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SYNTHESIS OF HETEROCYCLIC COMPOUNDS BY THE CYCLIZATION OF ISATIN AND ITS DERIVATIVES (REVIEW)

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Published data on the synthesis of heterocyclic compounds formed as the result of the recyclization of isatin and its derivatives are classified and summarized.

INTRODUCTION

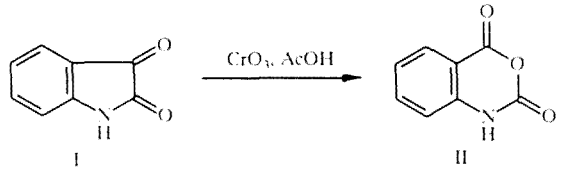
Compounds of the isatin series are multifunctional compounds from which it is possible to synthesize an enormous number of assorted organic compounds. The presence of several reaction centers in isatin and its derivatives makes it possible to bring these compounds into various types of reactions. Thus, keto groups at position 2 and, particularly, at position 3 can enter into addition at the C=O bond and into condensation with the release of water. Through the NH group compounds of the isatin series are capable of entering into N-alkylation and N-acylation and into the Mannich and Michael reactions. The benzene ring in these compounds enters readily into electrophilic substitution reactions. Of particular interest is the ability of compounds of the isatin series to split the bond between the nitrogen atom and the carbon atom at position 2 with the formation of derivatives of isatinic acid, thereby creating the basis for numerous transformations, including the Pfitzinger reaction and other processes leading to various heterocyclic systems. Such multiplicity and diversity of transformations make it possible to refer to isatin as an "organic chameleon."

Data on the recyclization reactions of isatin and its derivatives that appeared in the literature before 1973 were examined quite fully in the monographs [1, 2] and in the review [3].

In this connection, data on the recyclization of isatin that mainly appeared after 1973 are included in the present review. At the same time, certain papers that were published in 1973 and are important for the present article are also examined, and most of them were not cited in [1-3].

1. Action of Oxidizing Agents

The treatment of isatin (I) with chromium oxide in glacial acetic acid (2 h at 20°C, 3 h at 45°C, and 2 h at 60°C) led to the formation of isatinic anhydride (II) with a yield of 72% [4]:



I II

As established in [5-7], enlargement of the five-membered ring in compounds of the isatin (III) series can take place in two directions: Under the influence of hydrogen peroxide in the presence of catalytic amounts of sulfuric acid isatinic anhydride or its substituted derivatives (IV) formed; during oxidation with persulfuric acid $H_2S_2O_8$ 1,4-benzoxazine-2,3-(1H)-dione or its derivatives (V) are formed:

Academician A. N. Kosygin Moscow State Textile Academy, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 291-323, March, 1996. Original article submitted September 14, 1995.

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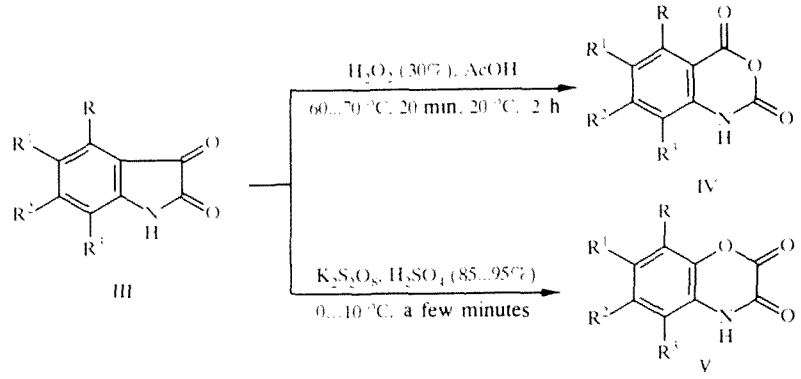
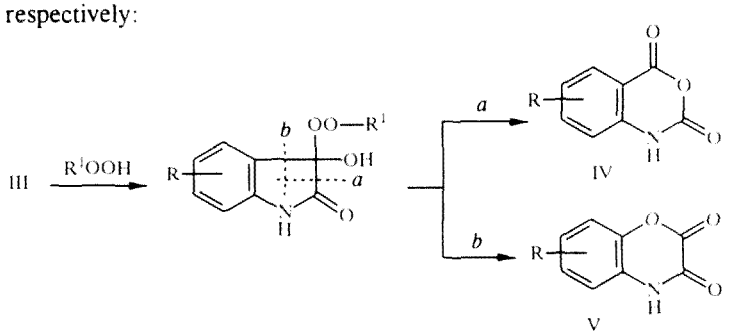


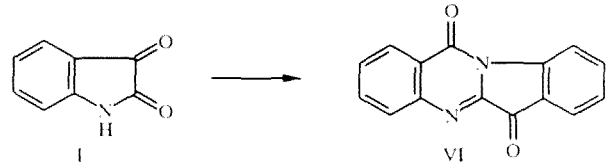
R, R^1, R^2, R^3, yields of (IV) and (V) %: H, H, H, H, 79, 95; H, H, H, Me 75, 89; H, H, H, CF_3, 81, 82; H, Cl, H, Cl, 90, 95; H, Br, H, H, 83, 95; H, NO_2, H, H, 80, —; H, H, H, Cl, 85, —; Me, H, H, OMe, 70, —; H, F, H, H, 83, —; H, H, F, H, 84, —; H, H, Me, H, —, 90

The oxidation of compounds (III) (R = R^2 = R^3 = H, R^1 = H or NO_2) with hydrogen peroxide in acetic acid at 20°C for 30 min or with persulfuric acid at 20°C for 1 h leads respectively to compounds (IV) with yields of 65-68% or compounds (V) with yields of 70-75% [8].

In [5] a scheme is proposed for the formation of (IV) or (V) during the oxidation of isatin or its derivatives with addition of the hydroperoxides R^1OOH to the C=O bond at position 3 followed by cleavage of the $C_{(2)}$—$C_{(3)}$ (path *a*) or $C_{(3)}$—$C_{(4)}$ (path *b*) bonds respectively:

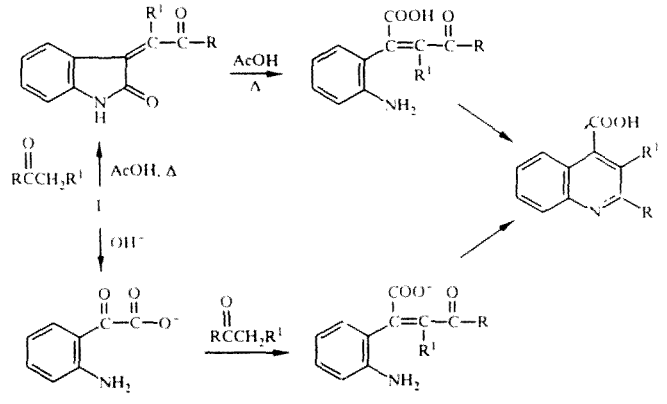


The oxidative self-condensation of isatin (I) results in the formation of the diketo derivative (VI), which exhibits antifungal activity [9].

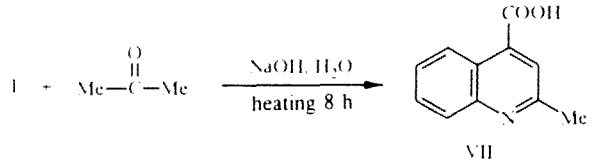


2. Reaction with Ketones or Keto Acids

2.1. Reactions with Ketones. This process, called the Pfitzinger reaction, is the best-known of the recyclization reactions of isatin (I) and its derivatives containing various substituents and leads to derivatives of 4-quinolinecarboxylic acid.

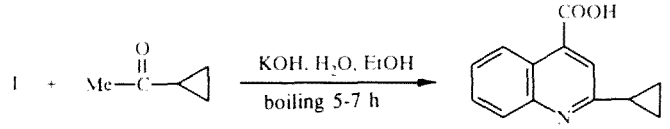


2.1.1. Reactions with Aliphatic Ketones. When isatin (I) was heated in the presence of 20% aqueous sodium hydroxide, 2-methyl-4-quinolinecarboxylic acid (VII) was obtained with a 53% yield [10]:



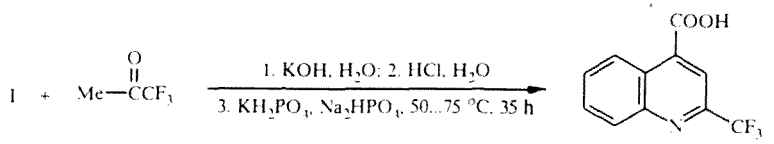
VII

The reaction of isatin (I) with methyl propyl ketone was conducted by boiling for 5-7 h in the presence of potassium hydroxide in an aqueous alcohol medium; the yield of the reaction product (VIII) amounted to 84% [11]:



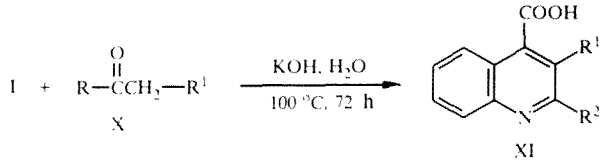
VIII

2-Trifluoromethyl-4-quinolinecarboxylic acid (IX) was obtained from isatin (I) and 1,1,1-trifluoroacetone by the successive action of 30% aqueous potassium hydroxide, neutralization of the mixture with 10% hydrochloric acid, and prolonged heating in a buffer solution (KH_2PO_4 and Na_2HPO_4 in water) [12]:



IX

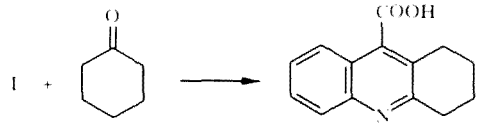
During investigation of the reaction of isatin (I) with alkyl pyridylmethyl ketones (X) it was established that cyclocondensation to the derivatives of 4-quinolinecarboxylic acid takes place through the methylene group situated between the keto group and the pyridyl radical [13, 14]:



X XI

For R^1 = 2-pyridyl, R, yield, %: Me, 49; CH_2=$CHCH_2$, 43; Ph, 60; Me_2CH, 88; Bu, 69; Me_2CHCH_2, 44; n-C_5C_{11}, 83 [13]; for R^1 = 3-pyridyl, R, yield, %: Me, 64; Et, 37; Pr, 34; Bu, 73; Me_2CHCH_2, 71; n-C_5H_{11}, 54 [14].

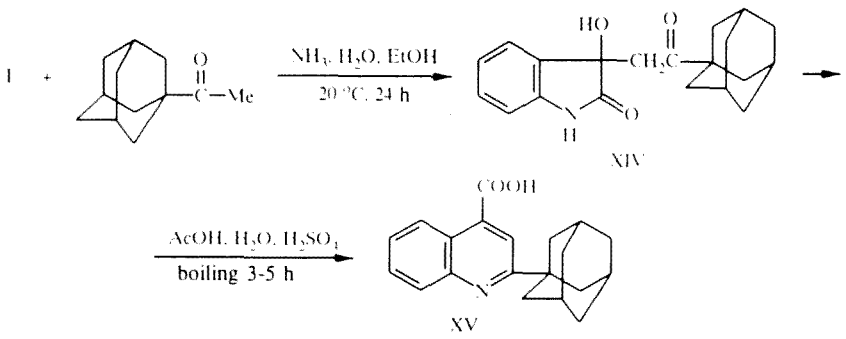
2.1.2. Reactions with Alicyclic Ketones. The tricyclic carboxylic acid (XII) was synthesized with yields of 80-89% [15-17] as a result of the reaction of isatin (I) with cyclohexane in the presence of ~30% potassium hydroxide at 100°C for 6-7 h in an aqueous alcohol medium:



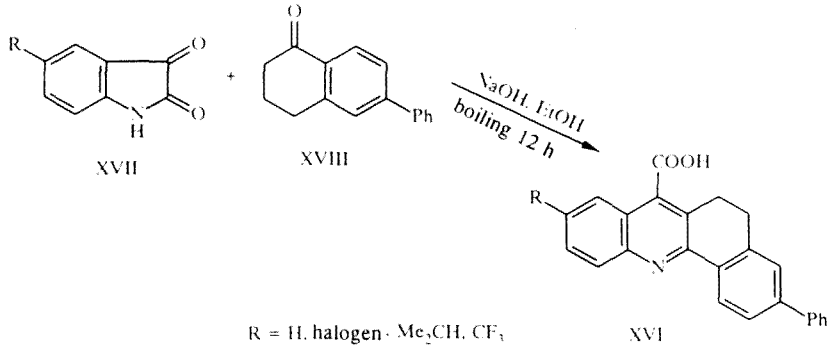
XII

The synthesis of the carboxylic acid (XII) by the condensation of isatin with cyclohexanol in the presence of potassium hydroxide by boiling in alcohol for 12 h was claimed in the patent [18].

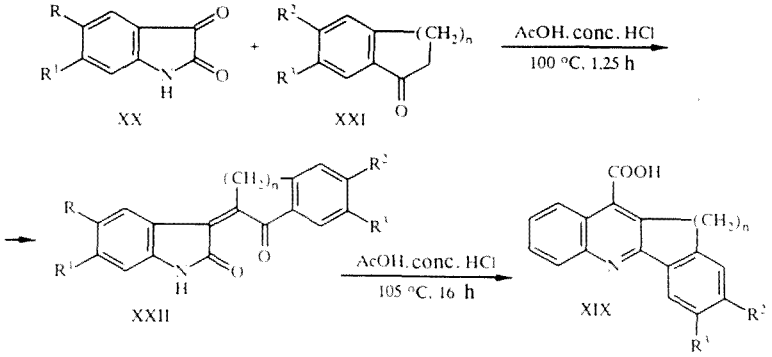
The reaction of isatin (I) and 1-acetyladamantane (XIII) in an aqueous alcohol solution of ammonia gave an 84% yield of the addition product (XIV), which was converted by boiling in aqueous acetic acid in the presence of sulfuric acid into 2-(1-methyladamantyl)-4-quinolinecarboxylic acid (XV) with a yield of 94% [11]:



The carboxylic acids (XVI) were obtained from isatin or its 5-substituted derivatives (XVII) by condensation with 6-phenyl-1-tetralone (XVIII) by boiling for 12 h in the presence of a 6N alcohol solution of sodium hydroxide; in the case of the 5-fluoro derivative (XVII) (R = F) the yield of the carboxylic acid (XVIII) (R = F) amounted to 78% [19]:



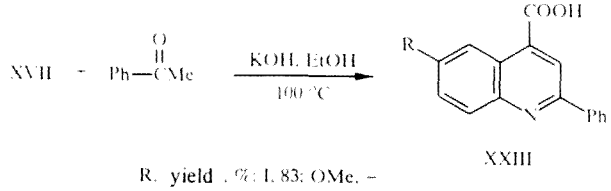
A two-stage synthesis of compounds (XIX), including the condensation of isatin derivatives (XX) and ketones (XXI) in an acidic medium followed by cyclization of the products (XXII) formed at the first stage by prolonged heating in the same medium, was described in [20]:



R, R^1, R^2, R^3, n, yield of XIX, %: Cl, H, OMe, OMe, 1.86; NO_2, H, OMe, OMe, 1.91; —OCH_2CH_2O—, OMe, OMe, 1.87; I, H, OMe, OMe, 1.92; H, H, OMe, OMe, 1.94; Cl, H, H, H, 2.71; F, H, H, H, 2.85; —OCH_2O—, H, H, 2.88; H, H, H, H, 2.89; I, H, H, H, 1.95; NO_2, H, H, H, 1.88

2.1.3. Reactions with Alkyl Aromatic Ketones. In the last twenty years, as in earlier years, many authors have used alkyl aromatic ketones in the Pfitzinger reaction.

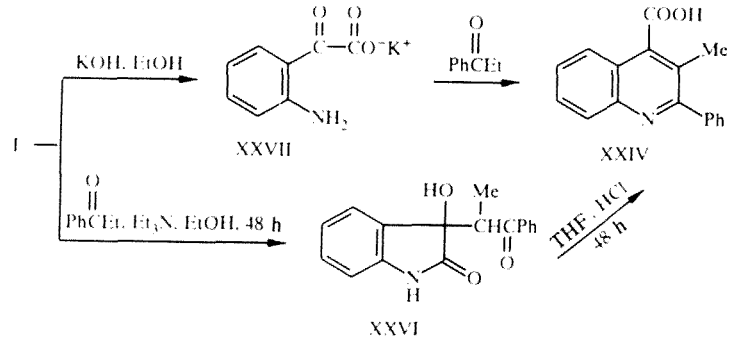
4-Quinolinecarboxylic acids (XXIII) were obtained from 5-substituted derivatives of isatin (XVII) (R = I, OMe) and acetophenone [21]:



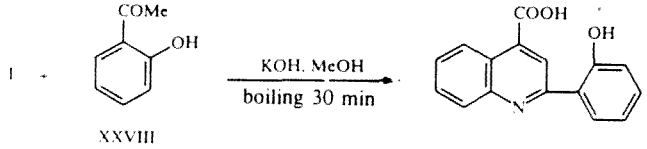
R, yield, %: I, 83; OMe, –

The synthesis of the acids (XXIII) (R = H, Me) from acetophenone and isatin or 5-methylisatin was described [22].

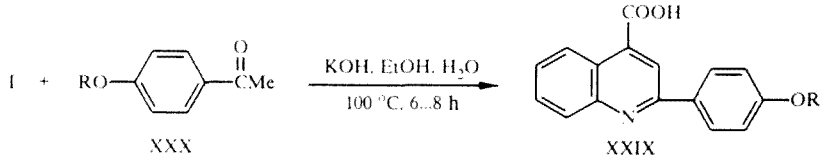
Two methods were used during the production of 2-phenyl-3-methyl-4-quinolinecarboxylic acid (XXIV): 1) A two-stage synthesis, including reaction of the isatin (I) with propiophenone (XXV) in the presence of triethylamine, followed by recyclization of the obtained addition product (XXVI) in the presence of concentrated hydrochloric acid; 2) condensation of isatin (I) with the ketone (XXV) in the presence of an alcohol solution of potassium hydroxide [through the salt of isatinic acid (XXVII) as intermediate compound] [20]:



The reaction of isatin (I) with 2-hydroxyacetophenone (XXVIII) takes place quickly in the presence of potassium hydroxide in methanol [23]:

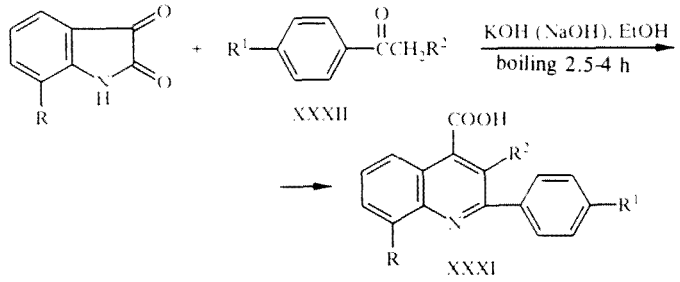


At the same time, prolonged heating is required for the production of the carboxylic acids (XXIX) from 4-alkoxyacetophenones (XXX) and isatin (I) in the presence of potassium hydroxide in aqueous ethanol [24]:



R, yield, %: Me, 85; Et, 70.8; Pr, 67.1; Bu, 68; n-C_5H_{11}, 66

Reactions of isatin or 7-methylisatin with derivatives of acetophenone (XXXII) in the presence of potassium hydroxide [25] or sodium hydroxide [26] were carried out in order to synthesize derivatives of 4-quinolinecarboxylic acid (XXXI):



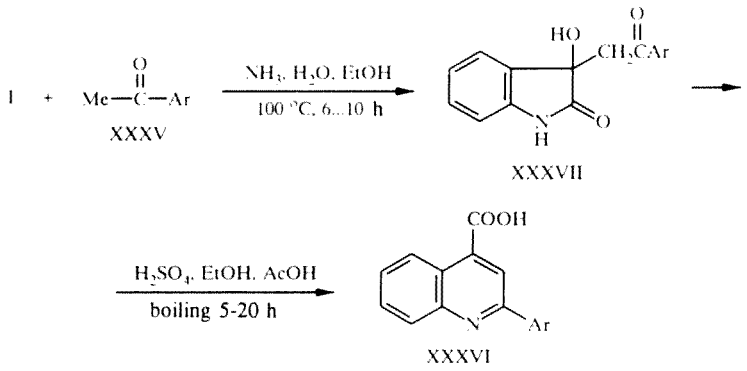
R, R^1, R^2, yield, %: H, H, OMe, 96.4; Me, Ph, OAc, 42.4

A series of derivatives of 4-quinolinecarboxylic acid (XXXIII) containing aryl or arylalkyl radicals at position 2 were synthesized by the condensation of isatin (I) with methyl aryl ketones (XXXIV) in the presence of an alcohol solution of potassium hydroxide [27,28]:

R, yield, %: 4-$Me_2CHC_6H_4$, — [27]; 4-$C_7H_{15}C_6H_4$, 95; 4-$C_8H_{17}C_6H_4$, 92; 4-$C_9H_{19}C_6H_4$, 96; 4-$C_{12}H_{25}C_6H_4$, 90; 3,4-$(CH_2)_3C_6H_3$, 80; 3-fluorenyl, 96 [28]

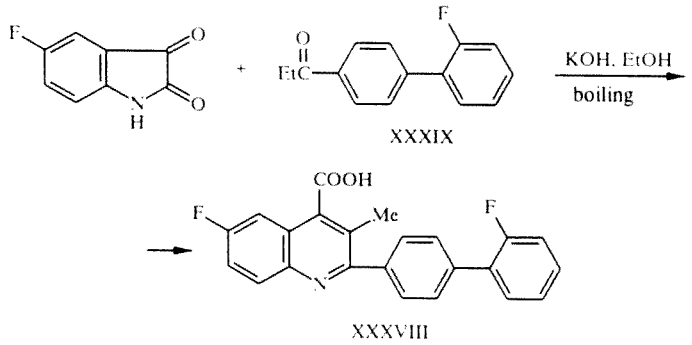
The synthesis of 6-bromo-2-aryl-4-quinolinecarboxylic acids from 5-bromoisatin and methyl aryl ketones was described [29].

The structure of the aryl radical in the initial methyl aryl ketones (XXXV) has a very large effect on the yields of the acids (XXXVI), which were obtained by a two-stage synthesis with isolation of the intermediate carbinols (XXXVII) [30]:



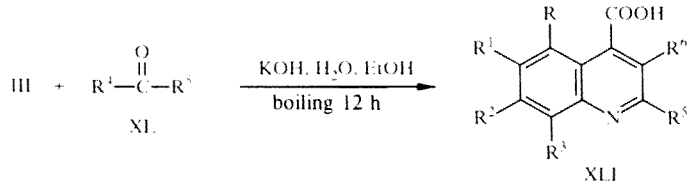
Ar, yield, %: 3-$NO_2C_6H_4$, 8; 4-$NO_2C_6H_4$, 7; Ph, 90; 3-$H_2NC_6H_4$, 52; 4-PhC_6H_4, 57; 4-(4-$NO_2C_6H_4$)C_6H_4, 68

A procedure for the synthesis of 6-fluoro-3-methyl-2-(2^1-fluoro-4-biphenylyl)-4-quinolinecarboxylic acid (XXXVIII) from 5-fluoroisatin (XVII) (R = F) and ketones (XXXIX) in the presence of potassium hydroxide in ethanol was patented [31, 32]:



The production of 4-quinolinecarboxylic acids, containing various substituents at positions 2, 3, 5, 6, 7, and 8, from the ketone (XXXIX) or its derivatives, and compounds of the isatin series containing the appropriate substituents at positions 4, 5, 6, and 7, was claimed in the patent [31].

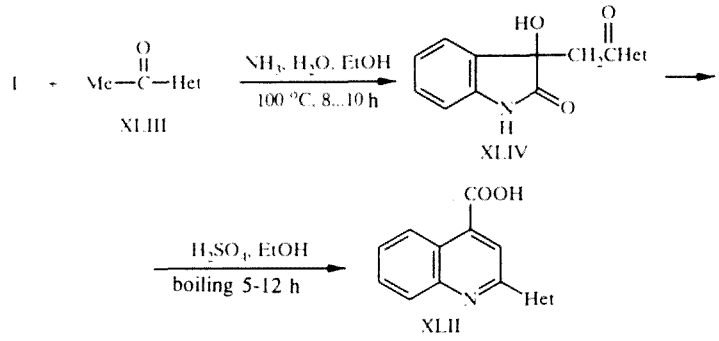
In two other patents [33, 34] the condensation of isatin derivatives (III) with the ketones (XL), leading to the acids (XLI), was described:



R, R^1, R^2, R^3 = H,halogen, Me, CF_3; R^4 = Me, Et; R^5 = substituted phenyl; R^6 = H, Me

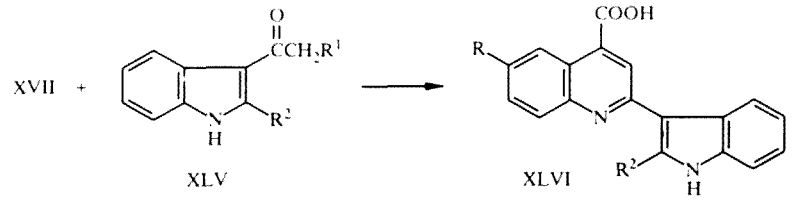
2.1.4. Reactions with Alkyl Heteryl Ketones. In recent years investigators have shown increased interest in study of the Pfitzinger reaction using ketones containing heterocyclic radicals.

2-Heteryl-4-quinolinecarboxylic acids (XLII) were obtained by a two-stage synthesis, i.e., by the condensation of isatin (I) with methyl heteryl ketones (XLIII) in the presence of aqueous ammonia followed by cyclocondensation of the obtained carbinols (XLIV) by boiling with sulfuric acid in ethanol [30]:



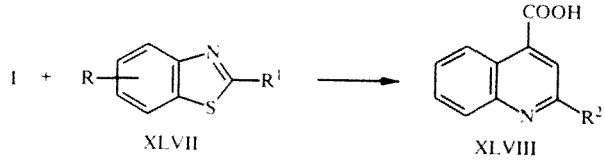
Het, yield of (XVII), %: 2-thienyl, 92; 2,2'-bithienyl-5

The condensation of compounds (XVII) (R = H, Me, Br) with the indole derivatives (XLV) led to 2-(3-indolyl)-4-quinolinecarboxylic acids (XLVI) [35]:



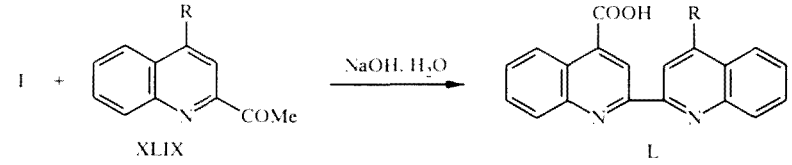
R = H, Me, Br; R^1 = H, Me, CH_2COOH; R^2 = H, Me, Ph

When isatin (I) is boiled with the acetal derivatives (XLVII) in a water—methanol solution of sodium hydroxide for 12 h, the corresponding 4-quinolinecarboxylic acids (XLVIII) are formed [36]:



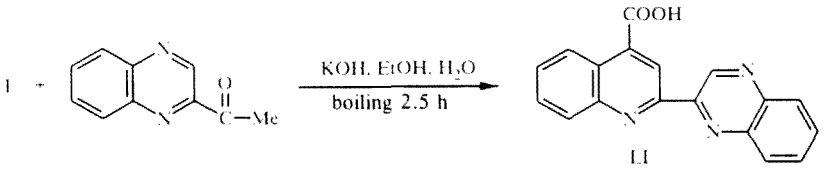
R, R^1, R^2, yield, %: 6-MeCO, Me, 2-methyl-6-benzothiazolyl, 50; 5-MeCO, Me, 2-methyl-5-benzothiazolyl, 20; H, COMe, 2-benzothiazolyl, 40.

Compounds containing two quinoline rings (L) were obtained by the reaction of isatin (I) with the ketones (XLIX) [37, 38]:

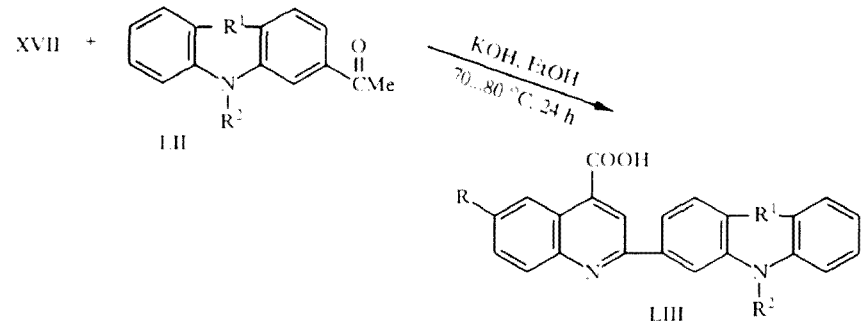


R, yield, %: Ph, 36 [37]; H, 80 [38]

The condensation of isatin (I) with 2-acetylquinoxaline was carried out by boiling in the presence of potassium hydroxide in an aqueous alcohol medium for 2.5 h; the yield of the condensation product (LI) was 35% [39]:

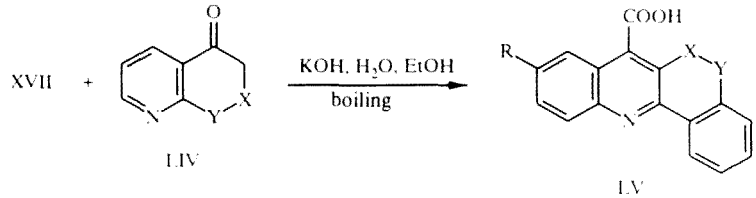


The carboxylic acids (LIII) were obtained from compounds (XVII) (R = H, Me, OMe, F, Cl) by the Pfitzinger reaction with the ketones (LII) [28, 40]:



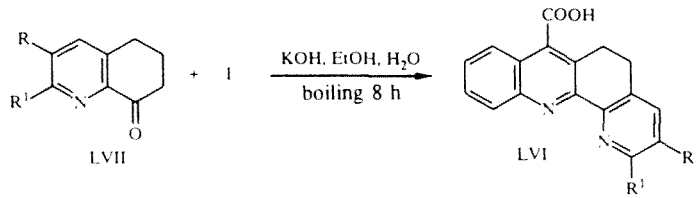
R, R^1, R^2, yield , %: H, S, H, 88; H, single bond , H, 78 [28]; H, S, H, —; H, S, $CH_2CH_2NMe_2$, —; F, S, H, —; F, S, CH_2CH_2NMe, —; Cl, S, H, —; Cl, S, $CH_2CH_2NMe_2$, —; Me, S, H, —; Me, S, $CH_2CH_2NMe_2$, —; OMe, S, H, —; OMe, S, $CH_2CH_2NMe_2$, — [40]

The reaction of isatin or its derivatives (XVII) (R = H, Me, F, Cl, Br, I) with the cyclic ketones (LIV) in the presence of potassium hydroxide in an aqueous alcohol medium resulted in the formation of the tetracyclic compounds (LV) [41-43]:



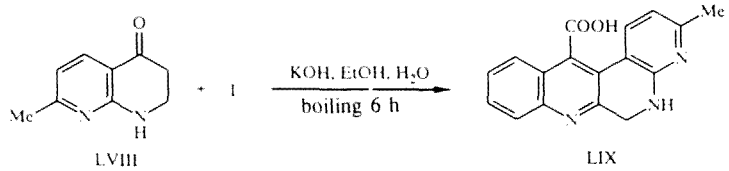
R, X, Y, yield , %: H, O, single bond *, 13; F, O, *, 12; Cl, O, *, 19; Br, O, *, 20; I, O, *, 22 [41]; H, O, CH_2, satisfactory yield **; Cl, O, CH_2, **; Br, O, CH_2, **; Me, O, CH_2, ** [42]; H, CH_2, O, 69,5; Cl, CH_2, O, —; Br, CH_2, O, —; Me, CH_2, O, — [43]

Partially hydrogenated derivatives of benzo[b]-1,10-phenanthroline-8-carboxylic acids (LVI) were synthesized from isatin (I) and ketones (LVII) by boiling in an aqueous alcohol solution of potassium hydroxide for 8 h [44]:

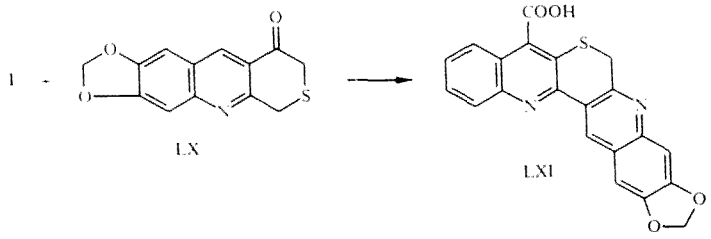


R, R^1, yield % $-(CH_2)_4-$ 78, $-CH=CH-CH=CH-$, 78

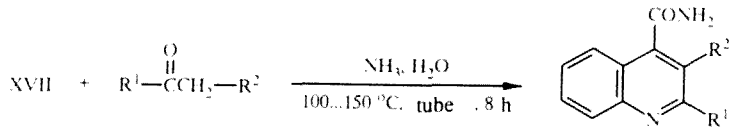
The recyclization of isatin (I) in reaction with the ketones (LVIII) in the presence of potassium hydroxide in boiling aqueous alcohol leads to 3-methyl-5,6-dihydroquino[3,2-c]-1,8-naphthiridine-7-carboxylic acid (LIX) [45, 46]:



Compound (LXI), containing six condensed rings of which four are heterocyclic, was synthesized by the Pfitzinger reaction from isatin (I) and the ketone (LX) [47]:

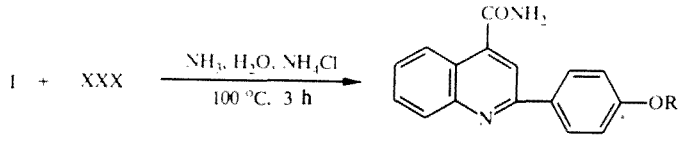


A series of authors [24, 48, 49] have shown that the realization of the Pfitzinger reaction in the presence of ammonia at 100-150°C leads to the formation of 4-quinolinecarboxamides. This modification of the Pfitzinger reaction was carried out with isatin or its derivatives (XVII) (R = H, Me, MeO, Br) and dialkyl ketones [48, 49], alicyclic ketones [49], alkyl aryl ketones [49], or alkyl heteryl ketones [49]:



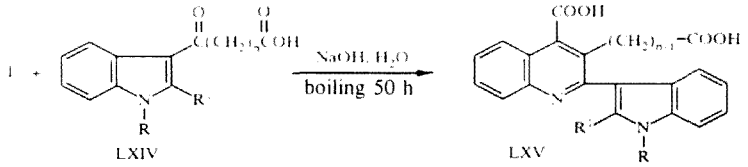
R, R^1, R^2, yield, %: H, Me, Me, 61,8 [48]; H, $—(CH_2)_4—$, 85; Me, $—(CH_2)_4—$, 84; MeO, $—(CH_2)_4—$, 70; Br, $—(CH_2)_4—$, 78; H, Et, Me, 84; H, Ph, H, 36; H, 4-piperidyl, H, 41 [49]

The reaction of isatin (I) with alkoxyacetophenones (XXX) was conducted at 100°C in aqueous ammonia in the presence of ammonium chloride [24]:



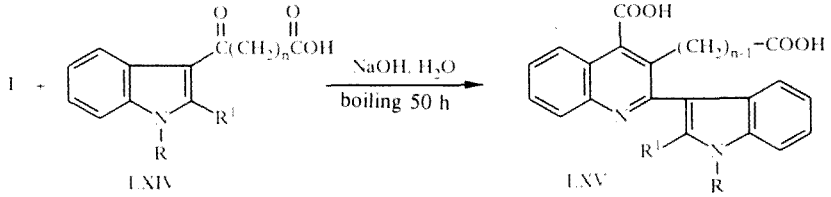
R, yield, %: Me, 55,5; Et, 58,1; Pr, 60; Bu, 54,4; $n\text{-}C_5H_{11}$, 50,5

2.2. Reactions with Keto Acids and Their Esters. In boiling ethanol in the presence of potassium hydroxide, γ-keto acids condense with isatin (I), giving the dicarboxylic acids (LXIII) [50, 51]:



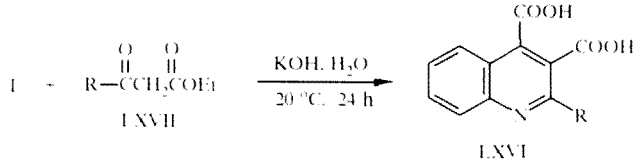
R, yield, %: $4\text{-}MeC_6H_4$, 53; $4\text{-}ClC_6H_4$, 66; Ph, 65, [50]; 1-naphthyl, —; Ph or substituted phenyl, —; 3-indolyl, — [51]

The reaction of β-, γ-, and δ-keto carboxylic acids of the indole series (LXIV) with isatin (I) in the presence of 33% aqueous sodium hydroxide with boiling for 50 h gave the dicarboxylic acids (LXV) [52, 53]:



R, R^1, p, yield, %: H, H, 1, 57; H, Me, 1, 53; Me, H, 1, 55; Me, Me, 1, 53; H, H, 2, 45; Me, H, 2, 53; H, Me, 2, 40; H, Me, 3, 41

There is one report on the synthesis of dicarboxylic acids of the quinoline series (LXVI) by the condensation of isatin (I) with the ethyl esters of β-keto acids (LXVII) [54]:

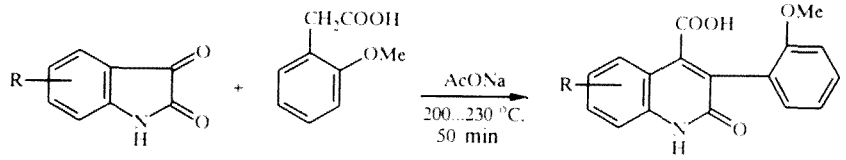


R, yield, %: Me, 88; Ph, 82 (75 h); $4\text{-}MeOC_6H_4$, 75; $3,4\text{-}(MeO)_2C_6H_3$, 71

3. Reactions with Carboxylic Acids and Their Derivatives

The use of carboxylic acids and their derivatives in the Pfitzinger reaction has made it possible to extend the application range of this important method for the synthesis of quinoline derivatives considerably. Over the last two decades the literature has contained data on the use of the acids themselves and their esters, acid chlorides, and anhydrides in this reaction.

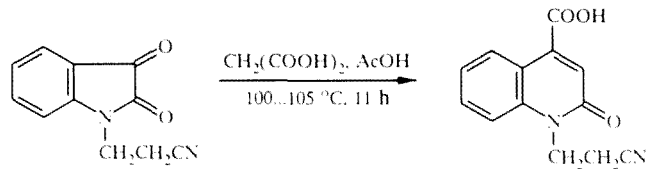
3.1. Reactions with Acids. Isatin and its derivatives (LXVIII) (R = H, Cl, Br, I, F) are converted into the carboxylic acids (LXIX) as a result of cyclocondensation with 2-methoxyphenylacetic acid at 200-230°C in the presence of sodium acetate [55, 56]:



LXVIII LXIX

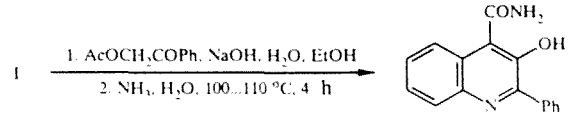
R, position of R in (LXIX), yield, %: H, –, 52 [55]; F, 6.49; Cl, 6.47; Br, 6.35; J, 6.26; F 7.58; Cl, 7.54; Br, 7.81; I, 7.81 [56]

When N-(β-cyanoethyl)isatin is heated with malonic acid in acetic acid, the monocarboxylic acid 1-(β-cyanoethyl)-4-carboxy-2-quinolone (LXX) and not the dicarboxylic acid is formed with a 65.8% yield [57]:



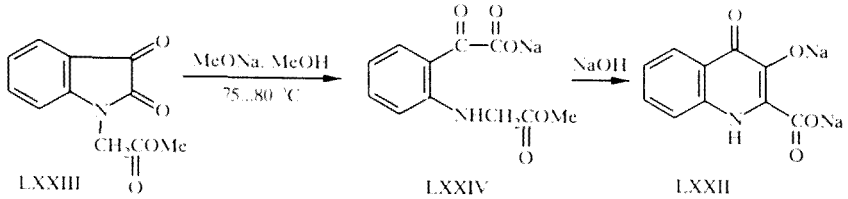
LXX

3.2. Reactions with Esters. The recyclization product [the amide (LXXI)] is formed with a 23% yield when a mixture of isatin (I) and phenacyl acetate is heated in an aqueous alcohol solution of sodium hydroxide, and the reaction mixture is then treated with an aqueous solution of ammonia in an autoclave [58]:



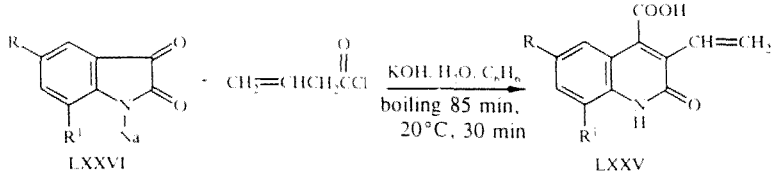
LXXI

The quinolone derivative (LXXII) was synthesized as a result of the treatment of N-(methoxycarbonylmethyl)isatin (LXXIII) with sodium methoxide in methanol. In this case the reaction begins with cleavage of the N—$C_{(2)}$ bond followed by cyclization of the cleavage product (LXXIV). The yield of the recyclization product is 40% [59].



LXXIII LXXIV LXXII

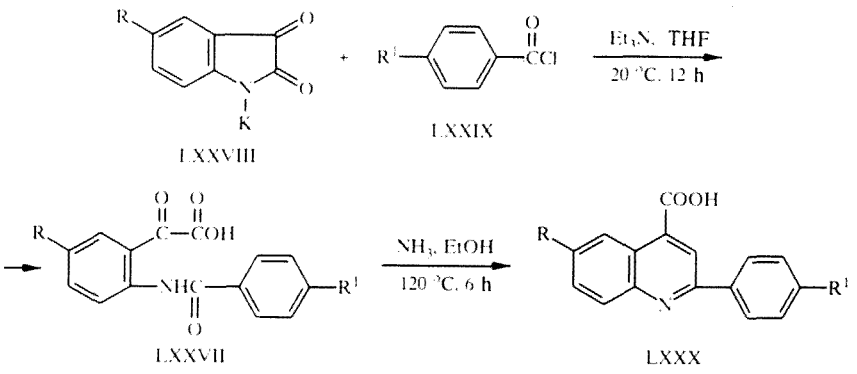
3.3. Reactions with Acid Chlorides. The condensation of isatin and its substituted derivatives (LXXVI) with vinylacetyl chloride gives high yields of 3-vinyl-2-oxo-4-quinolinecarboxylic acids (LXXV) [60, 61]:



LXXVI LXXV

R, R^1, yield, %: H, H, 80; Cl, H, 82; Me, H, 84 [60]; Br, H, –; Br, Br, – [61]

N-Acylisatinic acids (LXXVII), formed from the N-potassium derivatives (LXXVIII) and the acid chlorides (LXXIX) in the presence of triethylamine, are converted into the corresponding 2-aryl-4-quinolinecarboxylic acids (LXXX) when heated in an autoclave with an alcohol solution of ammonia [62]:

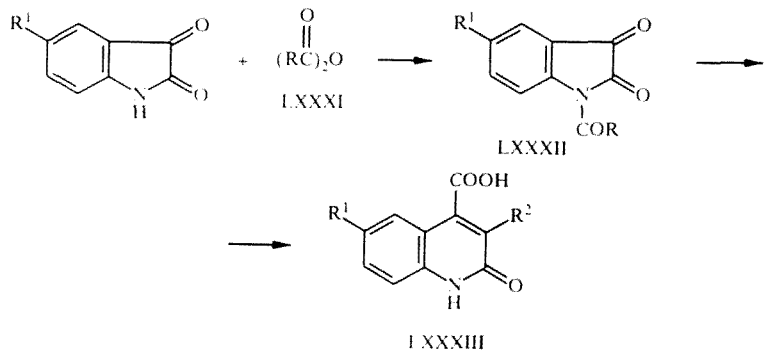


LXXVIII LXXIX LXXVII LXXX

R, R^1: H, Ph; F, Ph; Me, Ph; Me, n-C_5H_{11}

3.4. Reactions with Anhydrides. The N-acylation of 5-methylisatin with acetic anhydride (LXXXI) (R = Me) for 1 h in the presence of sodium hydride at 80°C gives the N-acyl derivative (LXXXII) (R = R^1 = Me).

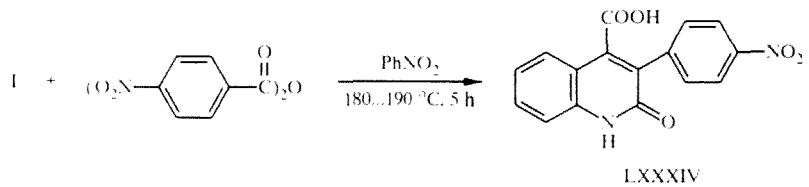
The N-acyl derivative (LXXXII) (R = Pr, R^1 = H) is formed when isatin (I) is heated with the anhydride (LXXXI) (R = Pr) at 140°C for 30 min in the presence of pyridine. The N-acyl derivatives (LXXXII) undergo recyclization when boiled with dilute aqueous solutions of sodium hydroxide for 30 min and form the carboxylic acids (LXXXIII) [63]:



LXXXI LXXXII LXXXIII

R, R^1, R^2, yield, %: Me, Me, H, 75; Pr, H, Et, 26

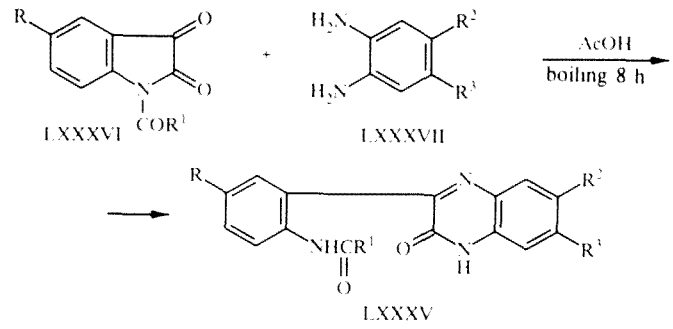
The condensation of isatin (I) with 4-nitrobenzoic anhydride was carried out under harsh conditions in the absence of bases. The yield of the condensation product (LXXXIV) amounted to 51.5% [64]:



LXXXIV

4. Reactions with Diamines, Hydroxyamines, and Mercaptoamines

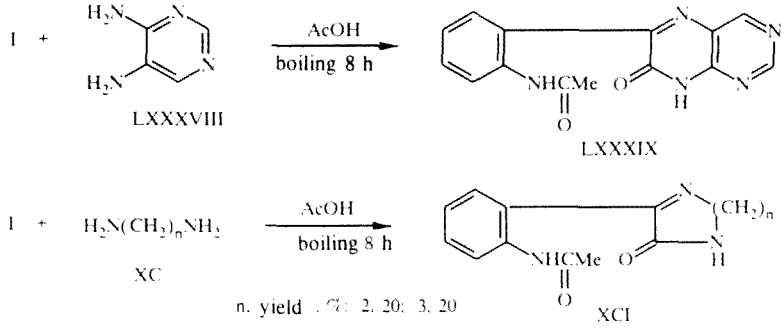
The condensation of isatin and its derivatives with bifunctional compounds is a convenient and promising method for the synthesis of heterocyclic systems containing a pyrazine, 1,4-oxazine, 1,4-thiazine, or 1,4-diazepine ring and also for the production of spiro compounds of the heterocyclic series.



R = H, Br; R^1 = Me, Et, Pr, Ph, 4-$O_2NC_6H_4$, 4-ClC_6H_4; R^2 = H, Me; R^3 = H, Cl, NO_2

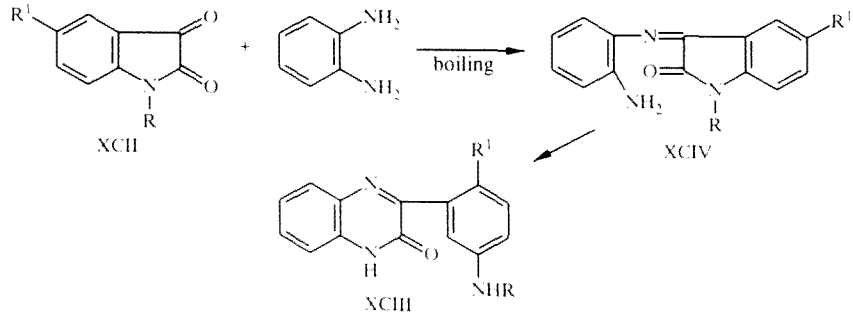
3-Arylquinoxalin-2-ones (LXXXV) were synthesized from the substituted thiazines (LXXXVI) and diamines (LXXXVII) [65].

Under the same conditions, compound (LXXXIX) was obtained from isatin (I) and 4,5-diaminopyrimidine (LXXXVIII), and 3-(2-acetylaminophenyl)-1,2,5,6-tetrahydropyrazine (XCI) (n = 2) or the 1,4-diazepine derivative (XCI) (n = 3) was obtained from isatin (I) and the diamines (XC) (n = 2, 3) [65]:



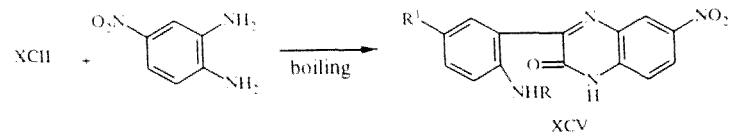
n, yield, %: 2, 20; 3, 20

A systematic study of the reaction of o-phenylenediamine with isatins (XCII) using various solvents made it possible to establish [66] that the nature of the solvent and the structure of the initial compound (XCII) have a substantial effect on the yield of the reaction products (XCIII). It was also shown that the process includes the formation of the azomethines (XCIV) as intermediate stage:



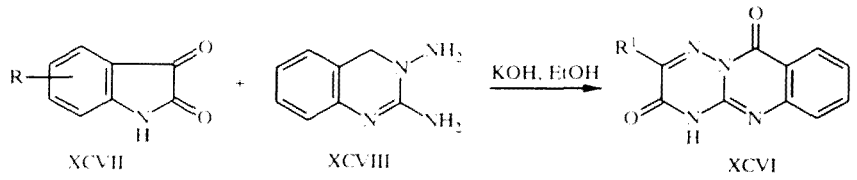
R, R^1, yield of XCIII, % in EtOH, EtOH + HCl, C_6H_6, C_6H_6 + 3% AcOH: H, H, 6, 15, 70, 78 and 0; H, Br, 8, 5, 97, 94 and 24; H, NO_2, 25, 19, 95, 91 and 66; Me, H, 4, 21, 42, 26, 0; Me, Br, 13, 0, 59, 60 and 2; Me, NO_2, 25, 14, 82, 81 and 44; COMe, H, 77, 0, 99, 95 and 93

In [67] the effect of solvents (acetic acid or ethanol + hydrochloric acid) on the yields of the products from the condensation of the isatin derivatives (XCII) with 4-nitro-1,2-diaminobenzene was investigated, and it was established that the yields of the required compounds (XCV) increase when the reaction is conducted in acetic acid:



R, R^1, yield, % in AcOH or EtOH + HCl: Me, NO_2, 64 or 46; COMe, H, 98 or 33

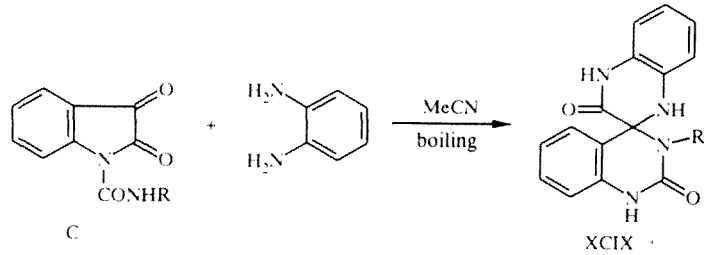
The tricyclic systems (XCVI) were synthesized by the condensation of compounds (XCVII) with the diamine (XCVIII) in the presence of an alcohol solution of potassium hydroxide [68]:



XCVII XCVIII XCVI

R, R^1 6-F, 2-H_2N-4-FC_6H_3; 5-F, 2-H_2N-5-FC_6H_3; 4-CF_3, 2-H_2N-6-$CF_3C_6H_3$

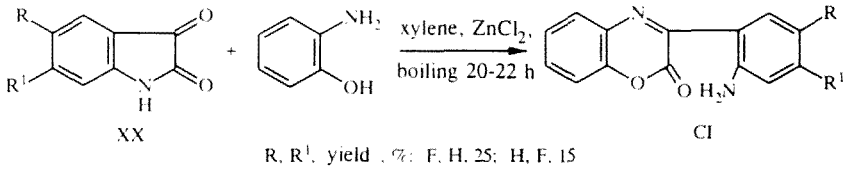
The spiro compounds (XCIX) are formed with excellent yields when the ureas (C) are boiled with o-phenylenediamine in acetonitrile [69]:



C XCIX

R, yield, %: Me, 95; Ph, 100

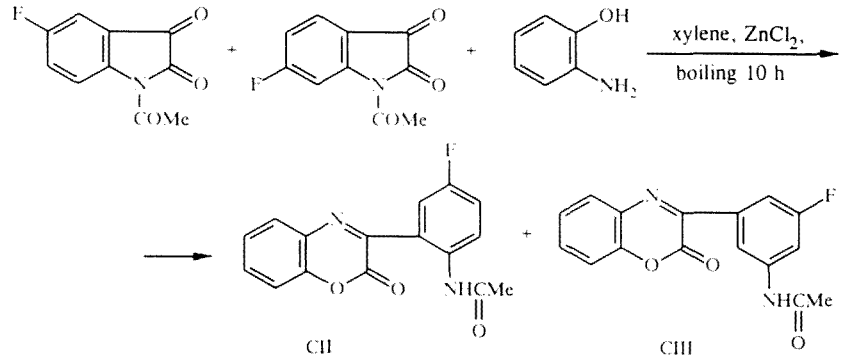
The introduction of a fluorine atom into the isatin molecule considerably reduces its reactivity in reaction with bifunctional reagents. The reaction between 5- or 6-fluoroisatin and o-aminophenol takes place more slowly than in the case of isatin itself, and the reaction products (CI) from the fluorine derivative are formed with lower yields [70]:



XX CI

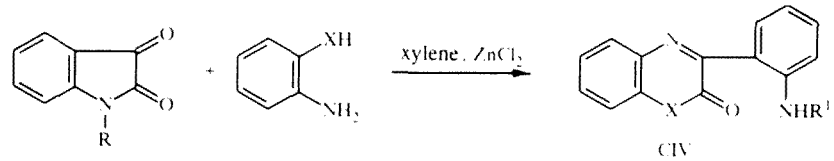
R, R^1, yield, %: F, H, 25; H, F, 15

N-Acetylation of fluoroisatins leads to an increase in the reactivity of 5- and 6-fluoroisatins and to an increase in the yields of the recyclization products. Thus, during the reaction of o-aminophenol with a mixture of the N-acetyl derivatives of 5-fluoroisatin and 6-fluoroisatin, compounds (CII) and (CIII) are formed with yields of 43 and 40% respectively [70]:



CII CIII

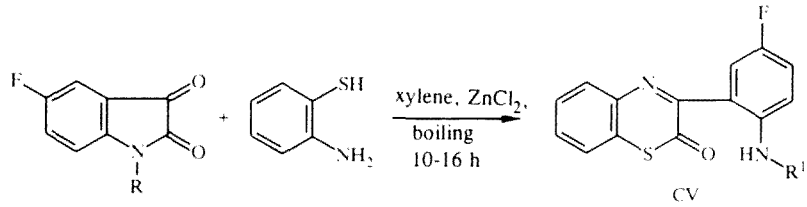
In [71-73] the reaction of compounds of the isatin series with o-aminophenol and o-aminothiophenol was studied in detail. The reactions of isatin and N-acetylisatin with o-aminophenol or o-aminothiophenol were conducted in xylene in the presence of anhydrous zinc chloride at 20°C or in the boiling solvent for 3 h. It was established that only the recyclization products were formed in the case of o-aminophenol, while deacylation of the HCOMe group [compound (CIV), R^1 = H] was observed in addition to recyclization [compound (CIV), R^1 = COMe] when o-aminothiophenol was used [71]:



CIV

R, R^1, X, yield, % at 20°C and with boiling (3 h): H, H, O, 0 and 25; COMe, COMe, O, 0 and 48; H, H, S, 18 and 20; (COMe, COMe, S, 15 and 40 + COMe, H, S, 20 and 30)

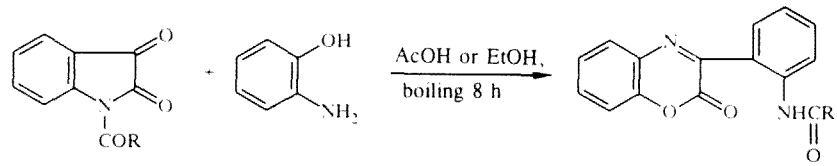
Whereas the reaction of isatin or N-methylisatin with o-aminophenol in boiling xylene requires 3 h, for the reactions with 5-fluoroisatin or 1-acetyl-5-fluoroisatin it is necessary to boil the reaction mixtures for 16 or 10 h respectively. It was noticed that when 1-acetyl-5-fluoroisatin was used the deacetylated product (CV) (R = H) was formed in addition to the recyclization product (CV) (R = Me) [72]:



CV

R, R^1, yield , %: H, H, 30; COMe, (COMe, COMe, 25 + COMe, H, 40)

Only the recyclization products (CVI) were obtained as a result of the reaction of N-acetylisatins (CVII) with o-aminophenol in boiling acetic acid or ethanol [73]:



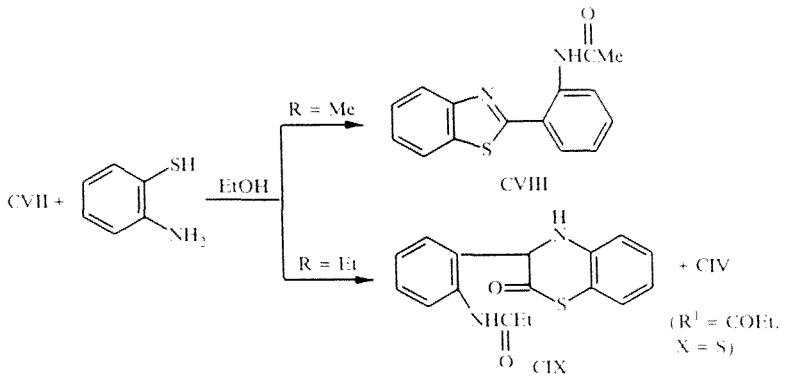
CVII

CVI

R = Me, Et, Pr, Ph

Deacylation also did not occur when the condensation of compounds (CVII) (R = Me, Et) with o-aminophenol was conducted in acetic acid, and the only reaction products were the recyclization products (CIV) (R^1 = COMe, COEt; X = S) [73].

Completely different results were obtained when the reaction of the N-acyl derivatives (CVII) (R = Me, Et) with o-aminothiophenol was carried out in ethanol. The reaction with compound (CVII) (R = Me) gave 2-(2-acetylaminophenyl)benzothiazole (CVIII), while the reaction with compound (CVII) (R = Et) gave 3-(2-propylaminophenyl)-3,4-dihydro-1,4-benzothiazin-2-one (CIX) [73]:

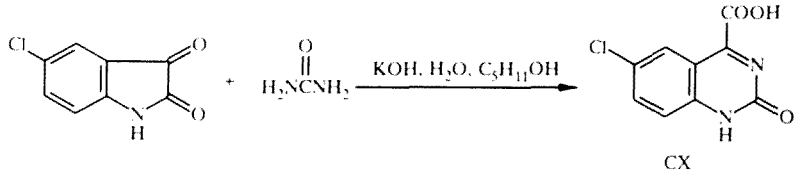


CVIII

CIX

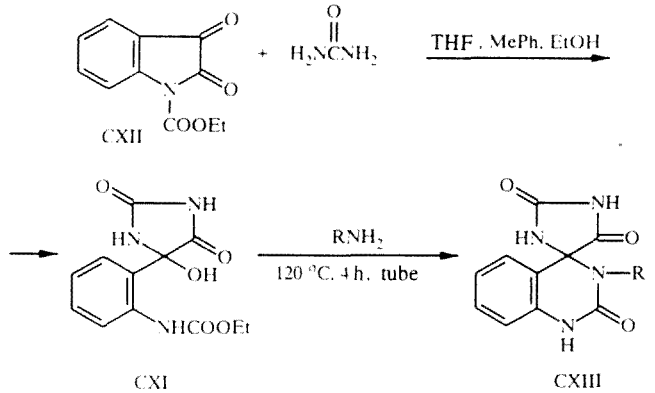
5. Reactions with Urea, Thiourea, and Their Derivatives

As a rule, quinazoline derivatives are formed as a result of the reaction of compounds of the isatin series with urea, thiourea, and their derivatives. Thus, the condensation of 5-chloroisatin with urea in the presence of an aqueous solution of potassium hydroxide in n-pentanol gave 6-chloro-2-quinazolone-4-carboxylic acid (CX) [74]:



CX

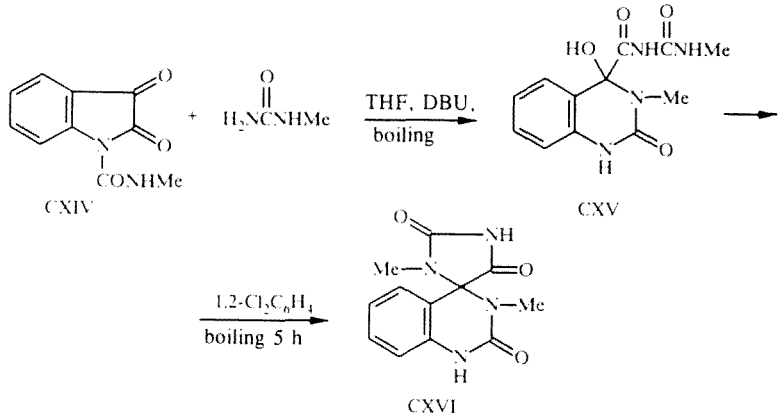
Compound (CXI), formed from N-ethoxycarbonylisatin (CXII) and urea, is converted into imidazoline-4-spiro-4[1](1H)-quinazoline-2,2[1],5(3[1]H)-triones (CXIII) when heated in a tube at 120°C for 4 h with ammonia, hydrazine, or hydroxylamine [75]:



CXII CXI CXIII

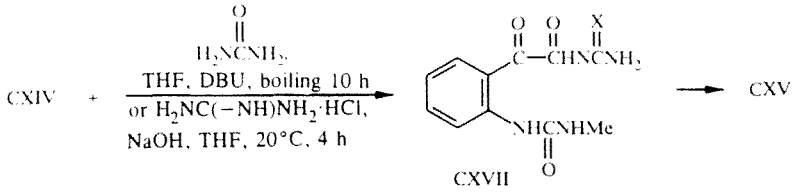
R, yield, %: H, 59; NH_2, 57; OH, 15

In reaction with N-methylurea in boiling THF for 5 h in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene, N-methylaminocarbonylisatin (CXIV) undergoes recyclization with a 29% yield to the 2-quinazolone derivative (CXV). When boiled in o-dichlorobenzene, the latter is transformed with a 97% yield into the spiro compound (CXVI) [75]:



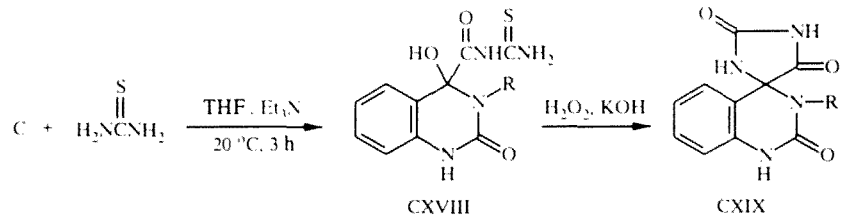
CXIV CXV CXVI

According to the data in [76], the synthesis of compounds of the (CXV) type from the isatin derivative (CXIV) and urea or guanidine takes place through the formation of the intermediate compounds (CXVII):



CXVII

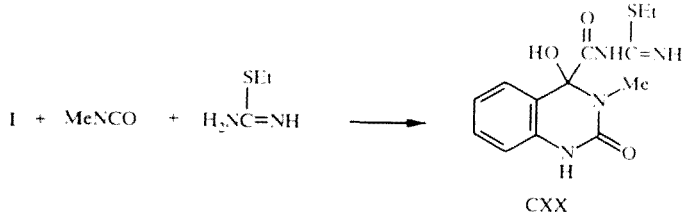
The isatin derivative (C) reacts with thiourea in the presence of triethylamine with the formation of compounds (CXVIII), which are transformed into the spiro compounds (CXIX) as a result of treatment with hydrogen peroxide in the presence of sodium hydroxide [77]:



CXVIII CXIX

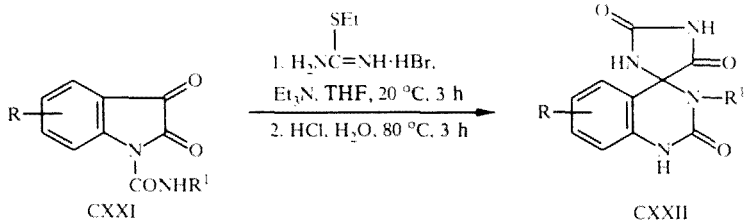
R, yield of CXIX, %: Me, 85; Et, 75; Me_2CH, 69; Bu, 53; $PhCH_2$, 69; Ph, 70

A method was patented for the synthesis of the 2-quinazolone (CXX) by the reaction of isatin (I) with methyl isocyanate and S-ethylthiourea [78]:



CXX

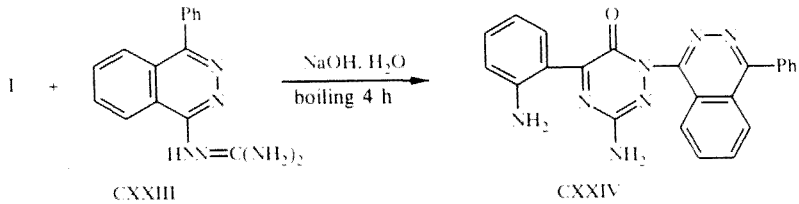
The reaction of the isatin derivatives (CXXI) with S-ethylthiourea hydrobromide was conducted in THF in the presence of triethylamine, and the reaction mixture was then treated with hydrochloric acid with heat, resulting in the formation of the spiro compounds (CXXII) [75]:



CXXI CXXII

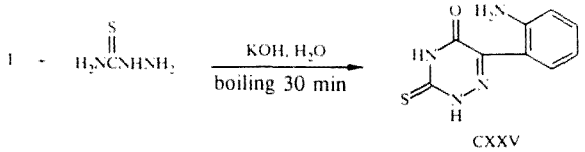
R, R^1 [position of substituent in (CXXII)], yield, %: H, Me, 91; H, Et, 75; H, Me_2CH, 69; H, Bu, 53; H, $PhCH_2$, 69; H, Ph, 72; 6-Cl, Me, 54; 6-Me, Me, 57; 7-F, Me, 66; 7-Cl, Me, 53; 7-Br, Me, 50; 7-NO_2, Me, 26; 7-OMe, Me, 8; 7-COOEt, Me, 55; 7-Me, Me, 73; 8-Cl, Me, 75; 8-Me, Me, 65; 8-OMe, Me, 73; 8-NO_2, Me, 50; 8-F, Me, 50; 7,8-Cl_2, Me, 68; 7-Cl, 8-Me, Me, 50; 7-Cl, 8-OMe, Me, 55; 6,7-OCH_2O-, Me, 51; 6,7,8-F_3, Me, 55)

The recyclization of isatin (I) in the reaction with the guanidine derivative (CXXIII) in a boiling aqueous solution of sodium hydroxide led to 3-amino-1-(4-phenyl-1-phthalazinyl)-5-(2-aminophenyl)-1,2,4-triazin-6-one (CXXIV) [79]:



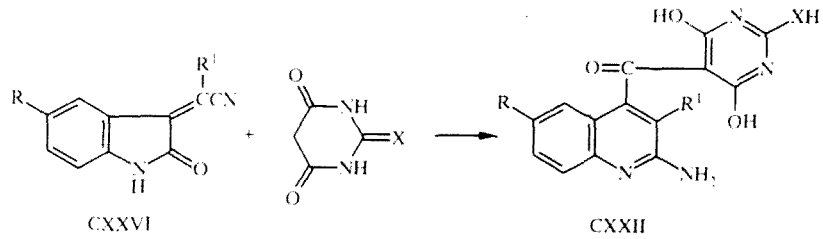
CXXIII CXXIV

6-(2-Aminophenyl)-1,2,4-triazine-3-thion-5(2H)-one (CXXV) is formed when a mixture of isatin (I) with thiosemicarbazide in a dilute aqueous solution of potassium hydroxide is boiled [80]:



CXXV

The ketones (CXXVII), containing quinoline and pyrimidine rings, were synthesized from the products of the condensation of isatin derivatives or of isatin itself with malononitrile or with cyanoacetic ester (CXXVI) and barbituric or thiobarbituric acid [81]:

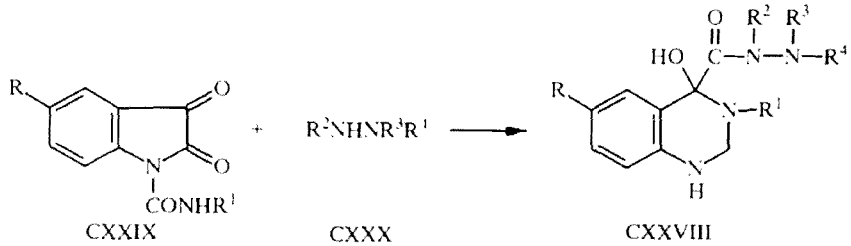


CXXVI CXXII

R, R^1, X: H, CN, O; H, CN, S; H, COOEt, O; H, COOEt, S; NO_2, CN, O; Br, COOEt, S

6. Reactions with Hydrazine and Its Derivatives

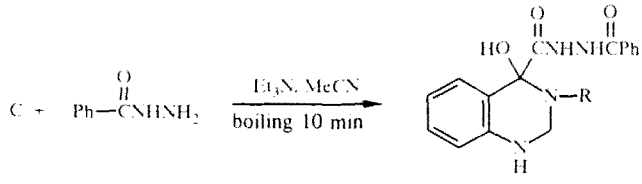
A large number of hydrazides (CXXVIII) have been synthesized by the reaction of compounds of the isatin series (CXXIX) with hydrazine or its derivatives (CXXX) (at 20°C, 2 h in chloroform [82] or 24 h in THF [83]):



CXXIX CXXX CXXVIII

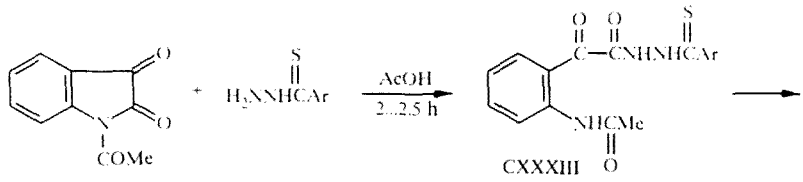
R, R^1, R^2, R^3, R^4, yield, %: H, Me, H, H, H, 99; H, Ph, H, H, H, 99; Br, Ph, H, H, H, 97; H, $MeOCH_2$, H, H, H, —; Br, Me, H, H, H, 73; H, Me, Me, H, H, —; H, Me, H, Me, Me, 85; H, Me, H, —; $NCH_2CH_2OCH_2CH_2$, —; H, Ph, H, —$NCH_2CH_2OCH_2CH_2$, —; H, Ph, H, H, $PhCH_2$, 44, H, H, Ph, H, H, —, H, Ph, H, Me, 2-(2-pyridyl)ethyl —; H, 4-$CF_3C_6H_4$, H, Me, Me, 66, H, 3-Cl, 4-$CF_3C_6H_3$, H, Me, Me, 59; H, 4-ClC_6H_4, H, H, H, 97; H, Me, H, H, Ph, —; H, Me, H, H, CH_2CH_2OH, 53 [82]; H, Me, H, Me, Me, —; H, Me, H, H, Ph, —, H, Ph, H, —$CH_2CH_2OCH_2CH_2$—, —; H, Ph, H, H, COOEt, — [83]

By briefly boiling the isatin derivatives (C) with benzoylhydrazine in acetonitrile in the presence of triethylamine, it is possible to obtain N^1-benzoylhydrazides (CXXXI) with yields of 94-95% [69]:

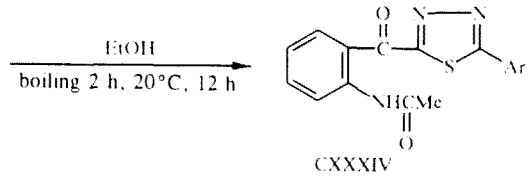


R = Me, Ph CXXXI

Opening of the five-membered ring of N-acetylisatin by the action of thioaroylhydrazines in acetic acid leads to compounds (CXXXIII), which are transformed when heated in alcohol into 2-(2-acetylaminobenzoyl)-5-aryl-1,3,4-thiadiazoles (XXXIV) [84]:



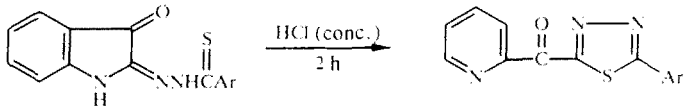
CXXXIII



CXXXIV

Ar, yield of CXXXIV, %: Ph, 98.6; 4-MeOC$_6$H$_4$, 32.4; Pr, Ph, —; 4-MeOC$_6$H$_4$, —

The ketones (CXXXV) (Ar = Ph, 4-MeOC$_6$H$_4$, 3-ClC$_6$H$_4$) are formed as a result of the treatment of compounds (CXXXVI) with concentrated hydrochloric acid [85]:

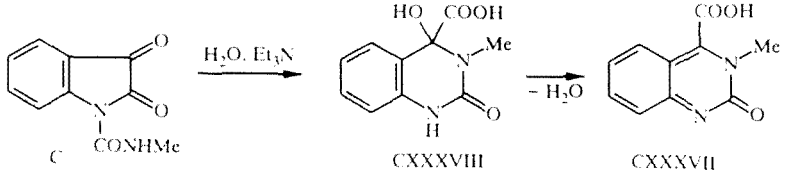


CXXXVI CXXXV

7. Reactions of N-Aminocarbonylisatins with Water, Alcohols, or Amines

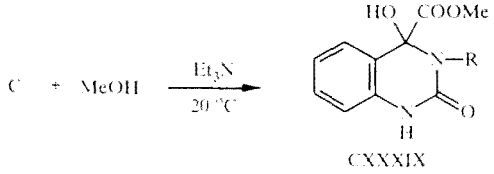
In these reactions, leading to compounds of the quinazoline series, the main starting materials are ureas — the products from the addition of isatin (I) or its derivatives to isocyanates.

The reaction of compound (C) (R = Me) with water in the presence of triethylamine at 20°C gave 3-methyl-2-oxo-4-quinazolinecarboxylic acid (CXXXVII) with a 78% yield. The initial reaction product is clearly the hydroxy acid (CXXXVIII), which is dehydrated in the reaction process and converted into the acid (CXXXIX) [83]:



C CXXXVIII CXXXVII

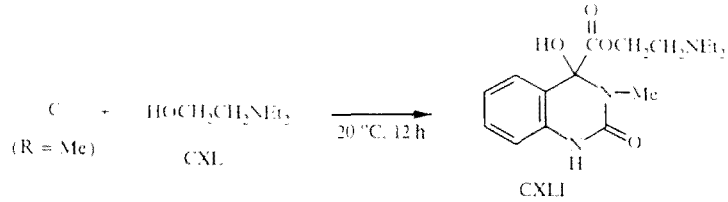
The ureas (C) (R = Me, Ph) react readily with methanol in the presence of triethylamine, and the esters (CXXXIX) are formed with high yields [69]:



CXXXIX

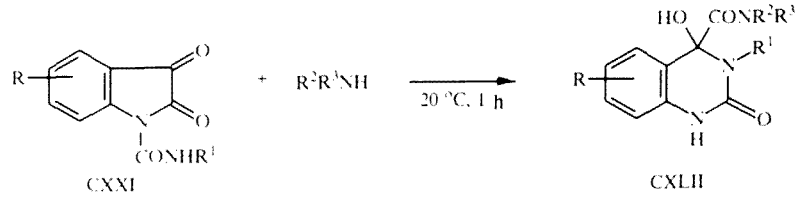
R, time (h), yield, %: Me, 1, 95; Ph, 12, 92

The alcohol (CXL), which contains a nucleophilic group in its molecule, is capable of reacting with the ureas in the absence of triethylamine, forming the quinazoline derivative (CXLI).



CXLI

The reaction of the N-aminocarbonyl derivatives of isatin with primary or secondary amines also does not require catalysts. Thus, a large number of amides (CXLII) were synthesized by the reaction of the ureas (CXXI) with amines of the aliphatic, alicyclic, aromatic, and heterocyclic series at 20°C in THF or dioxane [83, 8]:

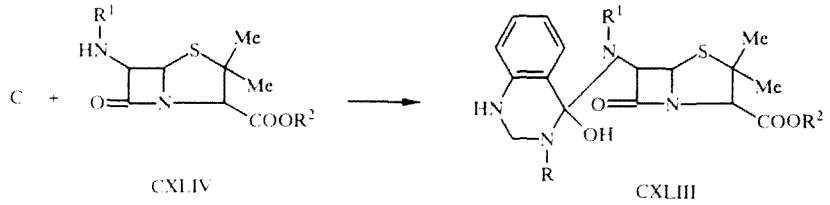


CXXI CXLII

R = H, Me, Br, R^1 = Me, $MeOCH_2$, Ph, COOEt, CH_2=$CHCH_2$, $(CH_2)_2COOCH_2CHMe_2$; R^2 = H, Me, $(CH_2)_6COOCHMe_2$, Ph, R^3 = CH_2CH_2OH, $(CH_2)_6NH_2$, —CH_2—CH—CH—CH, $PhCH_2$, 4-$MeOC_6H_4$, 1-adamantyl , Ph, $C_{12}H_{25}$, $(CH_2)_3NMe_2$, CH_2CH_2CN, $(CH_2)_6COOCHMe_2$, 2-pyridylmethyl , Ph, 1-naphthyl, 2-pyridyl, 2-furyl, Et, Me; $R^2 + R^3$ = —$CH_2CH_2N(Me)CH_2CH_2$—

However, the authors in [69] carried out the reaction of the ureas (C) (R = Me, Ph) with aniline in the presence of triethylamine in acetonitrile at 20°C and obtained the anilides (CXLII) (R = H, R^1 = Me, Ph, R^2 = H, R^3 = Ph).

The production of compounds (CXLIII) from the ureas (C) and the derivatives of 6-penicillanic acid (CXLIV) was patented [87]:



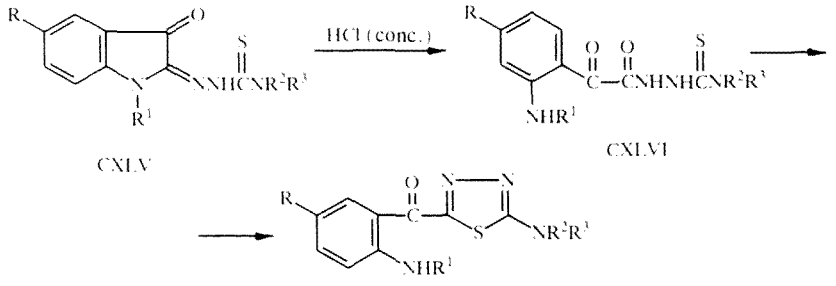
CXLIV CXLIII

R, R^1, R^2 = Me, CO, NHEt; CH_2OMe, CO, NHEt; $CH_2CH_2COOCH_2CHMe_2$, CO, NHEt; Ph, CO, Na; Me, CO, CH_2CH_2—C_6H_4Cl-4; Me, CONHCH(Ph)CO, Na

8. Recyclization of Thiosemicarbazones

With the 2-thiosemicarbazones or 3-thiosemithiocarbazones of isatin as starting compounds, it is possible to synthesize specific aryl 1,3,4-thiadiazolyl ketones or 1,2,4-triazine derivatives respectively.

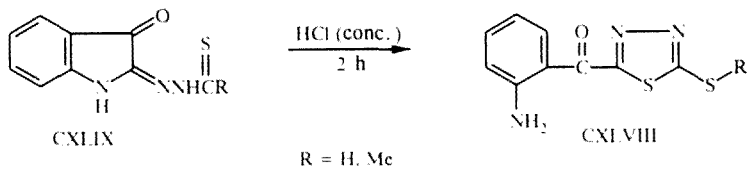
During treatment of the 2-thiosemicarbazones (CXLV) with concentrated hydrochloric acid, the five-membered ring is cleaved and compounds (CXLVI) are formed. They undergo cyclization and are transformed into the ketones (CXLVII)[85, 88]:



CXLV CXLVI CXLVII

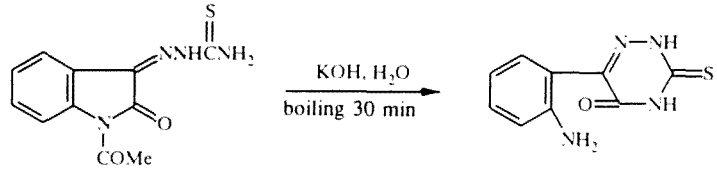
R, R^1, R^2, R^3 H, H, Me, Me (yield 94%), H, Me, H, H; H, Me, Me, Me; H, H, H, Me; H, Me, Ph, H, H, Me, H, C_6H_4COOEt-4, H, Me, H, 4-$MeOC_6H_4$ [88]; Br, H, H, H (yield 55.6%) [84]

The ketones (CXLVIII) were synthesized by treating the isatin derivatives (CXLIX) with concentrated hydrochloric acid [85]:

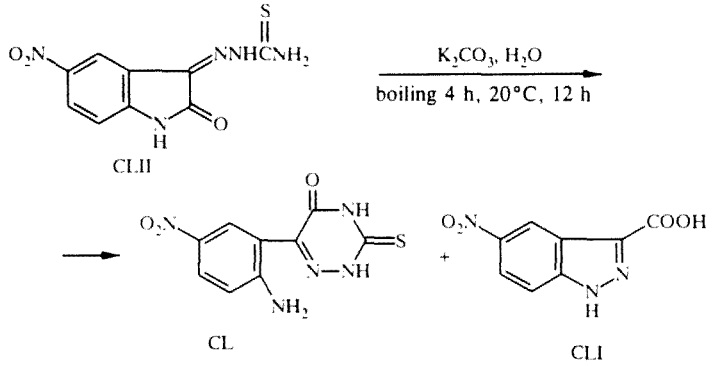


CXLIX CXLVIII

Thiosemicarbazones containing the $=NNHC(S)NH_2$ group at position 3 behave differently in the recyclization reaction. The recyclization of N-acetylisatin 3-thiosemicarbazone by the action of 10% aqueous potassium hydroxide at boiling point results in the formation of 6-(2-aminophenyl)-5-oxo-1,2,4-triazine-3-thione [89]:

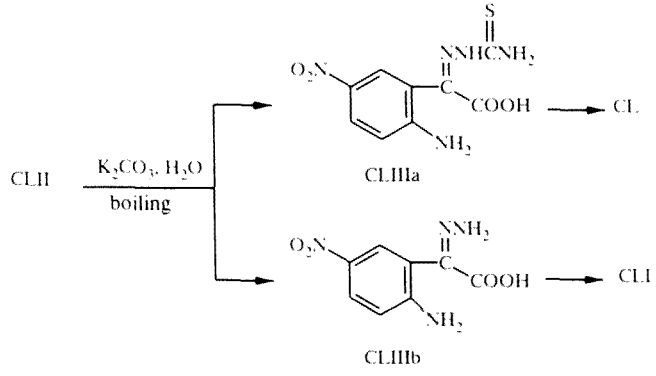


The two compounds (CL, CLI) were synthesized with yields of 64.8 and 16.2% respectively as a result of the treatment of 5-nitroisatin 3-thiosemicarbazone with an aqueous solution of potassium carbonate [90]:



CLII CL CLI

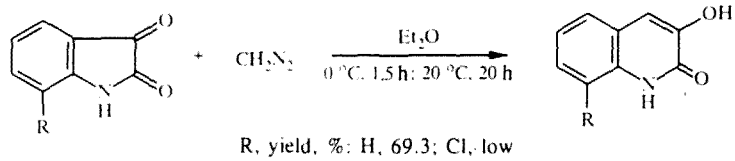
Compounds (CL, CLI) are presumably formed during the recyclization of the 3-thiosemicarbazone (CLII) through the respective intermediate products (CLII, CLIII):



CLIIIa CLIIIb

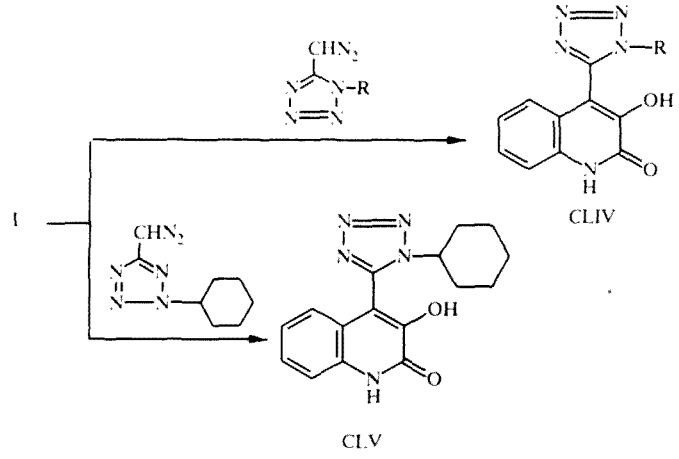
9. Reactions with Diazo Compounds

The products from the reaction of compounds of the isatin series with diazo compounds are derivatives of 3-hydroxy-2-quinolone or 8-chloro-3-hydroxy-2-quinolone respectively [91]:



R, yield, %: H, 69.3; Cl, low

The derivatives of 3-hydroxyquinolone (CLIV, CLV) (yield 63%) containing a tetrazole ring at position 4 were synthesized by the reaction of isatin with 5-diazomethyltetrazole [92], 1-cyclohexyl-5-diazomethyltetrazole, or 2-cyclohexyl-5-diazomethyltetrazole [93] in the presence of potassium hydroxide at 20°C in methanol.



CLIV

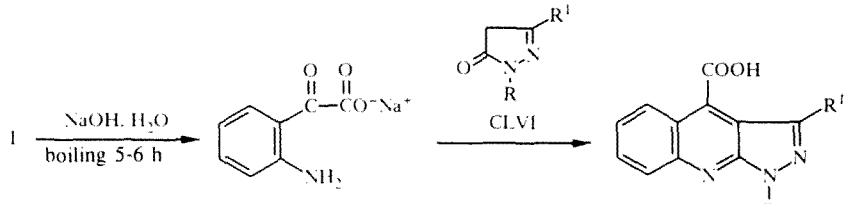
CLV

CLIV, R, yield, %: H, –; cyclohexyl, 54

10. Reactions with Derivatives of 5-Pyrazolone

This reaction results in the formation of tricyclic condensed heterocyclic systems.

Isatin (I) reacts with derivatives of 5-pyrazolone (CLVI) when boiled in 10% aqueous sodium hydroxide, and compounds (CLVII) containing condensed benzene, pyridine, and pyrazole rings are formed [94]:



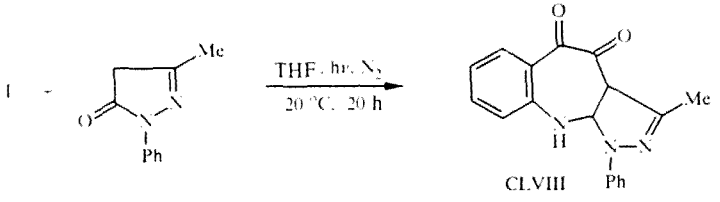
CLVI

CLVII

R, R^1, yield, %: H, Me, 65; Ph, Me, 62; Ph, NH_2, 58

The reaction does not go in the presence of 40% aqueous sodium hydroxide, since full enolization of the CH_2CO groups of compound (CLVI) occurs, and these groups lose reactivity.

The reaction of isatin (I) with 1-phenyl-3-methyl-5-pyrazolone (CLVI) (R = Ph, R^1 = Me) takes a different course — during UV irradiation the tricyclic compound (CLVIII), containing five-, six-, and seven-membered rings, is formed with a 32% yield [95]:

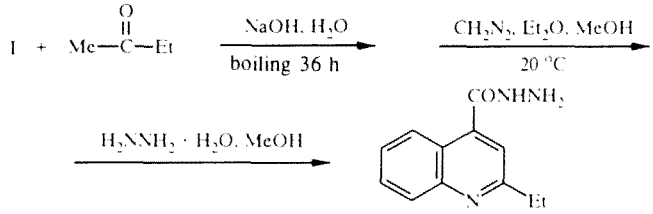


CLVIII

11. Recyclizations Related to the Pfitzinger Reaction

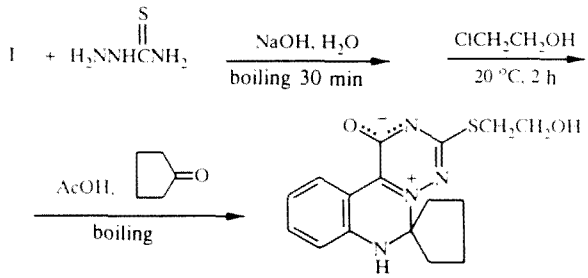
In this section we examine the recyclization reactions of isatin and its derivatives, reported in a single paper that appeared in the period under review [96]. The authors proposed two new processes for the recyclization of isatin (I), each consisting of three consecutive stages.

The first process, i.e., the synthesis of 2-ethyl-4-quinolinecarbohydrazide (CLIX) (yield 21%), involves reaction of isatin (I) with 2-butanone in the presence of sodium hydroxide in water and treatment of the product with diazomethane and then with hydrazine hydrate:



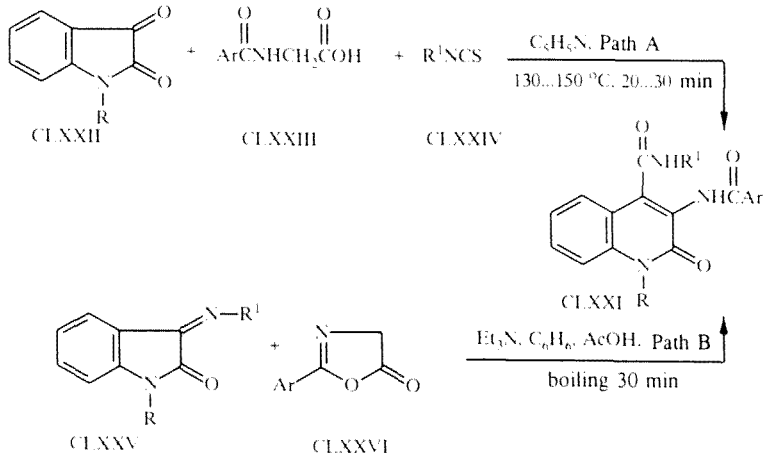
CLIX

The second is the three-stage synthesis of the bipolar ion (CLXX) with a yield of 18% by the reaction of isatin (I) with thiosemicarbazide in the presence of an aqueous solution of sodium hydroxide at boiling point, followed by treatment of the product first with 2-chloroethanol and then with cyclopentanone in boiling acetic acid:



CLXX

Two paths were developed for the derivatives of 2-quinolone (CLXXI): A) Condensation of N-substituted isatins (CLXXII) with acylamino acids (CLXXIII) and isothiocyanates (CLXXIV); B) reaction of the Schiff bases (CLXXV) with 2-aryloxazolin-5-ones (CLXXVI) [97, 98]:

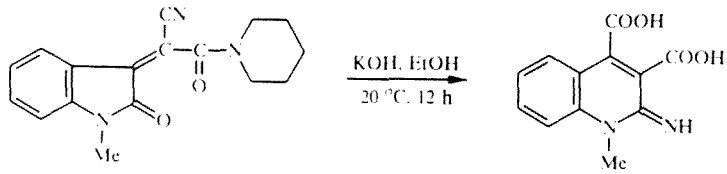


CLXXII CLXXIII CLXXIV CLXXI

CLXXV CLXXVI

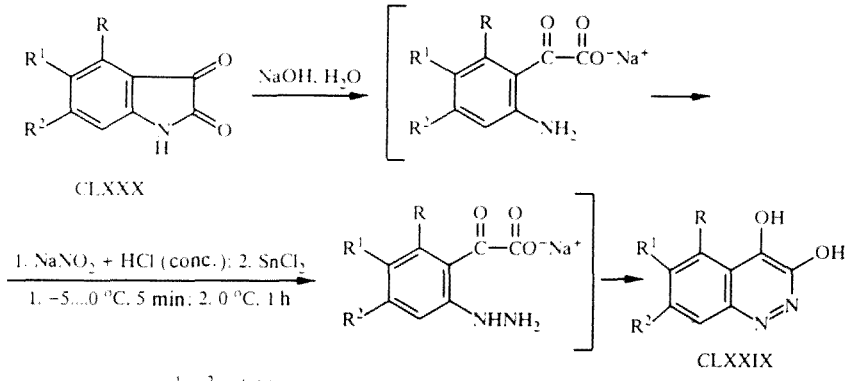
R, R², Ar, yield, %: H, Ph, Ph, 37; Me, Ph, Ph, 36 [97]. R, R¹, Ar, yield CLXXI, %: in A and B H, Ph, Ph, 37 and 33; H, Me, Ph, 29 and —; Me, Ph, Ph, 36 and 25; H, Ph, 4-MeC6H4, 49 and 45; H, C6H11, 4-MeC6H4, — and 46; H, 4-MeOC6H4, 4-MeC6H4, — and 43 [98]

Under the influence of an alcohol solution of potassium hydroxide at 20°C, compound (CLXXVII) undergoes recyclization with a 34% yield to 1-methyl-2-iminoquinoline-3,4-dicarboxylic acid (CLXXVIII) [99]:



CLXXVII CLXXVIII

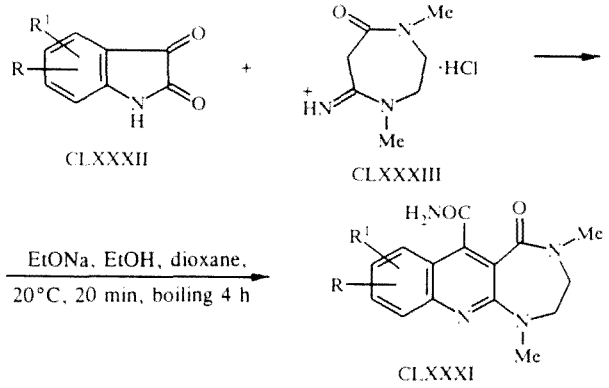
Compounds of the isatin series (CLXXX) undergo an interesting transformation [to derivatives of 3,4-dihydroxycinnoline (CLXXIX)] by the successive action of sodium hydroxide, nitrous acid, and stannous chloride in concentrated hydrochloric acid [100, 101]:



CLXXX CLXXIX

R, R^1, R^2, yield, %: H, H, H, 80 [100]; Me, H, Me, 80; H, Me, H, 85; H, OMe, H, 71; H, Cl, H, 91 [101]

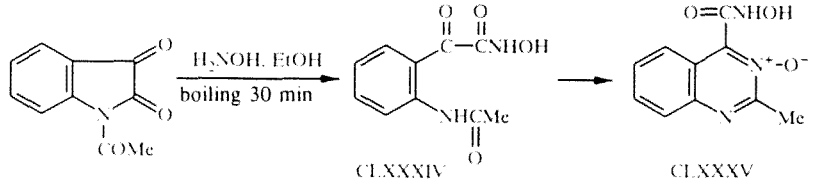
The diazepinoquinoline derivatives (CLXXXI) were synthesized by the condensation of isatin and its derivatives (CLXXXII) with 1,2,3,4,6,7-hexahydro-7-imino-1,4-dimethyl-5H-1,4-diazepin-5-one (CLXXXIII) in the presence of sodium ethoxide [102]:



CLXXXII CLXXXIII CLXXXI

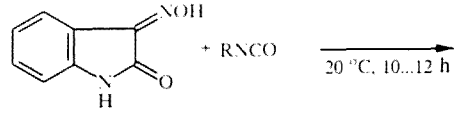
R, R^1, yield, %: H, H, 43; 8-Me, H, 32; 8-Br, H, 21; 8-Me, 10-Me, 18; 9-Cl, 10-Me, 27; 7-Cl, 10-Me, 15

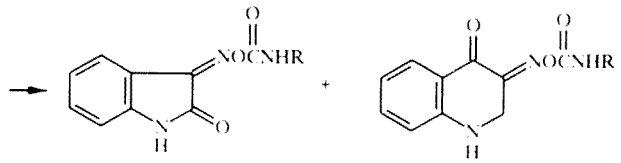
The first stage in the reaction of N-acetylisatin with hydroxylamine in boiling ethanol is clearly the formation of the intermediate compound (CLXXXIV), which undergoes cyclization to the N-oxide (CLXXXV) [103]:



CLXXXIV CLXXXV

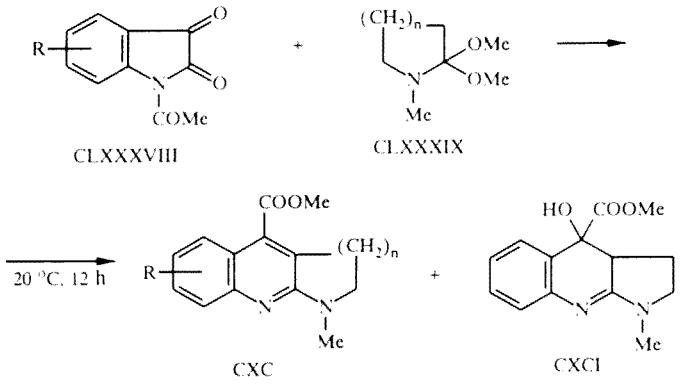
The reaction of isatin 3-oxime with isocyanates results in the formation of the recyclization products (CLXXXVII) as well as the addition products (CLXXXVI) [104]:





CLXXXVI CLXXXVII

The reaction of 1-acetylisatin (CLXXXVIII) (R = H) or 1-acetyl-5-chloroisatin (CLXXXVIII) (R = Cl) with the ketals of lactams (CLXXXIX) takes place with the release of heat and leads as a rule to compounds (CXC). However, when the initial compounds were (CLXXXVIII) (R = H) and (CLXXXIX) (n = 1) the "precursor," i.e., compound (CXCI) from which the water molecule had not yet been eliminated, was isolated in addition to the final products (CXC) [105]:

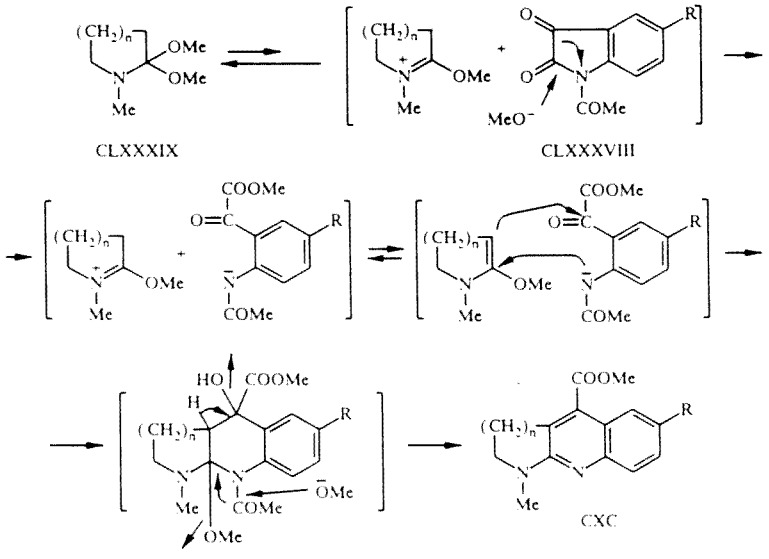


CLXXXVIII CLXXXIX

CXC CXCI

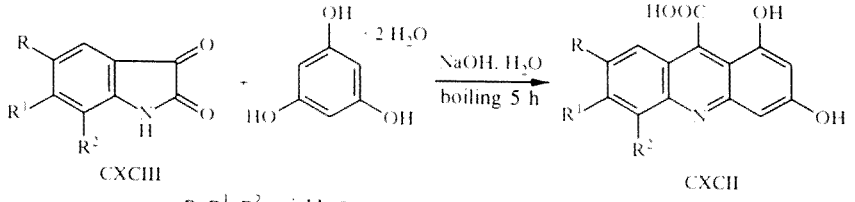
R, n, yield of CXC, %: H, 1, 46 (+ 11.5% CXCI); H, 2, 9; Cl, 1, 41.7; Cl, 2, 7.5

The authors [105] propose the following scheme for the formation of compounds (CXC):



CLXXXIX CLXXXVIII CXC

The derivatives of 9-acridinecarboxylic acid (CXCII) are formed with high yields from compounds of the isatin series (CXCIII) with phloroglucinol dihydrate after boiling in an aqueous solution of sodium hydroxide [106]:

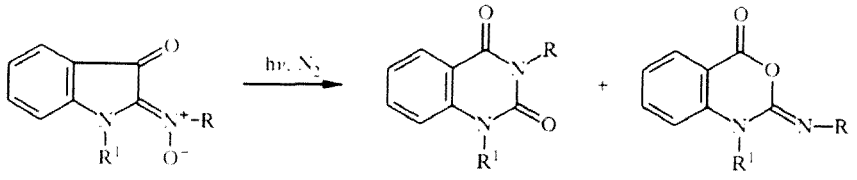


CXCIII CXCII

R, R^1, R^2, yield, %: F, H, H, 72; H, F, H, 72; H, H, F, 92

12. Photochemical Method of Recyclization

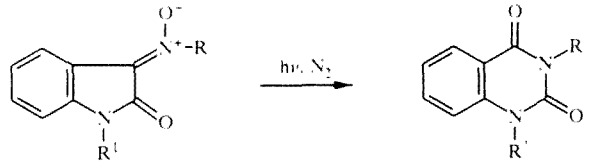
During exposure to a high-pressure mercury lamp (150 W) in benzene or THF in a nitrogen atmosphere, the nitrones (CXCIV) undergo recyclization with the formation of two compounds (CXCV, CXCVI) [107]:



CXCIV CXCV CXCVI

R, R^1, solvent, exposure time (min), yield of CXCV and CXCVI, %: CMe_3, H, THF, 70.33 and 47; CMe_3, H, C_6H_6, 155.18 and 36; Me_2CH, H, C_6H_6, 180.15 and 15; Ph, H, THF, 34.30 and 22; and Ph, H, C_6H_6, 70.40 and 18.

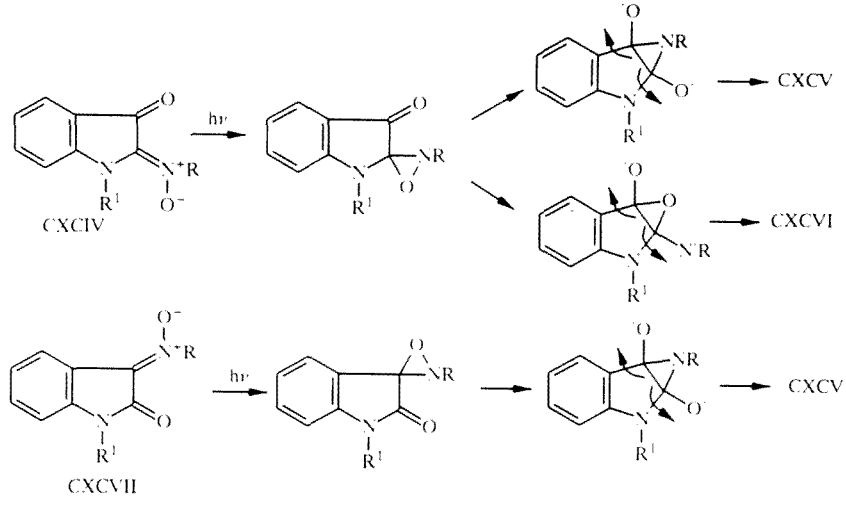
Compounds (CXCV) are also formed as a result of the recyclization of the nitrones (CXCVII) during exposure under the same conditions [107]:



CXCVII CXCV

R, R^1, solvent, exposure time (min), yield, %: Ph, H, THF, 148,46; Ph, H, MeOH, 20,95; Me, H, THF, 600,6; Me, H, MeOH, 840,72; Me, Me, THF, 270,4; 2-PhC_6H_4, Me, C_6H_6, 125,21; Me, Me, C_6H_6, 330,4; Me, Me, acetone , 340,2; Me, Me, MeOH, 430,26

To explain the formation of compounds (CXCV, CXCVI) from the nitrones (CXCIV), and also the formation of compounds (CXCV) from the nitrones (CXCVII), the authors [107] propose the following schemes:



CXCIV CXCVII

It can be concluded that the recyclization reactions of isatin and its derivatives provide convenient and promising methods for the synthesis of various nitrogen-containing heterocyclic systems.

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