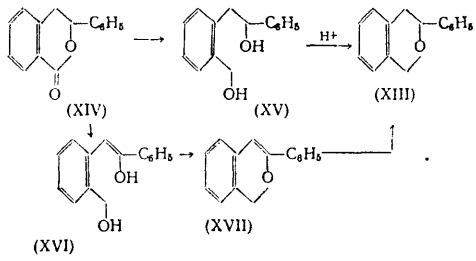
However, chloroalkylation and even more so chloroarylalkylation take place with low yields. 1-Methylisochroman and 1-phenylisochroman have been obtained in this way in 50% yield in the former case and in a yield as low as 7% in the latter case.[60,66]

3-Methylisochroman,[59,67–70] 3-ethyl- and 3-benzyl-isochromans,[68] 4-methylisochroman,[57,67,68] 4-nitroisochroman,[57] and 4,4-dimethylisochroman[71] have been synthesised by the chloromethylation of chain-substituted 2-phenylethanols. 4-Methylisochroman (X) has also been obtained by reducing 4-methyl-3-isochromanone (XI).[66] The latter is formed when hydratropic acid (XII) is chloromethylated:

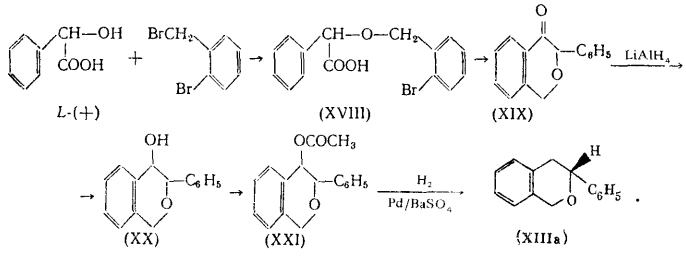


3-Phenylisochromanone (XIII) has been synthesised from 3-phenylisocoumarin (XIV).[52] The reduction of the latter with lithium aluminium hydride (LAH) afforded 2-(2-hydroxymethylphenyl)-1-phenylethanol (XV), which cyclises to compound (XIII) in an acid medium. The reduction of 3-phenylisocoumarin by LAH has been studied in greater detail by a series of investigators. Thus,

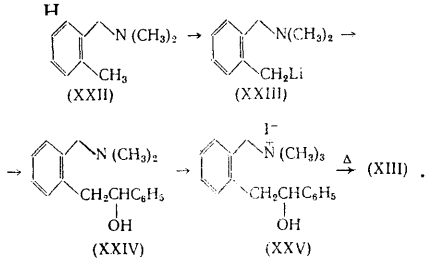
together with the main product, another readily oxidisable compound—the enediol (XVI)—has been obtained.[72] By reducing compound (XIV) at 0 °C, it was possible to isolate compound (XVI) as the main product in 86% yield. The enediol (XVI) cyclises on distillation with formation of 3-phenylisochromen (XVII), which is reduced to compound (XIII) in ethyl acetate by hydrogen in the presence of palladium on charcoal:



A stereoselective synthesis of (*R*)-(+)-3-phenylisochroman (XIIIa) has been achieved with the aid of consecutive reactions: the condensation of L-(+)-mandelic acid with *o*-bromobenzyl bromide; the cyclisation of the carboxyether (XVIII) formed in the presence of butyl-lithium to 3-phenyl-4-isochromanone (XIX); the reduction of the latter with LAH to the corresponding alcohol (XX); the conversion of the alcohol into the acetyl derivative (XXI); the hydrogenation of compound (XXI) to compound (XIIIa):[74]



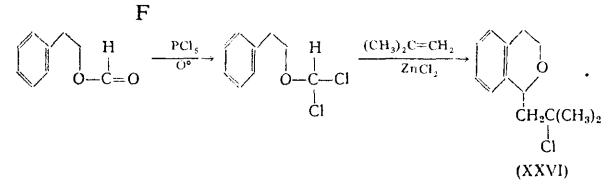
The synthesis of 3-phenylisochroman from dimethyl(*o*-methylbenzyl)amine (XXII) is unusual:[72]



By treating compound (XXII) with n-butyl-lithium, it is possible to obtain the lithio-derivative (XXIII), whose condensation with benzaldehyde affords the aminoalcohol (XXIV). 3-Phenylisochroman is then obtained via a stage involving the formation of the methiodide (XXV) and its subsequent decomposition by heating. 1,3-Diphenyl- and 3,3-diphenyl-isochroman have been obtained similarly.[72] 1,3-Diphenylisochroman has been synthesised by reducing 2,3-diphenylindene ozonide with sodium tetrahydroborate in trifluoroacetic acid.[75] 1,3-Diphenylisochroman has also been isolated as a side product in the reaction of benzaldehyde with benzylmagnesium chloride.[76]

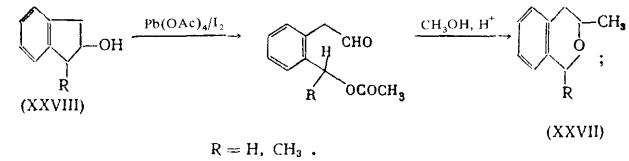
1-Methoxy-4,4-dimethyl-1,3-diphenylisochroman has been obtained by UV irradiation 2-(2-methyl-1-phenylpropenyl)benzophenone in methanol.[77]

It is of interest to note the synthesis of 1-β-chloroisobutylisochroman (XXVI) in accordance with the scheme[78]



The same compound can be obtained from 1-chloroisochroman and isobutene in the presence of a Friedel–Crafts catalyst.[79]

Substituted isochromans (XXVII) have been synthesised from indan derivatives (XXVIII) in accordance with the scheme[80]



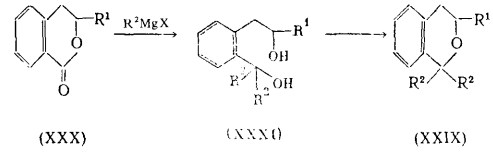
The cyclisation of allyl *o*-bromobenzyl ether on treatment with triethylamine in the presence of palladium acetate and tri-*o*-tolylphosphine leads to a mixture of isomeric derivatives of 2-benzopyran. One of them is 4-methyleneisochroman (XXI).[81]

The photochemical oxidation of 1,1-dimethylindene in methanol results in the formation, together with other products, of 3-hydroxy-1-methoxy-4,4-dimethylisochroman.[82]

The cyclisation of an *o*-polyene-substituted β-phenylethanol in the presence of a Lewis acid, leading to an isochroman derivative with a tetracyclic substituent in the 1-position, has been described.[83] It is notable that the compound cyclised was obtained by multistage synthesis.

Yet another unusual method of synthesis of isochroman derivatives involves the cyclisation of *o*-mercuriobenzyl alcohols with conjugated or non-conjugated dienes in the presence of a palladium catalyst.[84]

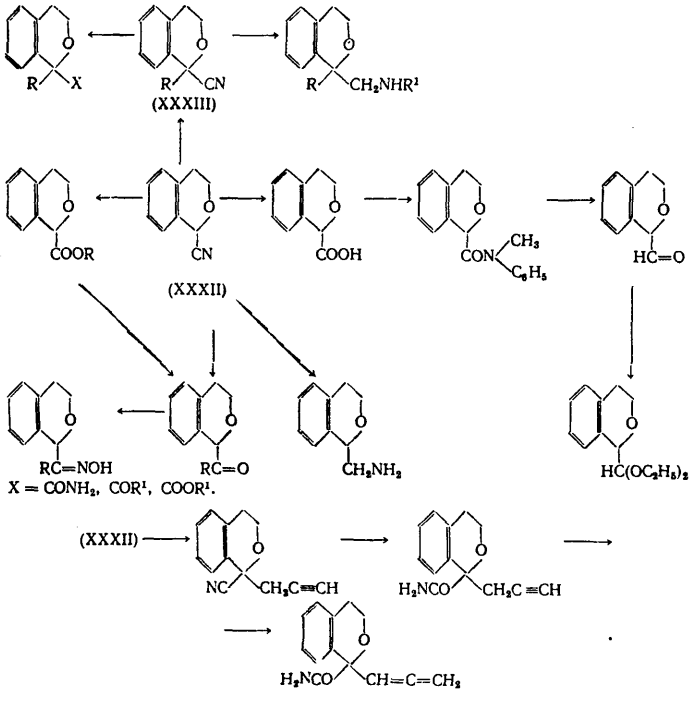
1,1-Disubstituted and 1,1,3-trisubstituted isochroman derivatives (XXIX) have been obtained from substituted 1-isochromanones (dihydroisocoumarins) (XXX).[59,66] Treatment of the lactones (XXX) with a fourfold excess of a Grignard reagent afforded the diols (XXXI). The latter cyclise to the final compounds (XXIX) at 100 °C in the presence of an equimolar amount of phosphoric acid:



The methods of synthesis of 1-monosubstituted and 1,1-disubstituted isochroman derivatives based on the reactivity of the methylene group in the 1-position in isochroman are of great practical value (Scheme 1). Thus 1-halogenoisochromans have been obtained by halogenating isochroman. On reaction with copper cyanide[58] or mercury cyanide,[85] they form 1-cyanoisochroman (XXXII). The latter has been converted into various 1-substituted isochromans: ketones,[85,86] aldehydes,[87] oximes,[24,86] an amine,[24,88,89] a carboxylic acid,[85,88] esters,[86,89] etc. (Scheme 1).

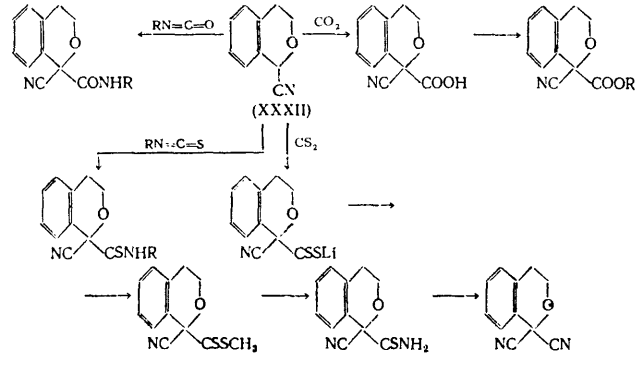
In the presence of strong bases (sodium amide or hydride, organosodium compounds), 1-cyanosiochroman (XXXII) was converted, on treatment with various halides, into a wide variety of 1,1-disubstituted isochromans (XXXIII) by virtue of the high reactivity of the hydrogen in the α-position relative to the nitrile group.[85,90–95] The isochromans (XXXIII) were then subjected to numerous transformations indicated in Scheme 1.

Scheme 1



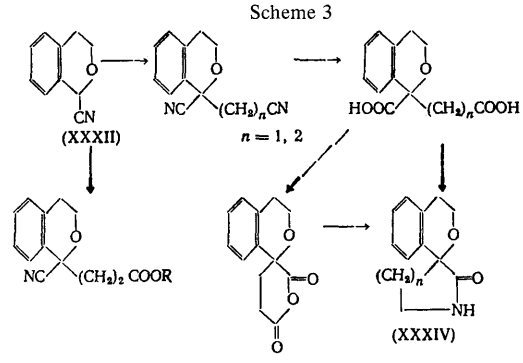
The dithioester, carboxy-, nitrile, and thiocarbamide groups have been introduced in the 1-position of 1-cyanoisochroman in the presence of phenyl-lithium (Scheme 2).[96,97] As in the previous case, certain reactions involving the final compounds obtained were carried out.[96,97]

Scheme 2



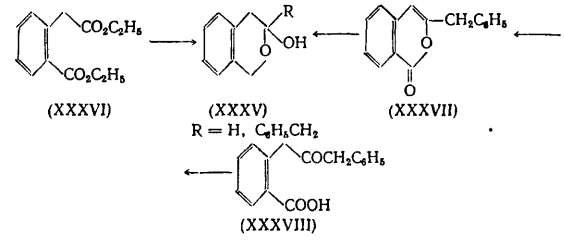
The cyanoethylation of 1-cyanoisochroman has also been achieved.[98,99] It has been shown that condensation takes place best in the presence of tetraethylammonium hydroxide.[99] The series of reactions of the bifunctional isochromans obtained leads to the spirocyclic product (XXXIV, n = 2)[98,99] (Scheme 3). Compounds (XXXIV, n = 1) have been obtained similarly.[91]

Scheme 3

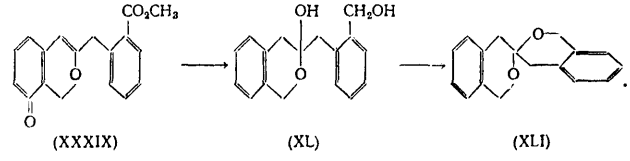


Thus syntheses based on 1-cyanoisochroman lead to extensive possibilities for the preparation of a wide range of varied 1,1-disubstituted isochroman derivatives.

Apart from the compounds with functional-group substituents described above, hydroxyisochromans are also of interest. 3-Hydroxyisochroman (XXXV, R = H) has been synthesised by reducing diethyl homophthalate (XXXVI) with three equivalents of di-isobutylaluminium hydride.[100] 3-Benzyl-3-hydroxyisochroman (XXXV, R = $C_6H_5CH_2$) has been obtained by reducing 3-benzylisocoumarin (XXXVII) with LAH.[73] The isocoumarin (XXXVII) was synthesised by the intramolecular condensation of benzyl 2-carboxybenzyl ketone (XXXVIII) in the presence of acetyl chloride:



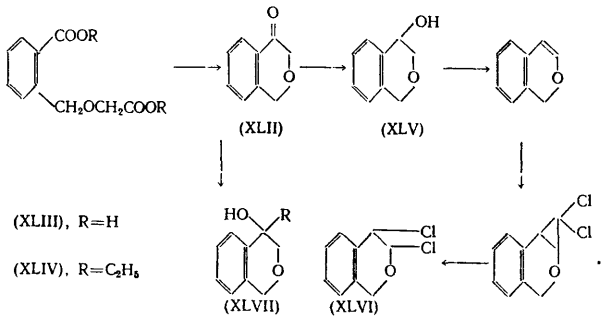
3-Hydroxy-3-(2-hydroxymethylbenzyl)isochroman (XL) has been obtained by reducing 3-(2-methoxycarbonylbenzyl)isocoumarin (XXXIX) with LAH.[101] On treatment with perchloric or sulphuric acid, compound (XL) is converted into the spiroketal (XLI):



The reduction of derivatives of 3,4-dihydroisocoumarin with sodium tetrahydroborate in the presence of boran trifluoride (hydroboration) leads to the elimination of the carbonyl group from the 1-position.[102]

The starting material for the synthesis of 4-hydroxy-derivatives is 4-isochromanone (XLII), obtained in 40% yield both by the Perkin reaction from (2-carboxyphenyl)methoxyacetic acid (XLIII) and via the Dieckman reaction from ethyl (2-ethoxycarbonylphenyl)-methoxyacetate (XLIV). 4-Hydroxyisochroman (XLV) has been obtained by the reduction of the ketone (XLII) with LAH[103,104] and was further converted into dichlorohomoisochroman (XLVI). The

same ketone has been converted into a 4-hydroxy-4-R-substituted isochroman (XLVII) by reaction with a Grignard reagent:[105]



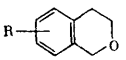
The reaction of DL-glyceraldehyde with benzene in the presence of liquid hydrogen fluoride is of interest. The interaction results in the formation of 1-(1,2-dihydroxyethyl)-3-hydroxymethyl-4-phenylisochroman.[106]

1,1,3,3,4,4-Hexachloroisochroman has been synthesised by treating 3,3,4,4-tetrachloroisocoumarin with phosphorus pentachloride.[107] The isocoumarin derivative was obtained by the reaction of homophthalic acid with the same chlorinating agent.

Thus the most convenient method of synthesis of isochroman derivatives with various substituents in the dihydropyran ring is the chloroalkylation of 2-phenylethanol and its derivatives substituted in the ethyl group. This method makes it possible to introduce substituents into the 1-, 3-, and 4-positions in any combination, usually with satisfactory yields of the substituted isochromans, with the exception of the 1-substituted derivatives. Synthesis based on 1-cyanoisochroman merits attention for the latter.

3. Derivatives of isochroman with substituents in the aromatic ring

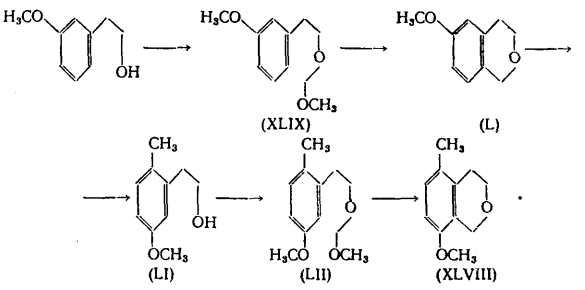
Compounds with substituents in the aromatic ring can be obtained by the chloromethylation reaction using arylethanols:[59,67,108,109]



R = 7-CH_3, 5,8-$(CH_3)_2$, 5,6-benzo, 6,7-$(OCH_3)_2$

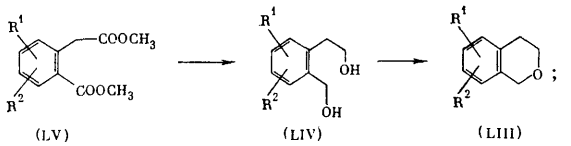
When hydrogen chloride is passed for a long time and also in the presence of an excess of formaldehyde, the chloromethyl group also enters in the *para*-position in the benzene ring relative to the chloromethoxyethyl substituent. 7-Chloromethyl- and 7-chloromethyl-5-methyl-isochromans were obtained respectively in this manner in the synthesis of isochroman and its 5-methyl derivative.[56,110] Various derivatives—the nitrile, the amide, and esters—have been synthesised by further reactions of 7-chloromethylisochroman.[110]

A method has been developed for the synthesis of 5,8-disubstituted derivatives of isochroman (XLVIII).[111] 2-(3-Methoxyphenyl)ethyl methoxymethyl ether (XLIX) has been synthesised by a Williamson reaction. The ether cyclises to 6-methoxyisochroman (L) in the presence of toluene-*p*-sulphonic acid and the isochroman is converted further into 8-methoxy-5-methylisochroman (XLVIII). The methyl group is introduced into the 5-position as a result of consecutive reactions: the degradative reduction of 6-methoxyisochroman in the presence of aluminium hydride, the condensation of 2-(5-methoxy-2-methylphenyl)ethanol (LI) with chloromethyl methyl ether, and the cyclisation of 2-(5-methoxyphenyl-2-methyl)ethyl methoxymethyl ether (LII):



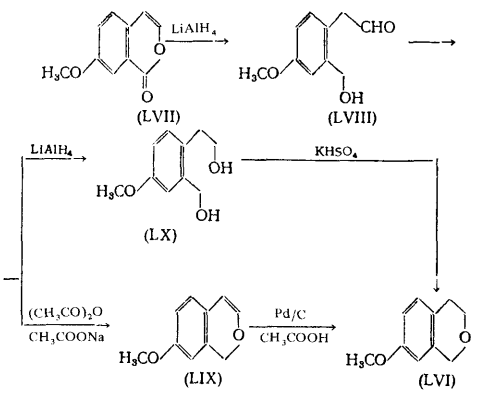
Thus an unusual feature of this method consists in the fact that the methyl group can be introduced into the 5-position in combination with various substituents in the 8-position in the isochroman ring.

A series of methoxy-derivatives of isochroman (LIII) have been synthesised by cyclising the arylethanols (LIV) on treatment with phosphorus pentoxide or potassium bisulphate.[112–116] The arylglycols (LIV) have been synthesised by reducing the diesters (LV):



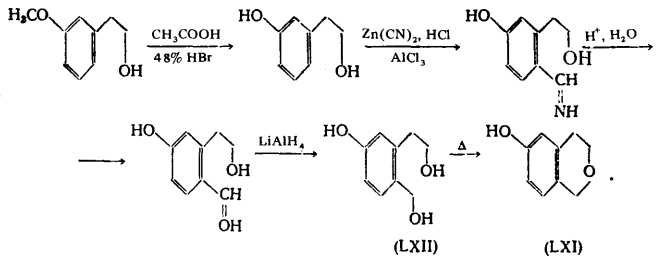
R^1=H, 5-OCH_3; 6-OCH_3;
R^2=H, 6-OCH_3, 7-CH_3, 7-OCH_3, 7-$OCH_2C_6H_5$; R^1R^2=6,7-OCH_2O.

7-Methoxyisochroman (LVI) has also been obtained as in the scheme[117]



(2-Hydroxymethyl-4-methoxyphenyl)acetaldehyde (LVIII) has been obtained by reducing 7-methoxyisocoumarin (LVII) with LAH. The acetaldehyde was converted into 7-methoxyisochroman (LVI) via two pathways: dehydration to 6-methoxyisochromene (LIX) and the catalytic hydrogenation of the latter or its reduction to the diol (LX) and then dehydration with ring closure. Both versions of the synthesis are of interest from the standpoint of the isolation of the intermediates (LVIII) and (LIX). On the other hand, in order to obtain the target product, it might be possible to reduce 7-methoxyisocoumarin immediately to the diol (LX) with its subsequent dehydration.

The hydroxy-derivative—6-hydroxyisochroman (LXI)—has been synthesised via the diol (LVII) using the Gatterman formulation:[118]

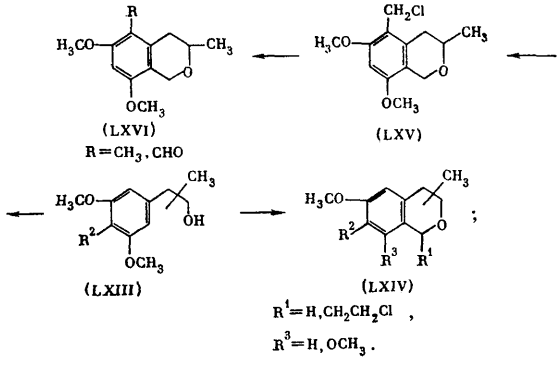


The above methods of synthesis of methoxy- and hydroxy-derivatives reduce mainly to the preparation of the substituted diols (LIV), (LX), and (LXII) with their subsequent cyclisation, described above for the synthesis of the unsubstituted derivative.

4. Derivatives of isochroman with substituents in the aromatic and dihydropyran rings

In order to obtain isochroman derivatives with substituents in both rings, the same cyclisation reactions are used as for the synthesis of the previous structures and sometimes the problem reduces to the preparation of the corresponding initial arylalkanols.

6,7,8-Trimethoxy-3-methyl- and 6,8-dimethoxy-3-methyl-isochromans (LXIV) have been obtained by the chloromethylation of 2-(3,4,5-trimethoxyphenyl)-1-methyl- and 2-(3,5-dimethoxyphenyl)-1-methyl-ethanols (LXIII).[119,120] Compound (LXIV) was synthesised in a low yield because of partial polymerisation of the phenol-formaldehyde type. A higher yield is obtained in the chloro-methylation of the arylalkanol (LXIII, $R^2 = H$) by monochloromethyl methyl ether in the presence of zinc chloride. The chloromethyl derivative (LXV) is formed for a specific ratio of the ether and zinc chloride and is subsequently converted into compound (LXVI):

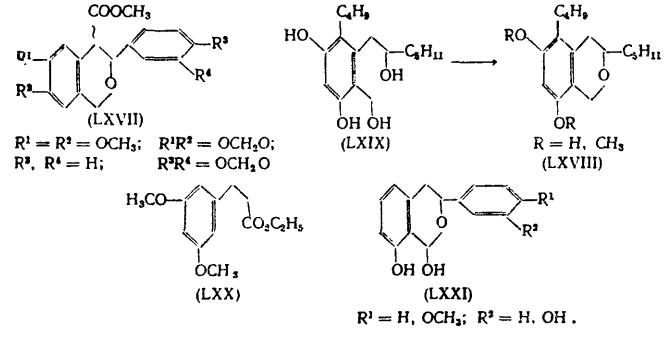


2-(3,4-Dimethoxyphenyl)-2-methylethanol has been condensed with chloroacetal in the presence of boron trifluoride to form 1-(2-chloroethyl)-6,7-dimethoxy-4-methylisochroman (LXIV, R^1 = CH_2CH_2Cl, R^2 = OCH_3, R^3 = H) and its stereochemistry has been investigated.[121]

The diastereoisomeric isochromans (LXVII) have been obtained from the methyl esters of *erythro*- and *threo*-2,3-diaryl-3-hydroxy-propionic acids and formaldehyde in methanol in the presence of sulphuric acids.[122]

The method of synthesis of (±)-5-butyl-6,8-dihydroxy-3-pentylisochromans (LXVIII) is based on the cyclisation of compound (LXIX). The latter has been obtained by multistage synthesis from ethyl β-(3,5-dimethoxyphenyl)propionate (LXX).[123]

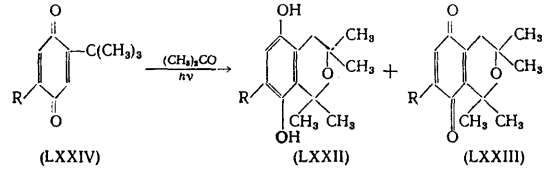
8-Hydroxy-4,4,7-trimethyl-1,3-diphenylisochroman has been obtained by the stepwise aromatisation of 4a-chloro-4,4,7-trimethyl-1,3-diphenyl-4a,5,6,7,8,8a-hexahydroisochroman-8-one. The latter was synthesised by condensing limonenone with benzaldehyde.[124,125] 8-Hydroxy-4,5,6,7-tetramethylisochroman has been obtained by reducing sclerin—8-hydroxy-4,5,6,7-tetramethylchroman-1,3-dione:[10]



Among hydroxy-derivatives, 3-aryl-1,8-dihydroxyisochromans (LXXI), obtained by reducing 8-hydroxyisocoumarins by complex hydrides, are also known.[126]

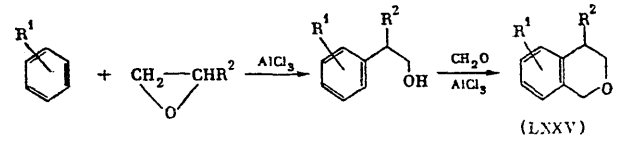
4-Hydroxyisochromans have been obtained from 4-isochromanone derivatives both by reduction[127] and by the Reformatskii reaction.[128]

The formation of the isochroman derivatives (LXII) and (LXIII) in the photolysis of the quinone (LXIV) in acetone[129] (other compounds are obtained as well) is of interest from the chemical standpoint:



The methods of synthesis of isochroman derivatives based on the cyclisation of *o*-alkenylbenzyl alcohols[130,131] and the catalytic reduction of indene ozonides[132] are distinguished by unusual features.

One of the common methods of synthesis of isochroman derivatives (LXXV) with substituents in the aromatic and dihydropyran rings involves the condensation of an arylalkanol with formaldehyde in the presence of aluminium chloride.[133,134] Arylalkanols can be synthesised in different ways. Thus they have been obtained[133,134] by the reaction of arenes with epoxyalkanes in the presence of aluminium chloride. Compounds (LXXV) have also been obtained by hydroxymethylation and cyclisation in the presence of a mixture of hydrochloric acid and phosphorus trichloride:[62]



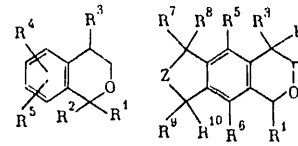
A number of investigators[135–141] have synthesised 1,1,6,7-tetrasubstituted isochromans (LXXVI) by condensing an arylethanol with carbonyl compounds (ketones, aldehydes or their acetals,

ketoacids). A solution of 3% trichloroacetic acid, toluene-*p*-sulphonic acid, and hydrogen chloride has been used as the initial catalyst.

A similar condensation has been used to synthesise 1-substituted and 1,4-disubstituted isochroman derivatives (LXXVI) with different positions of substituents in the aromatic ring (including also condensed fragments in the 6,7-positions) in the presence of polyphosphoric acid or toluene-*p*-sulphonic acid.[142–145] It is notable that the above condensation yielded tricyclic isochromans (LXXVII) which can be used in the perfume industry.[146–149] The similar compounds (LXXVIII), obtained by the reaction of isochroman derivatives with dichloroalkanes in the presence of aluminium chloride,[150] have the same properties. 1-Alkoxyalkylisochromans (LXXIX) and (LXXX), with a wide variety of substituents in different positions in both the aromatic and dihydropyran ring, are also known.[151–153] The above compounds are intermediates in the synthesis of hypotensive and psychotropic preparations.

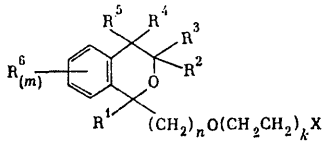
A series of isochroman derivatives (LXXXI)–(LXXXIII) have been obtained by condensing the corresponding arylalkanols with ketones or ketoacids.[154–157]

The hydrogenolysis of wood results in the formation of 1-ethyl-6-hydroxy-4-(4-hydroxy-3-methoxybenzyl)-7-methoxyisochroman.[158,159] Catalytic reduction of the *Chrysodin* metabolite yielded 3-hexyl-6,8-dihydroxy-7-methylisochroman:[160]

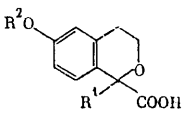


(LXXVI)

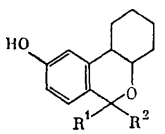
(LXXVII), $R^1=R^2=R^3=R^5=R^6=H$; R^4, R^7-R^{10} = Alk; $Z=CHR^{11}$, $R^{11}=H, CH_3$;
(LXXVIII), R^1-R^{10} = Alk; $Z=CH_2, CHCH_3, (CH_2)_2, CH_2CHCH_3$.



(LXXIX), X = OH;
(LXXX), X = Cl .



(LXXXI), R^1, R^2 = Alk;
(LXXXII), R^1 = Alk; R^2 = H .



(LXXXIII)

R^1, R^2 = Alk, Ar, alkoxycarbonyl; $R^1 + R^2$ = carbocycle .

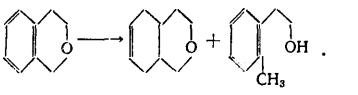
Thus isochroman derivatives with substituents in both the aromatic and dihydropyran rings can be obtained by the cyclocondensation of arylalkanols with various carbonyl compounds in the presence of both protic acids and Lewis acids. The variation of the substituents in the 1-position depends on the type of the carbonyl-containing component. It is notable that preference should be given to methods based on the application of polyphosphoric or toluene-*p*-sulphonic acid. When aluminium chloride is used as the catalyst, it is essential to take certain precautions, since the decomposition of the complexes formed is accompanied by the vigorous evolution of hydrogen chloride.

III. Chemical properties of isochroman and its derivatives

1. Hydrogenation

The catalytic hydrogenation of isochroman and its derivatives can involve hydrogenolysis accompanied by the opening of the cyclic ether as well as the reduction of the benzene ring. It is notable that the hydrogenolysis of isochroman derivatives is of practical value, especially in the perfume industry.[161–164]

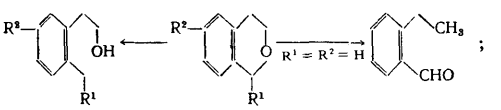
In the catalytic hydrogenation of isochroman in the presence of the Raney nickel catalyst at 200 °C and a pressure of 150 atm, the hydrogenolysis product 2-(2-tolyl)-ethanol was isolated in addition to the normal reduction product—tetrahydroisochroman:[58]



Other fractions have been isolated after distillation through a column as a result of a similar reaction but at normal pressure: (1) *cis*- and *trans*-1,2-dimethylcyclohexanes, 1,2-dimethylbenzene, and 2-ethyl-1-methylbenzene; (2) *trans*-hexahydroisochroman; (3) *cis*-hexahydroisochroman; (4) an unidentified high-boiling fraction.[165]

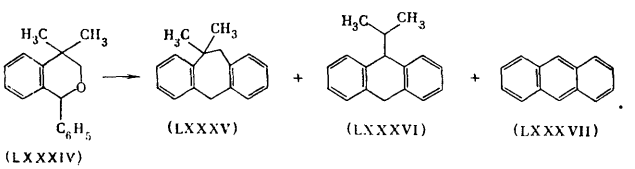
It is of interest that the tetrahydro- and hexahydro-derivatives of isochroman are obtained by special methods, involving the Dieckmann, Robinson, etc. cyclocondensation reactions, and not by the hydrogenation of the corresponding isochromans.[166–168]

Treatment of isochroman with hydrogen in the presence of Raney nickel at room temperature for 10 min affords a rearrangement product—2-ethylbenzaldehyde.[58] The catalytic reduction of 1-alkyl- or 1-aryl-isochromans in the presence of the Raney nickel catalyst at 200 °C and a pressure of 200 atm leads to ring opening with formation of 2-arylethanols.[58] The reduction of the benzene ring is not then observed. The substituent in the 1-position evidently increases the resistance of the aromatic ring to hydrogenation. Reduction with the opening of the dihydropyran ring occurs when 6-methoxyisochroman interacts with aluminium hydride:[111]



R^1 = H, Alk, Ar; R^2 = H, OCH_3 .

The reduction of 4,4-dimethyl-1-phenylisochroman (LXXXIV) by hydriodic acid in the presence of red phosphorus is of interest from the chemical point of view.[169] The reaction results in a rearrangement with the opening of the heterocycle, which leads to the formation of three tricyclic compounds—10,10-dimethyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (LXXXV), 9-isopropyl-9,10-dihydroanthracene (LXXXVI), and anthracene (LXXXVII):

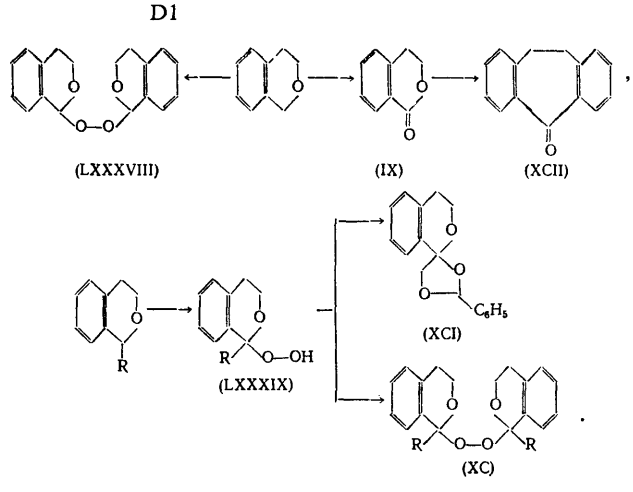


(LXXXIV) (LXXXV) (LXXXVI) (LXXXVII)

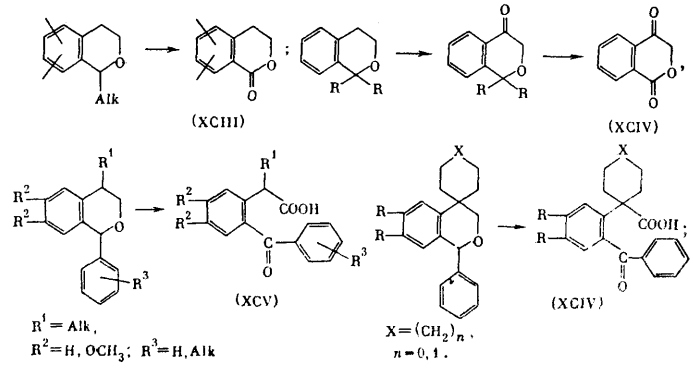
2. Oxidation

When isochroman is allowed to stand in air for several days at room temperature, the crystalline 1-isochromanyl peroxide (LXXXVIII) is formed, decomposing at 78 °C (2 mmHg).[52] It is possible to isolate the diastereoisomers of the peroxide (the *meso*-isomer and the racemate) from isochroman by allowing it to stand in the light for a month.[170] When isochroman and its 1-substituted derivative are oxidised by atmospheric oxygen at room temperature and under UV irradiation, the corresponding hydroperoxides (LXXXIX) are formed.[61,170] On treatment with dilute inorganic acids, the latter are readily converted into the symmetrical peroxides (XC). On interaction with benzaldehyde in the presence of potassium hydroxide, the hydroperoxide (LXXXIX, R = CH_3) affords 2-phenylspiro[1,3-dioxolan-4,1′-isochroman] (XCI).

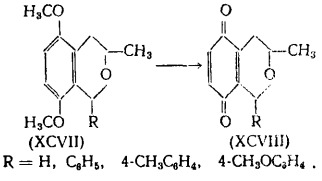
The oxidation of isochroman by nitric acid leads to 1-isochromanone (3,4-dihydroisocoumarin).[66,171] It is of interest to note the formation of the tricyclic system 10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclopentan-5-one (XCII) from the latter when it is involved in a Friedel–Crafts reaction in the presence of aluminium chloride in benzene:[171]



Isochroman and its derivatives with the substituents in both the aromatic and dihydropyran rings have been oxidised by chromium trioxide, selenium dioxide, hydrogen peroxide, pyridinium chlorochromate, and sodium hypochlorite.[58,59,67,112–114,172–177] It has been shown that the oxidation takes place in the 1-position with formation of the dihydroisocoumarins (XCIII). On the other hand, if the 1-position is occupied by two alkyl substituents, then the oxidation takes place in the 4-position and more prolonged oxidation leads to the ketolactone (XCIV).[172] It is of interest to note the influence of allyl groups in the 1-position in isochroman on the oxidation process. In this case the reaction is accompanied by the opening of the dihydropyran ring and leads to (2-benzoylphenyl)acetic acid (XCV, $R^2 = R^3 = H$)[172] and its derivatives (XCV, $R^2 = OCH_3$, R^3 = Alk)[178] or (XCVI):[179]



The anodic oxidation of isochroman in the presence of *N*-hydroxyphthalimide is also directed to the 1-position.[180] The electrochemical oxidation of 6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isochroman leads to a tetracyclic system containing in its structure the oxidised isochroman ring and to 1-(2-hydroxy-4,5-dimethoxybenzyl)-6,7-dimethoxyisochroman (oxidation of the aryl component of the side chain).[181] The oxidation of isochroman under UV irradiation in the presence of iron(III) chloride in the acetone–water mixture is notable. This entails the formation of 9% of 3,4-dihydroisocoumarin and 23% of β-(*o*-carboxyphenyl)ethanol.[182] The oxidative demethylation of 5,8-dimethoxyisochromans (XCVII) by silver oxide leads to the formation of the quinonoid structure (XCVIII):[138]



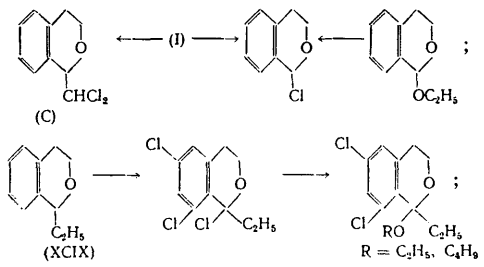
Thus the oxidation of isochroman and its derivatives is directed mainly to the 1-position. In addition, in certain cases the oxidation is accompanied, like the reduction, by the opening of the dihydropyran ring.

3. Halogenation

Both molecular halogens and bromosuccinimide are used for the halogenation of isochroman and its derivatives. It has been established that the halogenation proceeds preferentially in the 1-position, since this is most reactive. 1-Chloroisochroman was first obtained by chlorinating isochroman at −5 °C.[58] The same product has been synthesised in 60–80% yield by the reaction of 1-ethoxyisochroman with acetyl chloride.[60,61,183] The chlorination of 1-ethylisochroman (XCIX) at 0 °C is directed to the 1-, 6-, and 8-positions in the isochroman ring.[66,84] On treatment with an alkoxide, only the chlorine atom in the 1-position is substituted by the alkoxy-group.

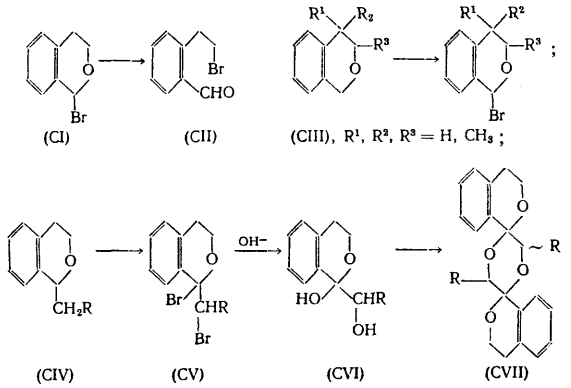
Isochroman is capable of being converted into 1-dichloromethylisochroman (C) on treatment with chloroform in an alkaline

medium in the presence of benzyltriethylammonium chloride by combining with dichlorocarbene:[87]

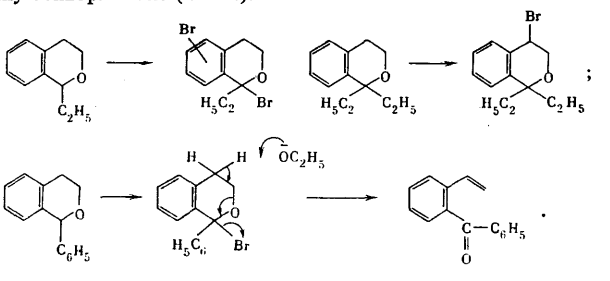


1-Bromoisochroman (CI) has been obtained by brominating isochroman in benzene or carbon tetrachloride under UV irradiation.[58,60,61,71,89] As a cyclic analogue of α-halogenoethers, this bromo-derivative rearranges to its structural isomer *o*-(β-bromoethyl)benzaldehyde (CII)[60,185] as a result of its high reactivity.[184] Isochromans substituted in the 3- or 4-position [compounds (CIII)] are also brominated in the 1-position under the same conditions.[70,71,90]

The bromination of 1-alkyl- and 1-benzyl-isochromans (CIV) does not stop at the stage involving the formation of the monobromo-derivative but leads to products of the substitution of the side chain, for example, the dibromo-derivatives (CV). The latter have been converted into the diols (CVI), which cyclise to the *cis,trans*-isomeric spirocyclic derivatives (CVII) in an acid medium:[61]

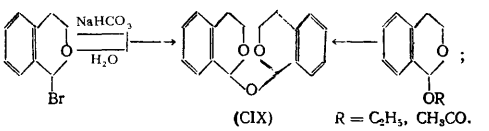


The bromination of isochroman and its 1-substituted-derivatives by *N*-bromosuccinimide has been investigated. It has been shown that, whereas isochroman is converted into 1-bromoisochroman,[58,84] its 1-ethyl derivative is brominated both in the 1-position and in the aromatic ring.[84] Furthermore, if the 1-position in isochroman is occupied by two alkyl groups, then bromination takes place in the 4-position.[84] The bromination of 1-phenylisochroman by *N*-bromosuccinimide in the presence of sodium ethoxide leads to 2-vinylbenzophenone (CVIII):[68]

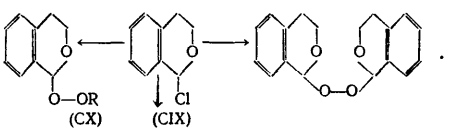


4. Certain substitution reactions of isochroman derivatives

Although 1-chloro- and 1-bromo-isochromans rearrange under certain conditions to structural isomers,[60] nevertheless, they are of special interest from the standpoint of their conversion into a wide variety of isochroman derivatives. Thus, when 1-bromoisochroman is treated with a solution of sodium bicarbonate or simply with water, di-1-isochromanyl ether (CIX) is obtained.[60] The latter is also formed from 1-ethoxy- or 1-acetoxy-isochroman in quantitative yield when they are allowed to stand in air:[40]

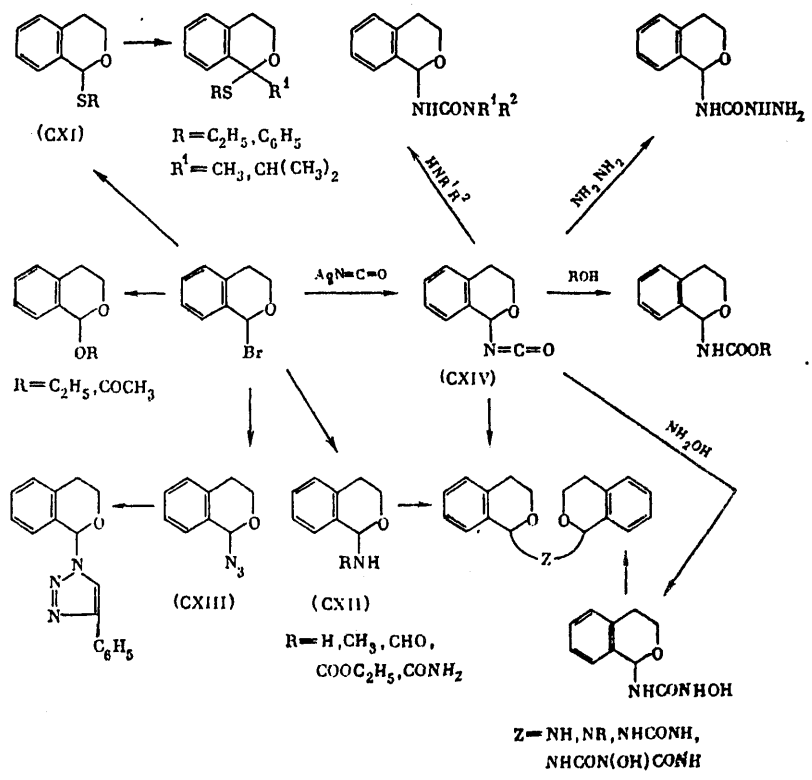


On treatment with water, 1-chloroisochroman behaves similarly to 1-bromoisochroman, forming di-1-isochromanyl ether.[58] 1-Chloroisochroman has been condensed with hydroperoxides with formation of the corresponding peroxides (CX) (yield 80–85%).[183] 1-Isochromanyl peroxide is obtained by treating 1-chloroisochroman with 30% hydrogen peroxide.[186] 1-Isochromanyl hydroperoxide is formed on treatment with 5.3% hydrogen peroxide:



The reactions of 1-halogenoisochromans with cyanide are described in Section II. We shall only note the formation of 1-cyano-4,4-R_2-substituted isochromans from the corresponding 1-bromo-4,4-R_2 derivatives and mercury(II) cyanide.[90] Compounds having different substituents in the 1-position have been synthesised in satisfactory yields by the reaction of a Grignard reagent and 1-halogenoisochroman as well as its 4,4-disubstituted derivatives.[58,60,61,66,165] Such 1-substituted isochroman derivatives are obtained in low yields on chloroalkylation of phenylalkanols. 1-Ethoxy- and 1-acetoxy-isochromans have been obtained by the reaction of 1-bromoisochroman with sodium ethoxide and potassium acetate.[58] 1-Acetoxyisochroman has been converted into 1-cyanoisochroman on treatment with trimethylsilyl cyanide in the presence of a Lewis acid.[187] 1-Ethoxyisochroman can be obtained also by treating 1-bromoisochroman with ethanol.[60] 1-Alkylthioisochromans (CXI) have also been obtained by an analogous procedure. They were then converted into 1,1-disubstituted isochromans.[188]

Scheme 4

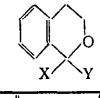


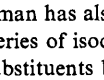
A series of nitrogen-containing compounds has been obtained from 1-bromoisochroman. Thus treatment of the latter with amines, aminoalcohols, amides, sodium azide, and silver isocyanate yielded the corresponding derivatives (CXII)–(XCIV).[189,190] These compounds were subjected to a series of transformations, which are illustrated in Scheme 4.

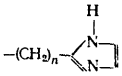
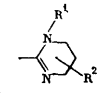
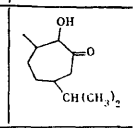
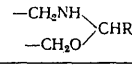
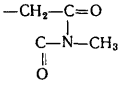
Isochroman derivatives containing substituents such as the alkoxy-, acyl-, acyloxy-, etc. groups in the 1-position are also capable of undergoing nucleophilic substitution reactions. The interaction of 1-ethoxyisochroman with sodium bisulphite, acetic anhydride,[60] aromatic and aliphatic alcohols,[191] nitrogen-containing compounds–amides, thioamides, sulphonamides, urea, thiourea,[192] and amines (aromatic, aliphatic, heterocyclic),[30,192] as well as benzoxazoline-2-thione has been achieved.[193] The final reaction products (CXVa–d), (CXVI), and (CXVIIa–c) are presented in Scheme 5.[33,191–193] It is notable that the reaction of 1-ethoxyisochroman with alcohols and amines takes place in different ways depending on their structure (type).

1-Ethoxyisochroman has also been used as the starting material for the synthesis of a series of isochroman derivatives (CXVIII) with functional group substituents by reaction with compounds having active methylene groups: diethyl malonate, α-tetralone, acetylacetone, malononitrile, and acetoacetic ester.[191,194] It is notable that the isochroman derivatives [CXVIII, XY = $(COOC_2H_5)_2$ or CHXY = 2-oxocyclohexyl] are converted into naphthalene or anthracene derivatives in the presence of alkali metal alkoxides.[194]

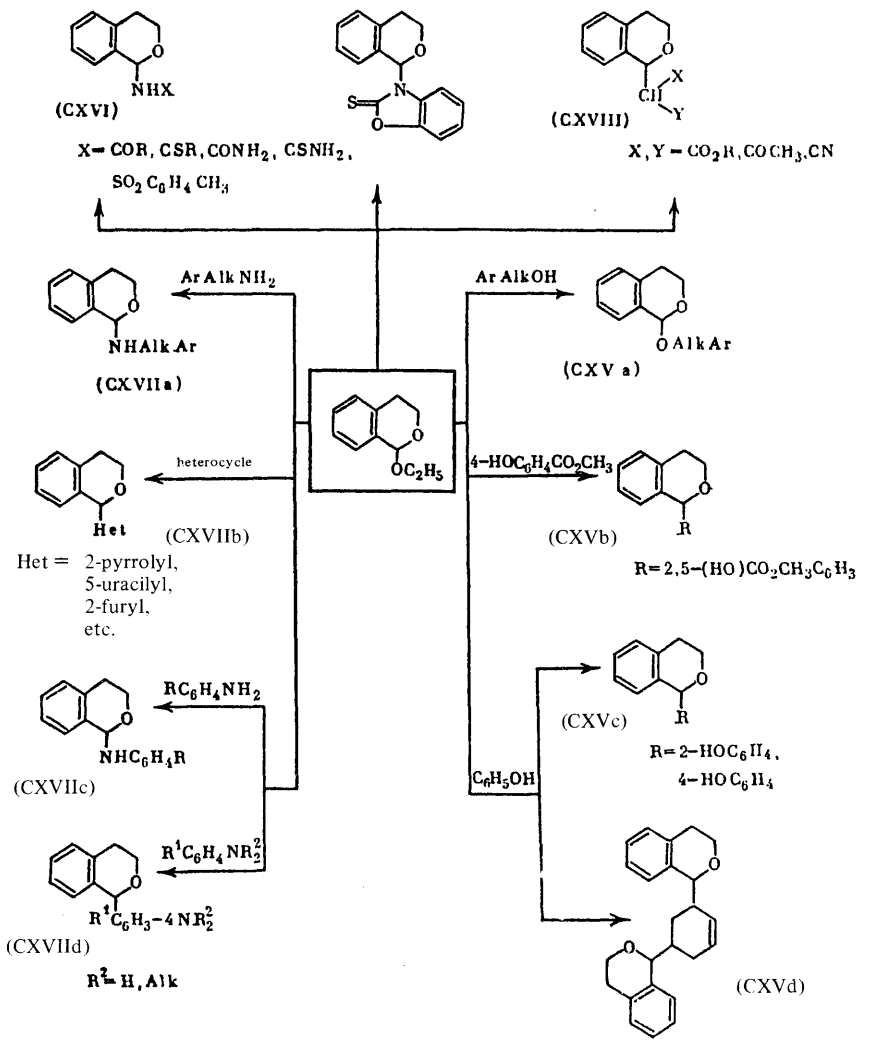
Table 1. Compounds (CXIX)–(CXXXI).



Compound	X	Y
(CXIX)	CH_2NHR (R=H, Alk)	H
(CXX)	$(CH_2)_nNHR$ (R=Ar, Alk, n=1,2)	H
(CXXI)	R^1CHNHR^2 (R^1=Alk, R^2=ArAlk)	H
(CXXII)	$CH_2NH(CH_2)_nNR_2$ (R=H, Alk, $C_6H_5CH_2$), 1-isochromanyl-methyl; NR_2=Het; n=2÷8)	H
(CXXIII)	 (Z=CH, N; R=H, Alk, allyl, Ar, ArAlk)	H
(CXXIV)	$(CH_2)_3NHR$ (R=H, CH_3)	C_6H_5
(CXXV)	$(CH_2)_nNR_2$ (R=C_2H_5; NR_2=Het; n=1,2)	CN

Compound	X	Y
(CXXVI)	$CH_2NHCOCH{=}CMe_2$	$(CH_2)_2N(C_2H_5)_2$
(CXXVII)	$COCH_3$	$(CH_2)_2N(C_2H_5)_2$
(CXXVIII)	R	
	H	
(CXXXI)	H	
X+Y		
(CXXIX)		(R=H, CH_3)
(CXXX)		

Scheme 5



IV. Biological activity of isochroman derivatives

Isochroman derivatives containing amino-groups in the dihydropyran ring have been most thoroughly investigated from the pharmacological point of view, since these compounds are in fact "rigidly fixed" analogues of arylalkylamines. They are all characterised by a broad spectrum of biological activity: antidepressant, diuretic, psychotropic, antiinflammatory, vasodilating, etc..

The study of the influence of 1-methyl aminoisochromans (CXIX) [compounds (CXIX)–(CXXXI) are presented in Table 1] on the cardiovascular system[24] showed that compound (CXIX, R = H) exhibits a hypertensive activity. The corresponding *N*-methyl analogue (CXIX, R = CH_3) possesses considerable adrenoblocking properties, while 1-*N*-ethylamino- and 1-*N*-isopropylaminomethylisochromans (CXIX, R = C_2H_5 or iso-C_3H_7) possess a weak hypotensive activity. According to the results of some workers who have investigated the effect of phenylethylamines on adrenoreceptors, the replacement of the hydrogen at the nitrogen atom in 2-phenylethylamines by higher alkyl groups leads to a transition from adrenomimetic to adrenolytic properties. Although the analogous isochroman derivatives exhibit a weak activity, they give rise to the same pattern. On the other hand, the replacement of the hydrogen atom at the nitrogen atom of 1-aminomethylisochroman by arylalkyl groups as well as the introduction of an additional methylene group between the nitrogen atom and the isochroman ring lead to compounds (CXX), which possess some sympatholytic and adrenolytic activity and exert an effect on the central nervous system (CNS).[195] This activity persists also in 1-aminoalkylisochromans (CXXI) containing an alkyl substituent at the carbon atom linked to the isochroman ring.[196] Many compounds (CXXII) in which two 1-aminomethylisochroman fragments or a 1-aminomethylisochroman fragment and another basic residue are separated by different numbers of methylene groups have been synthesised.[197,198] It has been established that they all exhibit cholinolytic activity, while compounds (CXXII, n = 8) exert a pronounced blocking action on sympathetic nerve fibres and adrenoreceptors.[198] 1-Piperidino- and 1-piperazinoisochromans (CXXIII) have antihistamine properties.[199,200]

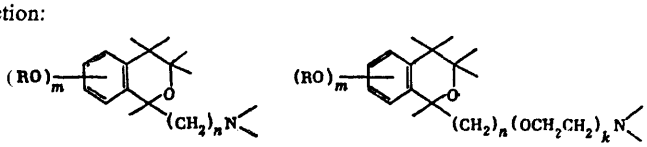
It is of interest to note that the simultaneous introduction of the phenyl and aminopropyl groups in the 1-position, as in compounds (CXXIV), leads to substances with a pronounced adrenomimetic effect, which can be used in psychotherapy, particularly in the treatment of endogenic depression.[200–202] The pharmacological properties also of other 1,1-disubstituted isochromans derivatives have been investigated. Thus 1-cyano-1-morpholinomethylisochroman [CXXV, $NR_2 = N(CH_2)_4O$, $n = 1$] exhibits a spasmolytic activity, while 1-cyano-1-(2-diethylaminoethyl)- and 1-cyano1-(2-piperidinoethyl)-isochromans [CXXV, $NR_2 = N(C_2H_5)_2$ or $N(CH_2)_5$, $n = 2$] exhibit an anti-cough effect whilst lacking spasmolytic activity.[94] In a dose of 2 mg kg^{-1}, the latter compound showed the same effect as the familiar drug Silomat in a dose of 5 mg kg^{-1}.[89] The diamino-derivative, namely 1-(β-diethylaminoethyl)-1-[*N*-(β-methylcrotonyl)amino-methyl]isochroman (CXXVI), is a muscle relaxant.[89]

1-Acetyl-1-(2-diethylaminoethyl)isochroman (CXXVII) exhibits a spasmolytic activity of the papaverine type and on an isolated intestine manifests an activity equal to that of papaverine in strength.[89]

The isochroman derivatives (CXXVIII), having nitrogen-containing cyclic fragments (imidazolylalkyl, tetrahydropyrimidyl) in the 1-position, are pesticides in large doses, while in small doses they exhibit a depressing effect on the CNS.[185] These compounds eliminate the convulsions induced by an electric shock more effectively than does hexobarbital and are corazole antagonists. They also show a local anti-inflammatory effect in the carrageenin oedema. Biological activity has also been discovered in a series of spiro-derivatives of isochroman. Spirooxazineisochromans (CXXIX) exhibit a psychotropic activity,[203] while 1-methyl-2,5-dioxopyrrolidine-3-spiro-1′-isochroman (CXXX) manifests a pronounced anti-inflammatory effect.[91]

In order to investigate the antitumour properties of 1-isochromanyl hydroperoxide, the latter was synthesised but did not exhibit a pronounced activity.[204] A compound of the isochroman series, namely 3-(1-isochromanyl)-6-isopropyltropolone (CXXXI),[205] showing an appreciable antitumour activity is known.[206] The introduction of substituents of different kinds (aryl, heteroaryl) in the 1-position in isochroman lowers appreciably the above activity.[207]

Further expansion of the research into biologically active isochroman derivatives has consisted in the simultaneous introduction of the amino-fragment in the 1-position and of hydroxy- or different alkoxy-groups in the aromatic ring of isochroman. Thus numerous 1-(aminoalkyl) derivatives of isochroman (CXXXII) have been patented.[141,208–217] Alkyl, arylalkyl, and heteroaryl groups are used as substituents at the nitrogen atom. In particular, many compounds containing substituted piperazine fragments have been described. The biological activity spectrum is extremely broad: anti-depressant, anticonvulsive, hypotensive, anti-inflammatory, analgesic, vasodilating, myorelaxing, anticoagulation, and other activities. Compounds (CXXXIII) are also of interest;[218,219] the presence of the poly(ethylene oxide) chain in them did not affect the selectivity of their action:



(CXXXII) (CXXXIII)

$m, n, k = 1–3$.

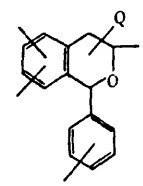
The biological properties of the isochroman derivatives (CXXXIV) and (CXXXV) containing a basic fragment in the 3- and 4-positions have also been investigated. Among them, 1-arylisochromans (CXXXIV) with the aminoalkylene chain in the 3-position, for example, can be used in the treatment of disturbances of the activity of the CNS: in particular, they exhibit anticonvulsant, anti-depressant, and appetite-depressant activities.[220,221] The most active compound—3-(*N*-methylaminomethyl)- and 3-(*NN*-dimethyl-aminomethyl)-1-phenylisochromans—exhibit a more pronounced activity than the familiar appetite depressant (d)-amphetamine. Furthermore, they are free from the disadvantages of the latter—the excitation of the CNS.[222] The introduction of a fluorine atom both in the aromatic ring of isochroman and in the phenyl group in the 1-position does not alter the activity. It is notable that the study of the pharmacodynamics of 3-aminomethyl-7-fluoro-1-phenylisochroman established that, in contrast to the anorexigenic preparations, this compound does not increase the pulmonary blood pressure.[223]

Isochroman derivatives (CXXXVI) containing simultaneously aryl and aminoalkyl substituents in the 3-position are known; in contrast to compounds (CXXXIV) and (CXXXV), they are effective drugs for the treatment of cardiovascular diseases (they exhibit hypotensive and diuretic activities).[224,225] Isochroman derivatives having the structure (CXXXVII) also possess hypotensive properties.[226] 1-Methyl- and 1-phenyl-isochromans with dialkylamino- or piperazinyl groups in the 4-position manifest antihistamine properties.[227] Piperidine-4-spiro-4′-isochromans (CXXXVIII) exhibit the same type of activity.[228] It is of interest that compounds (CXXXIX), which also contain the piperidine ring but the latter is linked to the isochroman ring by a C–C bond, manifest anti-allergic properties.[229,230]

N-Substituted piperidine-4-spiro-3′-isochromans (CXL) possess hypotensive and anti-depressant activities.[231]

Among semisynthetic cephalosporins, a substance with an isochromanyl residue exhibiting a bactericidal activity has been discovered.[232]

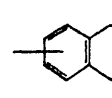
Among more complex structures (tri- and tetra-cyclic), dibenzopyran and morphine-like substances, possessing antipyretic, analgesic, and anti-inflammatory properties, are known.[233,234] Acids of the isochroman series also exhibit anti-inflammatory and antibacterial activities.[140,235]



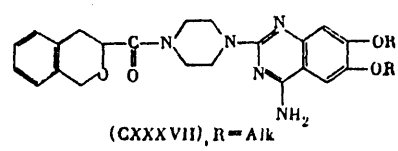
(CXXXIV), (CXXXV)

(CXXXIV): $Q = 3-$ or $4-(CH_2)_nNAlk_2$,

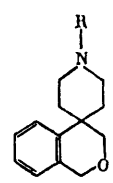
(CXXXV): $Q = 3-CHCH_2NR_2$ (CH_3)



(CXXXVI)

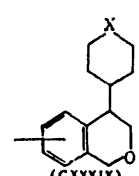


(CXXXVII), R = Alk



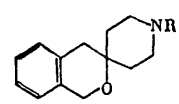
(CXXXVIII)

R = CH_3, $(CH_2)_nC_6H_5$; $n = 1,2$



(CXXXIX)

$X = CR^1R^2NR^1$; $R^1, R^2 = H$, Alk, ArAlk



(CXL)

R = H, $CH_2C_6H_5$, $COOC_2H_5$

Summarising, one should note that it is as yet too early to reach conclusions about the relation between the structure and activity of isochroman compounds, but the existence of a large number of substances with different biological activities suggests that deliberate search for preparations among individual groups of isochroman derivatives is desirable. The availability of the starting materials and the existence of methods of synthesis make it possible to use on a wide scale a series of isochroman derivatives as synthons for the preparation of biologically active substances.

References

1. French P. 2476085 (1981)
2. H G Floss *Antibiotics, 4 (Biosynthesis)*, 1981, p. 215
3. B Krone, A Zeeck, H G Floss *J. Org. Chem.*, 1982, **47** 4721
4. E Priers, R W Britton, N De Waal *Can. J. Chem.*, 1969, **47** 831
5. H H Warren, G Dougherty, E S Wallis *J. Am. Chem. Soc.*, 1949, **71** 3422
6. P S Steyn, C W Holzapfel *Tetrahedron*, 1967, **23** 4449
7. T Tokoroyama, S Maeda, T Nishikama, O Kubota *Tetrahedron*, 1969, **25** 1047
8. J Roberts, P Woollven *J. Chem. Soc. C.*, 1970, 278
9. M Yamazaki, Y Maebayashi, K Miyaki *Tetrahedron Lett.*, 1971, 2301
10. T Kubota, T Tokoroyama, T Kamitawa, V Satomura *Tetrahedron Lett.*, 1966, 5205
11. R F Curtis, C H Hassall, M Nazar *J. Chem. Soc. C*, 1968, 85
12. T Tokoroyama, T Kamikawa, T Kubota *Tetrahedron*, 1968, **24** 2345
13. R H Cox, O Hernandez, J W Dorner, et al. *J. Agric. Food Chem.*, 1979, **27** 999
14. Sh M Afzal, R Pike, N H Rama, et al. *J. Chem. Soc., Perkin Trans. 1*, 1978, 81
15. P Vleggaar, P S Steyn, D W Nagel *J. Chem. Soc., Perkin Trans. 1*, 1974, 45
16. US P. 4346039 (1982)
17. M Nukina, Sh Marumo *Tetrahedron Lett.*, 1977(30), 2603
18. P Boutibonnes, Y Auffray, C Malherbe, et al. *Mycopathologia*, 1984, **87**(1–2) 43
19. C G Crawley *J. Chem. Soc., Perkin Trans. 1*, 1981, 221
20. Y Nakada, Sh Ohno, M Yashimoto, Y Yura *Agric. Biol. Chem.*, 1978, **42** 1365
21. H Roensch *Symp. Pap. IUPAC Int. Symp. Chem. Nat. Prod. XI*, 1978, Vol. 2, p. 38
22. US P. 4256866; Chem. Abs., 1981, **94** 209514
23. N M Karayannis, S S Lee *Macromol. Chem.*, 1983, **184** 2275
24. A T Neyyarappally, J S Bindra, N Anand, R C Srimal *Indian J. Chem.*, 1971, **9** 89
25. W Wiegrebe, J Friecke, P L Budzikiewicz *Tetrahedron*, 1972, **28** 2849
26. W Wiegrebe, H Reinhart, J Friecke *Pharm. Acta Helv.*, 1973, **48**(6–7) 420
27. H M Stephan, G Langer, W Wiegrebe *Pharm. Acta Helv.*, 1976, **51**(6) 164
28. W Wiegrebe, S Prior *Chimia*, 1978, **32**(7) 256
29. W Wiegrebe, S Prior, K K Mayer *Arch. Pharm.*, 1982, **315** 262
30. S Prior, W Wiegrebe, G Sariyar *Arch. Pharm.*, 1982, **315** 273
31. R Ambros, S Prior, W Wiegrebe *Sci. Pharm.*, 1982, **51**(2) 179
32. S Prior, W Wiegrebe *Arch. Pharm., 1981,* **314** 577
33. M Yamato, T Ishikawa, T Kobayashi *Chem. Pharm. Bull.*, 1981, **29** 720
34. A S Rothenberg, G S Yayatilake, S F Hussain *Heterocycles*, 1976, **5** 41
35. V H Belgaonkar, R N Usgaonkar *Heterocycl. Chem.*, 1975, **15** 257
36. Japanese Appl. 8059171; *Chem. Abs.*, 1981, **94** 15758
37. W Meise, H Pfisterer *Arch. Pharm.*, 1977, **310** 501
38. W Meise, H Pfisterer *Arch. Pharm.*, 1977, **310** 495
39. L Laitem, L Christiaens, A Welter *Heterocycles*, 1976, **4** 1107
40. S R Ramadas, A P Chaudhuri, G K Prakash *Steroids*, 1976, **28**(2) 197
41. S R Ramadas, A P Chaudhuri *J. Chem. Soc., Chem. Comm.*, 1974, 521
42. Y Elliott, Y Nesley *J. Org. Chem.*, 1982, **47** 5398
43. N S Narasimhan, R S Mali, B K Kulkarni *Tetrahedron Lett.*, 1981, **22** 2797
44. S Yeganathan, D Kuila, M Srinivasan *Synthesis*, 1980, 469
45. S A Sisk, C R Hutchinson *J. Org. Chem.*, 1979, **44** 3500
46. F Kienzle, R E Minder *Helv. Chim. Acta*, 1980, **63** 1425
47. M Somei, T Shoda *Heterocycles*, 1982, **17** Spec. Issue, p. 417
48. T Kometani, E Yoshil *J. Chem. Soc., Perkin Trans. 1*, 1981, 1191
49. A V Bicherov, G N Dorofenko, E V Kuznetsov *Zh. Org. Khim.*, 1979, **15** 585
50. M Yamato *J. Synth. Org. Chem. (Japan)*, 1983, **41** 958
51. J Braun, F Zobel *Ber.*, 1923, **56B** 2142
52. S Siegel, S K Coburn *J. Am. Chem. Soc.*, 1951, **73** 5494
53. E L Anderson, F G Holliman *J. Chem. Soc.*, 1950, 1037
54. J L Warnell, R L Schriner *J. Am. Chem. Soc.*, 1957, **79** 3165
55. BRD P. 915811; *Chem. Abs.*, 1958, **52** 15593
56. German P. 614461; *Chem. Abs.*, 1935, **29** 5861
57. German P. 617646; *Chem. Abs.*, 1936, **30** 492
58. P Maitte *Ann. Chim. (Paris)*, 1954, **9** 431
59. J Colonge, P Boisde *Bull. Soc. Chim. Fr.*, 1956, **10** 1337
60. A Rieche, E Schmitz *Chem. Ber.*, 1956, **89** 1254
61. E Schmitz, A Rieche *Chem. Ber.*, 1956, **89** 2807
62. Japanese Appl. 8199467; *Chem. Abs.*, 1981, **95** 203757
63. J N Chatterjee *Chem. Ber.*, 1958, **91** 2636
64. J G Abramo, E C Chapin *J. Org. Chem.*, 1961, **26** 2671
65. A Rieche, E Schmitz *Chem. Ber.*, 1957, **90** 531
66. P Maitte *Colloq. int. CNRS*, 1955(64), 197; *Chem. Abs.*, 1961, **55** 10426
67. J Colonge, P Boisde *C. R. Acad. Sci.*, 1954, **239** 1047
68. J Thibault *Ann. Chim. (Paris)*, 1971, **6**(3–4) 263
69. C A R Baxter, G C Forward, D A Whitting *J. Chem. Soc. C.*, 1968, 1169
70. R P Singh, J N Srivastava *Indian J. Chem.*, 1982, **21B** 104
71. C Van der Stelt, P S Hofman, T N Nauta *Recl. Trav. Chim., Pays-Bas*, 1965, **84** 633
72. R L Vaulx, F N Jones, C R Hauser, *J. Org. Chem.*, 1964, **29** 1387
73. J Schnekenburger, R Kaufman *Arch. Pharm.* , 1970, **303** 760
74. E Von Angerer, W Wiegrebe *Arch. Pharm.*, 1979, **312** 385
75. T Fujisaka, M Nojima, S Kusabayashi *J. Org. Chem.*, 1985, **50** 275
76. S Siegel, S K Coburn, D R Levering *J. Am. Chem. Soc.*, 1951, **73** 3163
77. R K Huffman, E F Ullman *J. Am. Chem. Soc.*, 1967, **89** 5629
78. DDR P. 141159; *Chem. Abs.*, 1981, **94** 174884
79. DDR P. 141160; *Chem. Abs.*, 1981, **94** 192146

80. D G Talekar, A S Rao *Synthesis*, 1983, 595
81. L Shi, C K Narula, K T Mak, et al. *J. Org. Chem.*, 1983, **48** 3894
82. S L Mattes, S Farid *J. Am. Chem. Soc.*, 1982, **104** 1454
83. M E Garst, Y-F Cheung, W S Johnson *J. Am. Chem. Soc.*, 1979, **101** 4404
84. R C Larock, L W Harrison, M H Hsu *J. Org. Chem.*, 1984, **49** 3662
85. H Böhme, P Priesner, B Unterhalt *Arch. Pharm.*, 1966, **299**, 931
86. A G Samodurova, S O Vartanyan, E A Markaryan *Arm. Khim. Zh.*, 1979, **32** 397
87. H Böhme, P Sutoyo *Liebigs Ann. Chem.*, 1982, 1643
88. A L Mndzhoyan, V E Badalyan, A N Sadatierov, A G Samodurova *Arm. Khim. Zh.*, 1973, **26** 486
89. H Böhme, K lindenberg, R Priesner, B Unterhalt *Arch. Pharm.*, 1968, **301** 326
90. H Böhme, R Schweizer *Arch. Pharm.*, 1970, **303** 170
91. H Böhme, U Sitorus *Arch. Pharm.*, 1974, **307** 27
92. BRD P. 1 215 727; *Chem. Abs.*, 1966, **65** 15337
93. H Böhme, K Lindenberg *Arch. Pharm.*, 1968, **301 584**
94. H Böhme, F Ziegler *Arch. Pharm.*, 1974, **307** 287
95. H Böhme, U Sitorus *Arch. Pharm.*, 1974, **307** 24
96. H Böhme, F Ziegler *Synthesis*, 1973, 297
97. H Böhme, F Sitorus, F Ziegler *Arch. Pharm.*, 1974, **307** 218
98. H Böhme, K Lindenberg *Arch. Pharm.*, 1968, **301 544**
99. A L Mndzhoyan, V E Badalyan, A G Samodurova, et al., *Arm. Khim. Zh.*, 1973, **26** 591
100. G Kraiss, M Povarny, K Nador *Acta Chim. Acad. Sci. Hung.*, 1976, **88**(1) 93
101. J Knabe, K Schaller *Arch. Pharm.*, 1968, **301 457**
102. US P. 3 880 885; *Chem. Abs.*, 1975, **83** 58658
103. C Normant-Chefnay *Bull. Soc. Chim. Fr.*, 1971, 1362
104. C Normant-Chefnay, J Thibault, P Maitte *C.R. Acad. Sci.*, 1968, **267C** 547
105. J Thibault *Ann. Chim. (Paris)*, 1971, **6** 381
106. F Micheel, Z-H Schleifstein *Chem. Ber.*, 1972, **105** 650
107. V B Milevskaya, R V Belinskaya, L M Yagupol'skii *Zh. Org. Khim.*, 1973, **9** 2145
108. W Schneider, E Kaemmerer *Arch. Pharm.*, 1966, **299** 817
109. G Hazebroucq *Ann. Chim (Paris)*, 1966, **1** 221
110. US P. 2 701 254; *Chem. Abs.*, 1956, **50** 1088
111. A L Meyer, R B Turner *Tetrahedron*, 1971, **27** 2609
112. J N Srivastava, D N Chaudhury *J. Org. Chem.*, 1962, **27** 4337
113. D Mikhopadhyay, D N Chaudhury *J. Indian Chem. Soc.*, 1963, **40** 433
114. J N Srivastava, D N Chaudhury *J. Indian Chem. Soc.*, 1963, **40** 865
115. D Prasad, D N Chaudhury *J. Indian Chem. Soc.*, 1962, **39** 672
116. N K Bose, D N Chaudhury *J. Indian Chem. Soc.*, 1964, **41** 103
117. J N Chatterjee, B K Banerjee, H C Jha *Chem. Ber.*, 1965, **98** 3279
118. L Schieler, R D Sprenger *J. Am. Chem. Soc.*, 1951, **73** 4045
119. J N Chatterjee, C Bhakta, N D Sinhe *J. Indian Chem. Soc.*, 1975, **52** 158
120. J N Chatterjee, C Bhakta, S K Mukherjee *J. Indian Chem. Soc.*, 1981, **58** 888
121. J M McCall, R E Tenbrink, B V Kamdar, C Chidester *J. Heterocycl. Chem.*, 1979, **16** 363
122. M Palamareva, M Khaimova, B Kurtev *Chem. Ber.*, 1976, **109 274**
123. S M Afzal, W B Whalley *Pak. J. Sci. Rec.*, 1981, (Publ. 1984), **33**(1–4) 52
124. C A R Baxter, G C Forward, D A Whiting *J. Chem. Soc. C.*, 1968, 1162
125. C A R Baxter, G C Forward, D A Whiting *Tetrahedron Lett.*, 1967, 3997
126. M Yamato, T Ishikawa, T Nagamatsu, et al. *Chem. Pharm. Bull.*, 1980, **28** 723
127. P J Card *J. Org. Chem.*, 1982, **47** 2169
128. I R Trehan, R L Kaul, R K Sharma, J Singh *Indian J. Chem.*, 1982, **21B**(3) 197
129. S Farid *J. Chem. Soc. D.*, 1970, 303
130. R G Giles, I R Green, J A X Pestana *J. Chem. Soc., Perkin Trans. 1*, 1984, 2389
131. R C Larock, C L Liu, H H Lau, S Vareptath *Tetrahedron Lett.*, 1984, **25** 4459
132. G Bringman, J R Jansen *Liebigs. Ann. Chem.*, 1985, 2116
133. US P. 3 532 719.
134. Europ P. 61 267; *Chem. Abs.*, 1983, 71725
135. D Satoh, T Hashimoto, K Aoyama *Yakugaku Zasshi*, 1974, **94**, 774; *Chem. Abs.*, 1974, **81** 105333
136. D Satoh, T Hashimoto, K Aoyama *Yakugaku Zasshi*, 1975, **95** 1183
137. T A Dobson, L G Humber *J. Heterocycl. Chem.*, 1975, **12** 591
138. J I Retamal, V M Ruiz, R A Tapia, et al. *Synth. Commun.*, 1982, **12** 279
139. B P 1 049 538; *Chem. Abs.*, 1979, **91** 20326
140. US P. 4 021 451; *Chem. Abs.*, 1975, **87** 102303
141. A Miyake, K Itoh, N Tadu, Y Oka *Takeda Kenkyushoho*, 1982, **41**(1–2) 24; *Chem. Abs.*, 1982, **97** 215837
142. US P. 3 910 964.
143. US P. 3 978 090.
144. BRD P. 3 306 200; *Chem. Abs.*, 1985, **102** 6204
145. A Miyake, N Tada, Y Oka *Takeda Kenkyushoho*, 1982, **41**(1–2), 14; *Chem. Abs.*, 1982, **97** 215838
146. US P. 4 250 200; *Chem. Abs.*, 1981, **95** 60183
147. US P. 4 301 076.
148. US P. 4 308 412; *Chem. Abs.*, 1982, **96** 142708
149. US P. 4 315 951; *Chem. Abs.*, 1982, **97** 4915
150. French P. 1 369 595; *Chem. Abs.*, 1965, **62** 530
151. US P. 4 166 062.
152. US P. 4 191 665.
153. Japanese P. 77 105 174; *Chem. Abs.*, 1978, **88** 37614
154. Japanese Appl. 60-20390; *Byull. Izobret.*, 1985(23) 172
155. T Kometani, K Kigasawa, M Kiiragi, et al. *Heterocycles*, 1975, **3** 521
156. Japanese Appl. 60-11710; *Byull. Izobret.*, 1985(19), 165
157. Japanese Appl. 60-20391; *Byull. Izobret.*, 1985(23), 172
158. S Yasuda, A Sakakibara *Mokazai Yakkaishi*, 1976, **22** 606
159. S Yasuda, A Sakakibara *Mokazai Yakkaishi*, 1975, **21** 639
160. A Closse, D Hauser *Helv. Chim. Acta*, 1973, **56** 2694
161. US P. 6 546 208; *Chem. Abs.*, 1986, **104**, 174385
162. US P. 4 549 983; *Chem. Abs.*, 1986, **104** 192939
163. US P. 4 512 918; *Chem. Abs.*, 1985, **103** 42415
164. US P. 4 524 021; *Chem. Abs.*, 1985, **103** 128817
165. S F Birch, R A Dean, E V Whitehead *J. Org. Chem.*, 1954, **19** 1449
166. K Yoshida, P A Grieco *J. Org. Chem.*, 1984, **49** 5257
167. S A Godleski, E B Willhauer *J. Org. Chem.*, 1984, **49**, 2246
168. B Fraser-Reid, M A Rahman, D R Kelly, R M Srivastava *J. Org. Chem.*, 1984, **49** 1835

169. C Van der Stelt, P S Hofman, C Van der Vlies, F Bickelhaupt *Recl. Trav. Chim. Pays-Bas,* 1967, **86** 1316
170. A Rieche, E Schmitz *Chem. Ber.*, 1957, **90** 1082
171. Hungarian P. 28473; *Chem. Abs.*, 1984, **101** 38225
172. J Thibault, P Maitte *Bull. Soc. Chim. Fr, 1969, 915*
173. G Balavoina, C Eskenazi, F Meunier *J. Mol. Catal.*, 1985, **30**(1–2) 125
174. F Bonadies, R Di Fabio, C Bonini *J. Org. Chem.*, 1984, **49** 1647
175. S M Afzal, M Ashraf *Pak. J. Sci.*, 1981 (Publ. 1984), **33**(1–4) 80
176. N S Narasimhan, C P Bapat, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2099
177. M Yamato, K Sato, A Taniguchi, et al. *Chem. Pharm. Bull.*, 1978, **26** 1990
178. F Gatta, G Settimj *Gazz. Chim. Ital.*, 1984, **114**, 103
179. F Gatta, G Settimj *J. Heterocycl. Chem.*, 1983, **20** 1267
180. M Masui, S Hara, T Ueshima, et al. *Chem. Pharm. Bull.*, 1983, **31** 4209
181. U Palmquist, A Nilson, T Petterson et al. *J. Org. Chem.*, 1979, **44** 196
182. M Barbier *Helv. Chim. Acta*, 1984, **67** 866
183. A Rieche, E Schmitz *Chem. Ber.*, 1957, **90** 1225
184. Yu V Pokonova *Galoidefiry* (Halogenoethers), Izd. Khimiya, Leningrad, 1966
185. US P. 3438995; *Chem. Abs.*, 1969, **71** 13126
186. A Rieche, E Schmitz *Chem. Ber.*, 1957, **90** 1094
187. M T Reetz, J Chatziiosifidis, H Kuenzer, H Mueller-Starke *Tetrahedron,* 1983, **39** 961
188. H Böhme, N Sutoyo *Arch. Pharm.*, 1983, **316** 505
189. H Böhme, F Ziegler *Liebigs Ann. Chem.*, 1974, 734
190. H Böhme, F Ziegler *Liebigs Ann. Chem.*, 1974, 1474
191. M Yamato, T Ishikawa, T Kobayashi *Chem. Pharm. Bull.*, 1980, **28** 2967
192. M Yamato, T Ishikawa, S Yamada *Chem. Pharm. Bull.*, 1982, **30** 843
193. M Yamato, Y Takeuchi, K Hashigaki, et al. *Chem. Pharm. Bull.*, 1983, **31** 1733
194. T Ishikawa, M Yamato *Chem. Pharm. Bull.*, 1982, **30** 1594
195. A G Samodurova, A S Tsatinyan, Zh S Zastukhova, E A Markaryan *Arm. Khim. Zh.*, 1984, **37** 493
196. A G Samodurova, S O Vartanyan, M R Barkhudaryan, et al., *Arm. Khim. Zh.*, 1979, **32** 481
197. V E Badalyan, A G Samodurova, D A Gerasimyan, et al., *Arm. Khim. Zh.*, 1977, **30** 762
198. A G Samodurova, A S Tsatinyan, D A Gerasimyan, et al., 1982, **35** 391
199. Japanese Appl. 57-159713; *Chem. Abs.*, 1983, **98**, 65460
200. B. P. 1102762.
201. Dutch Appl. 6603603; *Chem. Abs.*, 1967, **66** 37770
202. Dutch Appl., 6603606; *Chem. Abs.*, 1967, **66** 65392
203. H Böhme, K Lindenberg *Arch. Pharm.*, 1970, **303** 229
204. A Rieche, M Schulz *Z. Naturforsch.*, 1963, **18b**, 583; *Chem. Abs.*, 1964, **60** 2205
205. Japanese Appl. 59-134754; *Chem. Abs.*, 1984, **101** 210754
206. Japanese Appl. 59-134720; *Chem. Abs.*, 1985, **102** 17648
207. M Yamato, K Hashigaki, S Ishikawa, et al. *J. Med. Chem.*, 1985, **28** 1026
208. B. P. 1552004.
209. Japanese P. 76-125287; *Chem. Abs.*, 1977, **87** 23045
210. BRD P. 2624693; *Chem. Abs.*, 1977, **87** 152020
211. Japanese P. 77-83846; *Chem. Abs.*, 1978, **88** 37613
212. **Japanese P. 59-19549; *Byull. Izobret.*, 1985(1), 203**
213. US P. 4066648.
214. J M McCall, R B McCall, R E TenBrink, et al. *J. Med. Chem.*, 1982, **25** 75
215. US P. 4247553; *Chem. Abs.*, 1981, **95** 42940
216. BRD P. 2846043; *Chem. Abs.*, 1979, **91** 74447
217. A Kumar, J M Khana, P C Jain, N Anand *Indian J. Chem.*, 1978, **16B** 793
218. US P. 4206123.
219. US P. 4179510; *Chem. Abs.*, 1980, **92** 146636
220. US P. 3840561.
221. US P. 3840562.
222. US P. 3851062.
223. K U Seiler, O Wasserman, H Wensky *Clin. Exp. Pharmacol. Physiol.*, 1976, **3**(4) 323
224. B.P. 1374337.
225. French P. 2178718; *Chem. Abs.*, 1974, **80** 95735
226. BRD P. 3015676; *Chem. Abs.*, 1981, **94** 139832
227. S Ram, A K Saxena, P C Jain, G K Patnacik *Indian J. Chem.*, 1984, **23B** 1261
228. M Yamato, K Hashigaki, M Ikeda, et al. *J. Med. Chem.*, 1981, **24** 194
229. Japanese P. 60-97975; *Chem. Abs.*, 1985, **103** 123369
230. M Yamato, K Hashigaki, K Hiromatsu, K Tasaka *Chem. Pharm. Bull.*, 1983, **31** 521
231. US P. 3686186; *Chem. Abs.*, 1972, **77** 164534
232. G Alexandrscu, M Ungureanu, Z Cojocaru, V Zvoristeanu *Rev. Med. Chir.*, 1984, **88** 715
233. Japanese P. 76-138681; *Chem. Abs.*, 1977, **87** 39282
234. Japanese Appl. 52-105936; Ref. *Zh. Khim.*, 1980, 70136
235. Japanese P. 76-138680; *Chem. Abs.*, 1977, **87** 23046