HOMOPHTHALIC ANHYDRIDES AND THEIR APPLICATION TO THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS (REVIEW)

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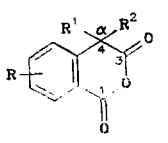
This review covers the reactions of homophthalic anhydrides and their related C–H-acid anhydrides with compounds containing carbon–oxygen or carbon–nitrogen double bonds, which yield compounds with a substituted or condensed α-pyrone or α-pyridone ring.

Homophthalic anhydrides have been known for a long time and are widely used in organic synthesis. Unsubstituted homophthalic anhydride is an industrial product [1]. Lately interest in the homophthalic anhydrides has grown, thanks mainly to their successful use as starting materials in the synthesis of heterocyclic compounds. In some cases homophthalic acids that are converted to the respective anhydrides during the reaction are used. The anhydrides of related C–H-acidic dicarboxylic acids have also been investigated.

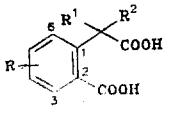
The literature on condensation reactions of homophthalic acids and anhydrides was reviewed by V. P. Oshkaya [2] in 1973. The present article considers mainly publications that have appeared since 1973 or were omitted from [2].

SYNTHESIS AND SOME PROPERTIES OF HOMOPHTHALIC ANHYDRIDES

According to IUPAC nomenclature the homophthalic anhydrides I should be called 1H-2-benzopyrane-1,3(4H)-diones. Points of substitution in the benzene nucleus are usually indicated by the numbering system for the respective 2-carboxy-phenylacetic (homophthalic) acids II, and substitution at the methylene group is called α-substitution:



I



II

R = H, OH, OAlk, Alk, NO_2; R^1, R^2 = H, Alk, Ar

Synthesis of homophthalic anhydrides consists of synthesizing the homophthalic acids, which are converted to the respective anhydrides by heating with acetyl chloride or acetic anhydride [3]. Lately various substituted homophthalic acids have been synthesized that are needed for the synthesis of natural products, by known, modified, or new methods. Homophthalic acids were synthesizad by hydrogen peroxide oxidation of 1,2-indanediones [4] or 1-indanone-2-glyoxylates [5], or the Beckmann rearrangement of 2-nitrosol-1-indanones followed by hydrolysis of the resulting acetonitriles [6-8].

Homophthalic acids form easily by the oxidation and subsequent hydrolysis of 1H-2-benzopyrane-3(4H)-ones like III [9, 10]. The 3,4-disubstituted acids were obtained by selective introduction of a methoxy [Russian says hydroxymethyl but structural formula says methoxy] group ortho to the phenolic hydroxyl. Thus homoisovanillic acid (V) with paraformaldehyde and phenylbovic acid gives the 1,3,2-benzodioxoborine IV. The latter hydrolyzes without separation from the reaction mixture to III [11, 12].

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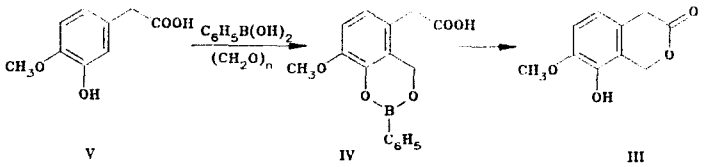
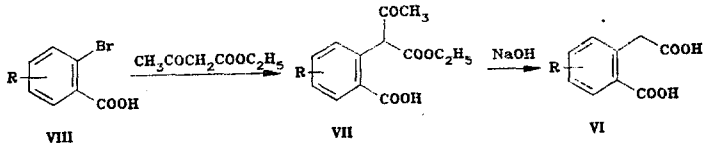


V IV III

Homophthalic acids are obtained in high yield by the direct arylation of β-dicarbonyl compounds with an ortho-halobenzoic acid VIII in the presence of a strong base and a copper(I) halide, followed by retro-Claisen condensation of the intermediate α-aryl-β-dicarbonyl compound VII [13-15]:



VIII VII VI

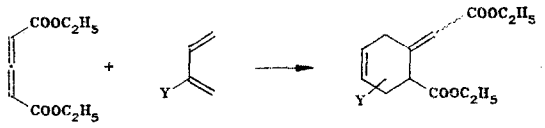
R=H, 3,4-$(OCH_3)_2$, 3,4-OCH_2O, 4-OCH_3, 5-CH_3

Arylation of malonic ester with bromobenzenes in the presence of a strong base also gives homophthalic acids. In this case it is believed that a cyclobutane intermediate forms during the condensation with the participation of arynes [16].

Homophthalic and α-methylhomophthalic acids [17, 18] and homophthalic anhydride [19] were recently synthesized by metallization of the aromatic nucleus of appropriate starting compounds with butyllithium or thallium(II) trifluoroacetate, followed by carboxylation or carbonylation, respectively.

Homophthalic acids were also synthesized by deprotonation of the methyl group of ortho-toluic acids and carboxylation of the resulting dianion [20-22]. α-Methylhomophthalic acids were obtained by methylation of the reactive methylene of homophthalic esters, acids, or mononitriles [18, 23-25].

By means of the Diels-Alder reaction homophthalic acids were synthesized from nonaromatic compounds, viz., allene IX and various substituted butadienes X. The cycloadducts XI which are obtained in high yield are easily dehydrogenated by treatment with sulfur in boiling decalin [26]:

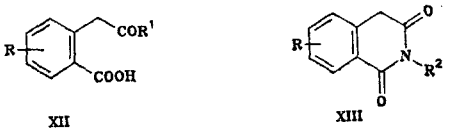


IX X XI

Y = alkyl, alkenyl, OAlk

The IR [19, 27, 28], PMR [19, 27, 28], and UV [27] spectra of homophthalic anhydrides, obtained in nonpolar solvents, agree with the dioxo tautomer of I. The PMR sepctrum of I (R = R^1 = R^2 = H) obtained in $CDCl_3$ in the presence of deuteromethanol shows that the 4-H protons enter into deutero exchange slowly [27]. The PMR spectra of alkoxysubstituted homophthalic ahydrides have been published [6, 12, 15, 17, 28].

Nucleophiles containing oxygen and nitrogen such as methanol [29], and primary and secondary amines [30-35] attack anhydride I at position 3 of the anhydride ring, to form derivatives of homophthalic acid XII. These data agree with the ^{13}C NMR spectrum of I (R = R^1 = R^2 = H), showing that the $C_{(3)}$ atom is the location with the lowest electron density on the molecules [36]. Heating I and II with ammonia and primary amines forms homophthalimides XIII [30, 37-40].



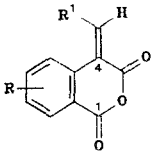
XII XIII

R^1=OCH_3; NHR^2: R^2=H, Alk, Ar

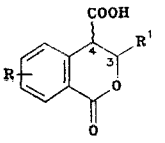
With bifunctional aliphatic and aromatic amines [32, 40-47] condensed isoquinolines are formed that include intermediates in the synthesis of vat [41] and azo [42] dyes and compounds with antiinflammatory and analgesic action [43, 44].

REACTIONS WITH ALDEHYDES

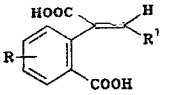
The reactions of homophthalic anhydrides with aldehydes have been investigated in detail [2]. Study is continuing mainly of the reactions of aromatic aldehydes in the presence of bases such as pyridine [48, 49], sodium amide in liquid ammonia [50, 51], and sodium acetate in benzene [52]. Depending on the structure of I and the reaction conditions there are obtained 4-arylene-2-1H-benzopyran-1,3(4H)-diones such as XIV, 3-aryl-4-carboxy-3,4-dihydro-2-1H-benzopyranones such as XVI [51]. In the latter case it is presumed that XVI is obtained from intermediate 4-arylene derivatives of XIV [51]. It was observed that trans-XV and E-XVI are the sole or predominant diastereomers [48, 50-52].



E-XIV



trans-,cis-XV



E-XVI

R^1=Ar; R=H, 8-CH_3O, 6,8-$(OCH_3)_2$, 6,7-$(OCH_3)_2$, 6,7-(OCH_2O)

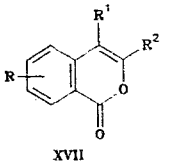
Homophthalic acids and anhydrides react with citral in the presence of pyridine to form 3-(2-carboxyphenyl)-2-pyranones. The proposed mechanism involves the aldol addition of the active methylene of I and III to citral [49].

The relative configurations of the diastereomeric dihydrobenzopyranones XV were determined from the PMR spectra of the free acids [48, 50] or the methyl esters [51, 52]. The relative configurations of the 2-arylcinnamic acids XVI were established from the PMR spectra of their methyl esters, in which the chemical shift of the vinyl proton is typical [51]. The configurations of some type XIV isomers were determined in analogous manner [51].

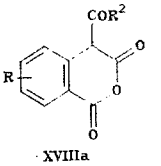
The fungicidal action of some 3-arylbenzopyrones XV and their derivatives has been studied [52]. Benzopyrone XV, appropriately substituted, was the starting compound for the synthesis of (±) zearalenone dimethyl ether, a plant growth stimulator [48].

REACTIONS WITH ACID CHLORIDES, ACID ANHYDRIDES, AND OTHER ELECTROPHILES

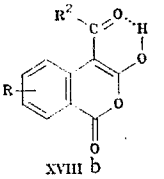
The reactions of homophthalic acids and anhydrides with acid chlorides and acid anhydrides have been widely studied for the synthesis of 2-1H-benzopyrones [22, 53-66] and 1(2H)-isoquinolones [59, 67-76]. Thus, when heated in the presence of bases, 3-alkyl-2-carboxy-2-1H-benzopyrones XVII form (R^1 = COOH) [22, 53-63]. Reaction in the cold yields α-acylhomophthalic anhydrides XVIII [53, 54, 59, 60], which according to spectral data exist mainly as the enol tautomer XVIIIb [53, 54, 60]. The α-acylhomophthalic anhydrides XVIII are considered to be intermediates in the reaction of I and II with acylating agents [53], because when heated in the presence of pyridine they rearrange to the benzopyrones XVII (R^1 = COOH).



XVII



XVIIIa



XVIII b

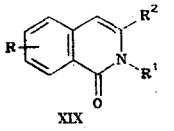
R=H, OH, OAlk, NO_2; R^1=H, COOH, $COOCH_3$, $COOC_2H_5$; R^2=Alk, Ar

The action of acidic reagents [53, 54, 56, 62, 64] and various primary amines and ammonia [59, 67-76] on acylhomophthalic anhydrides XVIII was studied. Sulfuric acid in the cold causes rearrangement of XVIII to 4-carboxy-3-alkylbenzopyrones XVII (R^1 = COOH). With heating,

simultaneously with rearrangement there occurs decarboxylation to form XVII (R^1 = H) [53, 54, 61, 62]. With hydrogen chloride in methanol or ethanol, XVIII forms the respective XVII esters (R^1 = $COOCH_3$, $COOC_2H_5$) [65].

The reaction of homophthalic anhydrides with acid chlorides was studied for the synthesis of natural isocumarones and 3,4-dihydroisocumarinones: 3-propylisocumarin [63], artemidinal (3-formylisocumarin) [64], and dihydroisocumarins separated from fungi [22]. A series of 3-arylisocumarins with fungicidal activity was synthesized [66].

α-Acylhomophthalic anhydrides XVIII rearrange to 2,3-disubstituted 1(2H)-isoquinolones XIX when heated with ammonia or aliphatic amines [59, 67-72] or hydroxylamine [73, 74]. The reaction is accompanied by decarboxylation. With hydrazine, along with the expected 2-amino-1(2H)-isoquinolones, there are formed benzopyranopyrazolones [76].



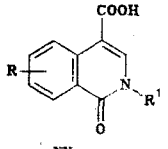
XIX

R=H, OAlk; R^1=Alk, Ar; R^2=H, Alk, OH, NH_2

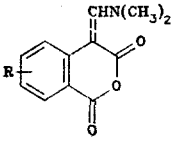
The reaction of anhydrides XVIII with amines was used for the synthesis of some isoquinoline alkaloids such as dorianine and talactamine [71].

Homophthalic anhydrides react with dimethylformamide in the presence of phosphorus oxychloride (Wilsmaier reagent) [77-79] to form, on heating, 2-methyl-4-carboxy-1(2H)-isoquinolones (XX) (R^1 = CH_3), and in the cold 4-[(dimethylamino)methylene]benzopyrane-diones (XXI). The latter was heated in the presence of phosphorus oxychloride rearrange to 1(2H)-isoquinolones XX (R^1 = CH_3); they can therefore be considered intermediates in the synthesis of isoquinolones XX. By the action of hydrogen chloride in methanol XXI rearranges to isocumarin-4-carboxylic esters [77-79].

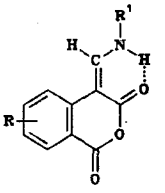
The α-aminomethylenehomophthalic anhydrides XXII were obtained by various methods [80-82]. In alkaline medium XXII rearrange to the isoquinolones XX; some of these fluoresce strongly in the visible region [82]. Similarly the reaction of aryldiazonium salts [83] with homophthalic anhydride forms α-arylhydrazones that are converted by treatment with sodium hydroxide to 2-aryl-4-carboxy-1(2H)-phthalazinones.



XX



XXI

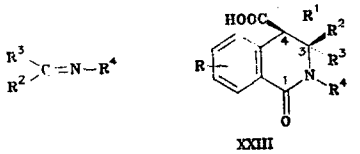


XXII

R=H, OAlk; R^1=H, CH_3, C_6H_5, $C_6H_4CH_2COOH$, 2-pyridyl; R^2=H, Alk, OH, NH_2

REACTIONS WITH IMINES

The homophthalic anhydrides I react in one step and in high yield with various acyclic and cyclic imines (azomethines [84]) to form adducts that contain a substituted or condensed isoquinolone system. The reaction is carried out in aprotic solvents and without a catalyst. Thus, with Schiff bases or hydramines they form diastereomeric substituted 4-carboxy-3,4-dihydro-1(2H)-isoquinolones (XXIII) [28, 81, 85-87].

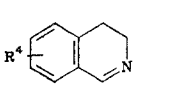


XXIII

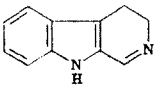
R=H, OH, OAlk; R^1=H, CH_3, R^2, R^3=H, Ar, Alk, spirocyclohexa, 2-furyl, 3-(1-methylindolyl); R^4 = H, Alk, cyclohexyl, Ar, Alk

1(2H)-Isoquinolones XXIII form from homophthalic esters and Schiff bases by slow base-catalyzed condensation [7].

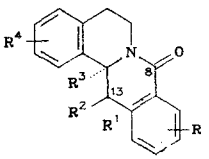
With 3,4-dihydroisoquinolines XXIV and 3,4-dihydro-β-carbolines XXV, homophthalic anhydrides form diastereomeric 13-carboxytetrahydroprotoberberin-8-ones (8-oxoberbines) XXVI [81, 85, 86] and 14-carboxyhexadehydroyohimban-21-ones XXVII [28, 87, 88], respectively.



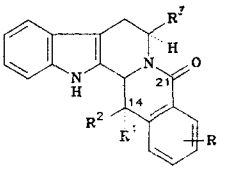
XXIV



XXV



XXVI



XXVII

XXVI R, R^4=H, OH, OAlk; R^1, R^2=H, COOH; R^3=H, Alk, Ar; XXVII R=H, OAlk; R^1, R^2=H, COOH; R^3=H, $COOCH_3$

In all these cases mixtures of diastereomers are obtained in proportions that are determined by the reaction conditions [17, 28, 86, 89]. Sometimes the conditions were chosen so that mainly the thermodynamically more stable isomers were obtained. In their respective groups they are the trans-isoquinolones [81, 85, 87], cis-protoberberinones [81, 85], and cis-yohimbanones [87]. It was detremined that cis-isoquinolones and trans-protoberberinones are obtained as the result of a kinetically controlled reaction, and it was shown that they can epimerize to the thermodynamically more stable trans- or cis-isomers, respectively [6, 17, 86, 89, 90]. Conditions were found from the stereoselective synthesis of trans- and cis-yohimbanones [28].

The relative configurations of trans- and cis-4-carboxy-isoquinolones XXIII were determined directly by comparison of their methyl esters with compounds previously obtained by independent methods [85] and by comparison of their PMR spectra. The PMR and ^{13}C NMR spectra of the free acids show a specific chemical shift of the 4-H proton and the carboxyl carbon [86]; the PMR spectra of the methyl esters show a specific shift of the 4-methoxycarbonyl proton signals [51, 85, 91]. The relationship observed in the spectra of the methyl esters was used to determine the relative configuration of the newly synthesized XXIII, and for quantitative analysis of their mixtures [28, 81, 87].

The relative configurations of the protoberberinones XXVI were determined from the PMR spectra of the free acids and their methyl esters [6, 85, 86]. The relative configurations of the yohimbanones XXVII were determined from the PMR spectra of the methyl esters [28, 87, 88].

As already observed in the first investigation of this series [85], the reaction of homophthalic anhydrides with 3,4-dihydroisoquinolines can be used for the synthesis of berbine structures with an additional carbon atom at $C_{(13)}$. Similar structures are present in protoberberine alkaloids of the corydaline and cevadine types. Indeed, on the basis of the above reaction a convergent synthesis of 13-methyltetrahydroprotoberberines was developed in which the manner of substitution is determined by the location of substituents in the starting structural blocks [86]. In this way the alkaloids corydaline [6], thalictricavine [92], cevadine [8, 93], and thalictripholine were synthesized in racemic and optically active forms.

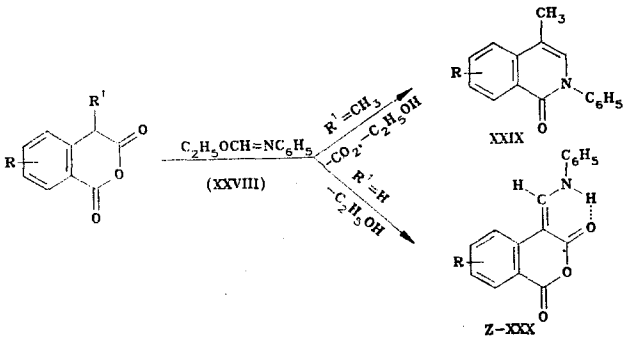
The reaction of homophthalic anhydrides with 3,4-dihydro-β-carbolines for the synthesis of hexadehydroyohimbane derivatives was used to obtain 14-isogambyrtanines and related compounds that are structural isomers of natural alkaloids.

Isoquinolones XXIII (R^1=CH_3 or H) were converted to racemic or optically active benzophenanthridine alkaloids [17, 18, 24, 25, 94].

REACTIONS OF HOMOPHTHALIC ANHYDRIDES WITH IMIDATES, IMIDOYL CHLORIDES, AND 1-CHLOROISOQUINOLINE

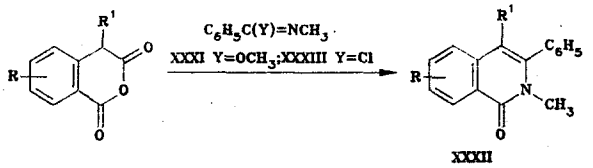
The reactions of homophthalic anhydrides with imidoacid derivatives [84] such as imidates [95], imidoyl chlorides [96], and their cyclic analogs, viz., lactim esters [97] and lactam complexes with acylating agents [97-99] have been studied. These reactions are condensations that take place in aprotic solvents with heating. Like the reactions of homophthalic anhydrides with acid chlorides and acid anhydrides, they form α-aminoalkylidene derivatives of compound I or compounds containing a substituted or condensed 1(2H)-isoquinolone system; in the latter case the reaction is accompanied by decarboxylation.

Homophthalic anhydrides I react with imidate XXVIII; depending on the presence or absence of an α-methyl group in the anhydride, they form 1(2H)-isoquinolones XXIX or z-α-anilinomethyl-enehomophthalic anhydrides XXX [80, 81].



R=H, OCH_3; R^1=CH_3, H

Anhydride I reacts with imidate XXXI to form isoquinolones XXXII. Replacement of XXXI by iminyl chloride XXXIII gives a significant increase in yield of XXXII [80, 100].

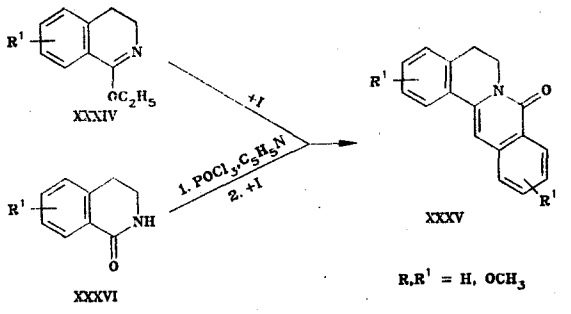


R=H, OCH_3; R^1=H, CH_3

With mono- and bicyclic lactim ethers, the anhydrides I are converted to various condensed isoquinolones [100-102].

Reaction of I with the lactim ethers XXXIV forms 5,6-dihydro-8H-dibenzo[a,g]quinolizin-8-ones (13, 13a-didehydro-berbin-8-ones) (XXXV) in medium yield. Replacement of XXXIV by lactams XXXVI activated with phosphorus oxychloride in pyridine forms compound XXXV in very high yield [100].

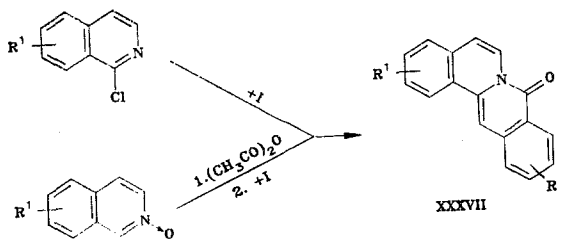
A substance of the type of XXXV, substituted by a suitable method, was converted to the tetrahydroprotoberberinic alkaloid (±)-xylopinine [100].



In none of the cases studied when homophthalic anhydrides react with imidates or imidoyl chlorides was there any simultaneous α-condensation of anhydrides and 1(2H)-isoquinoline derivatives. This was to be expected because it is known that α-aminomethylene derivatives of homophthalic anhydrides are converted to 1(2H)-isoquinolones by acidic reagents and high temperature [77, 78]. The opinion was expressed that homophthalic anhydrides react with imidates and imidoyl chlorides by nucleophilic attack on the imine carbon by the $C_{(4)}$ atom to form an aldol-like intermediate that is subsequently stabilized with or without participation of the anhydride group. It has been presumed that homophthalic anhydrides react analogously with other imines [28, 80, 103]. A probable mechanism of the reaction of homophthalic anhydrides with lactim ethers was formulated, and some confirmatory experimental data were shown. The mechanism is based on formation of an aldol-like intermediate followed by its transformation [101].

The reactivity of I was studied with respect to 1-chloroisoquinolines considered as iminohalide systems [96, 104]. The reaction goes easily to form 8H-dibenzo[a,g]quinolizin-8-ones (XXXVII) in high yield [105]. During this study it was also established that homophthalic

anhydrides react with isoquinoline N-oxides in the presence of acetic anhydride to form identical quinolizinones XXXVII, but in lower yield. The reaction of I with isoquinoline-N-oxides is explained by the generally accepted mechanism for the reaction of aromatic N-oxides with C–H acids [106].



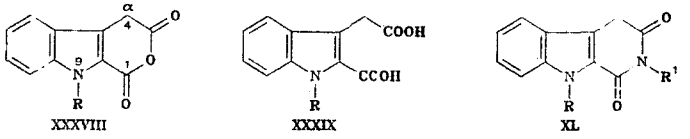
R, R¹=H, OAlk

The tetrahydroprotoberberine alkaloid (±)-caseidine was synthesized from the corresponding substituted type-XXXVII compound [105].

C–H ACIDIC ANHYDRIDES RELATED TO HOMOPHTHALIC AND THEIR REACTIVITY

Lately homophthalic anhydride analogs have been studied, in which the benzene ring is substituted with a heteroaromatic system.

2-Carboxyindone-3-acetic acid ahydrides XXXVIII (in systematic nomenclature, 4H,9H-pyrano-[3,4-b]indole-1,3-diones) are synthesized from the respective dicarboxylic acids XXXIX [107]. The IR and PMR spectra of XXXVIII (R = CH_3) [107], obtained under conditions suitable for homophthalic anhydrides [28], are very similar to them and agree with the dioxo tautomer structure. With aliphatic and aromatic amines, XXXVIII forms 3,4-dihydro-1H,9H-pyrido[3,4-b]indole-1,3-diones (XL) [108, 109].



R=H, CH_3, C_2H_5; R¹=C_6H_5, $CH_2C_6H_5$, $CH(CH_3)C_6H_5$-(*R*)

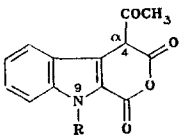
Like homophthalic anhydride, XXXVIII undergoes condensation at the C_4 (α) nucleophilic center in the presence of acidic or basic reagents. With ethyl orthoformate it forms α-alkylene derivatives of XXXVIIII; with aromatic aldehydes, α-arylidene derivatives; and with diazonium salts, α-arylhydrazones. When heated with acids the α-arylhydrazone ring opens and recloses to form 4(3H)-pyridazinon-[4,5-b]indole-1-carboxylic acids [107, 108].

Acid XXXIX (R = H) and its anhydride XXXVIII (R = H) react with acid anhydrides and Wilsmaier reagent similarly to homophthalic acid and anhydride. With acetic anhydride at room temperature in the presence of pyridine the methylene group is acylated to form the α-acetyl derivative XLI (R = H). When XLI is melted, 3-methylpyrano[3,4-b]indole-1(9H)-one (XLII) (R = R¹ = H) is formed and at the same time decarboxylation occurs. XLI are considered intermediates in the conversion of XXXVIII or XXXIX to pyranoindolones XLII, because when heated with acetic anhydride they form XLII (R = $COCH_3$, R¹ = H) [110]. When XLII (R = H, R¹ = COOH) is heated with ammonia or amines, pyrido[3,4-b]indole-1(9H)-ones (β-carbolinones) form a high yield [110, 111].

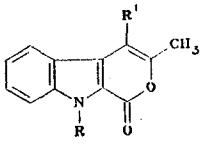
With phosphorus oxychloride and dimethylformamide in the cold, XXXIX (R = H) forms the α-dimethylaminomethylene derivative XLIV, which when heated with $POCl_3$ is converted to the β-carbolinone XLV, and with hydrogen chloride in methanol is converted to pyrano[3,4-b]indole-1(9H)-one (XLVI) [112].

The reactions of anhydride XXXVIII (R = CH_3) with Schiff bases, imidates, and lactim ethers were investigated. Various products form by the separate or concurrent participation of the $C_{(4)}$ nucleophilic center and the anhydride group. The difference in reactivity of anhydrides I and XXXVIII (R = CH_3) toward imines is explained by the conjugation of the indole nitrogen with the C-1 carboxyl of XXXVIII (R = CH_3) [28, 103].

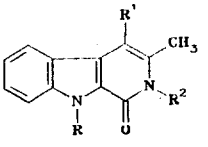
1-Alkylindole-3-carboxy-2-acetic anhydrides [113, 114] react with primary amines to form 3-carboxyindole-2-acetamides. When these compounds are melted, the ring closes to form 3-carbolin-2,4-diones.



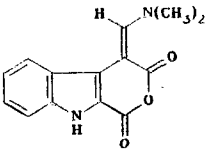
XLI



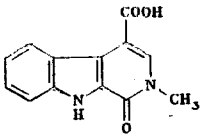
XLII



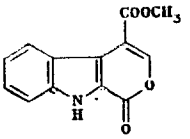
XLIII



XLIV



XLV



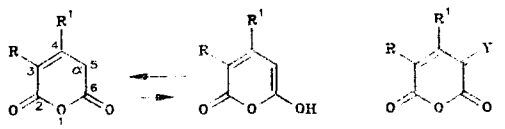
XLVI

R=H, CH_3CO; R^1=H, COOH; R^2=H, Alk, Ar

The reaction of 1,2-diamines and ortho-aminophenols with the same anhydrides was investigated, and polycondensed heterocyclic compounds were synthesized [115].

Recently investigation began of the cycloaddition of homophthalic anhydrides as a method of synthesizing linearly condensed phenolic compounds that are synthetic precursors of antitumor antibiotics [116, 117]. Analogs of homophthalic anhydride containing an indole or benzofuran ring system yielded heterocyclic analogs of anthracyclinones [118].

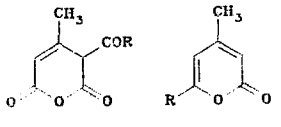
Lately there has been increased interest in the chemistry of the glutaconic anhydrides XLVII. The IR and PMR spectra of the unsubstituted compound in nonpolar solvents is consistent with the dioxo tautomer XLVIIa. In the presence of deuteromethanol in chloroform the protons at the 3 and 5 positions undergo deuterium exchange. A certain amount of tautomer XLVIIb appears in the UV spectrum in acetonitrile [119]. Glutaconic anhydrides react with aromatic aldehydes to form the α-arylidene derivatives XLVIII (Y = CHR^2). With acetaldehyde, an α-hydroxymethyl derivative forms [120-122].



XLVIIa XLVIIb XLIII,LI

XLVIIa R=Alk(C_1—C_6); XLVII b R^1=Alk, Ar; XLVIII Y=CHR^2; LI Y=$NNHR^2$; R^2=Ar

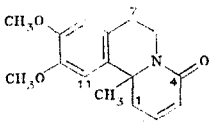
Anhydride XLVII (R = H, R^1 = CH_3) is acylated by acid chlorides and anhydrides in pyridine to form the α-acyl derivatives XLIX, which when heated are converted to 4-methyl-6-alkyl-2-pyrones L with simultaneous decarboxylation [123, 124]. Anhydrides XLVII (R = H, R^1 = Alk, Ar) react with aryl diazonium salts to form the 5-arylhydrazones LI. Isomerization of the latter in alkaline medium forms the substituted 6(1H)-pyridazinone-3-carboxylic acids [121, 125, 126].



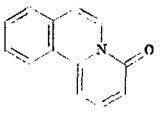
XLIX L

R=Alk

During investigations on the synthesis of emetine it was established that glutaconic anhydride reacts with 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline in pyridine to form tetrahydrobenzo[a]quinolizine-4-one (LII). It was suggested [127] that the reaction begins with an attack on the electrophilic center of dihydroisoquinoline by the $C_{(5)}$ nucleophilic center of the anhydride. Glutaconic anhydride reacts similarly with 1-chloroisoquinoline to form benzo[a]quinolizinone (LIII) [80].

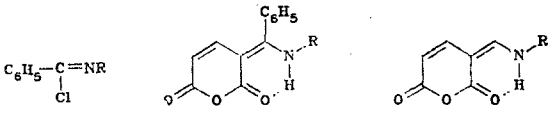


LII



LIII

The reaction of glutaconic anhydride with the imidoyl chlorides LIV in an inert solvent forms α-aminobenzylidene derivatives LV [80]. Like the α-aminomethylene derivatives LVI obtained by another method [128], these compounds exist in the dioxotautomer form, and have the z-configuration and the s-cis-conformation.



LIV LV LVI

LIV, LV R=CH_3, C_6H_5; LVI R=C_6H_5, $CH_2C_6H_5$

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