ADVANCES IN THE CHEMISTRY OF PYRAZOLIDONES, IMINOPYRAZOLIDINES, AND AMINO- AND HYDROXYPYRAZOLES (REVIEW)

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Literature data on 3-pyrazolidones, 3-iminopyrazolidines, 3- and 5-aminopyrazoles, 3-hydroxypyrazoles, and 2-pyrazolin-5-one are correlated.

3-Pyrazolidones, 3-iminopyrazolidines, and 3- and 5-aminopyrazoles, as well as 3-hydroxypyrazoles and 2-pyrazolin-5-ones, are the most important representatives of cyclic derivatives of hydrazine in both a synthetic and theoretical respect. Compounds of these classes are widely used as photographic developers, dyes, herbicides, and medicinals with antiphlogistic and analgesic action. In addition, aminopyrazoles are intermediates in the synthesis of purinelike antimetabolites and antagonists of cyclic adenosine monophosphate. The advances made in this field of research after the publication of earlier reviews [1-3] are examined systematically in the present paper.

1. 3-Pyrazolidones and 3-Iminopyrazolidines

1.1. Syntheses (Scheme 1). α,β-Unsaturated carboxylic acid esters V, which contain at least one R^1—R^3 = alkyl or R^2 = phenyl substituent, react with an equimolar amount of hydrazine hydrate to give 3-pyrazolidones IV (for example, see [4-7]). In the case of acrylic ester 3-pyrazolidone IV (R^1—R^3 = H) is obtained in 3-4% yield [8, 9]. The first acceptable synthesis of 3-pyrazolidone was based on the thermal cyclization of methyl β-hydrazinopropionate hydrochloride [10], however, the best method for its preparation is the hydrolysis of 3-iminopyrazolidine sulfate [9]. The reaction of unsaturated esters IV with 0.5 mole of hydrazine hydrate gives 1,5-dioxoperhydropyrazolo[1,2-a]pyrazole II, the reduction of which gives 1,5-diazacyclooctane III as a result of hydrogenolysis of the N—N bond [4]. Similar cleavage of the N—N bond in 3-pyrazolidones IV leads to the formation of β-aminocarboxylic acid imides I [4].

A mixture of 1- and 2-substituted 3-pyrazolidones X and IX with predominance of the X form is formed in the reaction of monosubstituted hydrazines VI (R^5 = alkyl, cycloalkyl, and aralkyl) with unsaturated acids or esters V. Compounds of the X type, which have more acidic character, are isolated from the mixture by means of anion-exchange resins [7, 11, 12]. Only IX is formed in the case of phenylhydrazine [7]. 1-Substituted 2-pyrazolidones X (R^5 = alkyl, aralkyl, and aryl) can be obtained by acid hydrolysis of the corresponding 3-iminopyrazolidine XIII [7, 13-15], as well as by reduction of N-nitroso-β-aminopropionic acid esters VII with zinc in acetic acid [13, 14, 16, 17]. 2-Substituted 3-pyrazolidones IX (R^5 = alkyl, cycloaklyl, and aralkyl) are obtained in 2 N HCl from the corresponding 1-acetyl derivative XII [18, 19] or by hydrogenation (Pt, 200 atm) of β-hydrazinopropionamide hydrazone VIII [20]. When R^5 = aryl, they are formed by acid hydrolysis of the corresponding 2-aryl-3-aminopyrazolidines XI [21].

Both 1- (XIII) and 2-substituted (XI) 3-iminopyrazolidines are stable in the form of salts, but the corresponding bases are colored in the presence of oxygen. Two bands of N—H stretching vibrations, for which the expression $\nu_s = 345.5 + 0.876\nu_{as}$ [23] that is characteristic for νNH_2 [22] is not satisfied, are observed in their IR spectra (in chloroform). 3-Iminopyrazolidines XI (R^5 = aryl) are obtained in the cyclization of β-cyanoethylhydrazines XIV in ethanol [24] or, preferably, water [21]. It should be noted that in both cases this reaction was carried out under acid catalysis conditions. At the same time, cyclization of β-cyanoethylhydrazines XVI to 1-substituted 3-iminopyrazolidines XII (R^5 = alkyl, cycloalkyl, aralkyl [13, 14], and aryl [25]) is possible under both acid and basic catalysis conditions. The nucleophilic nitrogen atom of monosubstituted hydrazine VI adds to α,β-unsaturated nitriles

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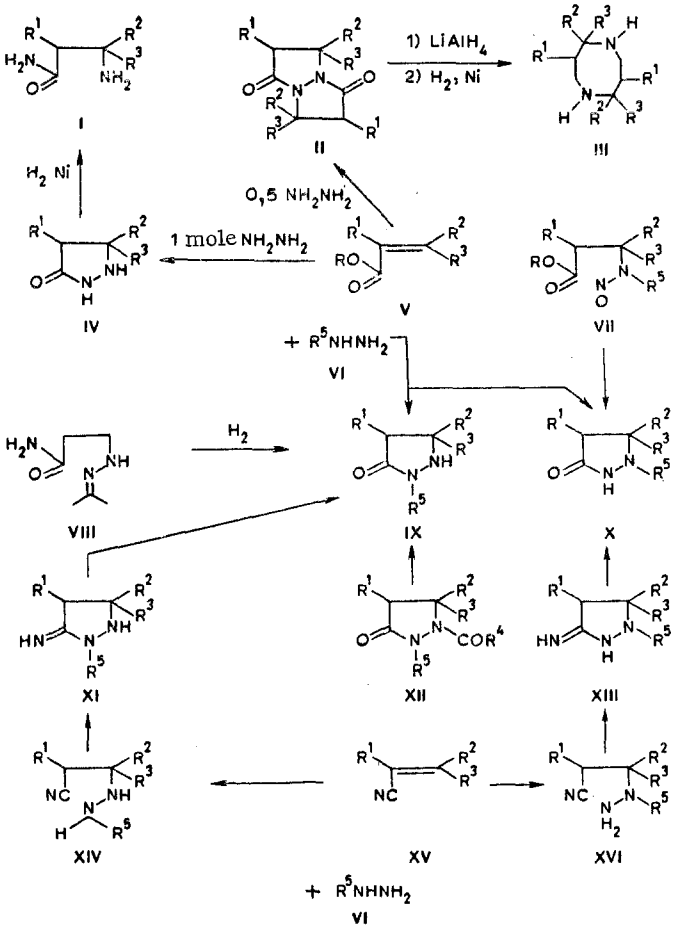
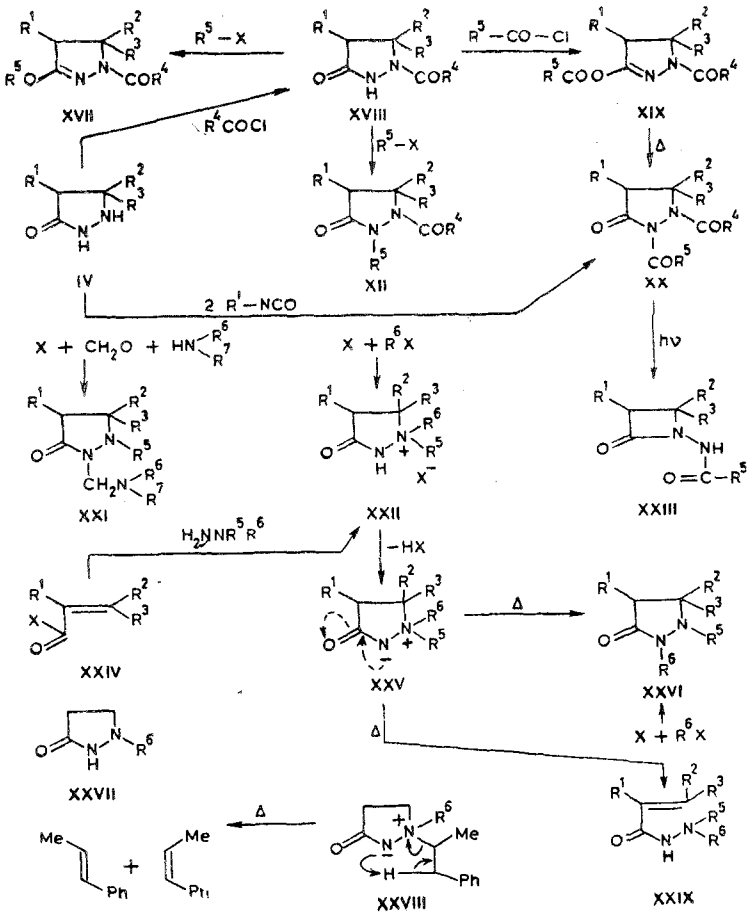
Scheme 1



XV. Thus 1-aryl-2-(β-cyanoethyl)hydrazine XIV is obtained from XV and arylhydrazines in aqueous or alcohol solutions [21, 24], while 1-substituted 1-(β-cyanoethyl)hydrazine XVI is obtained from alkyl-, cycloalkyl-, and aralkylhydrazines [13, 26]. In the presence of bases the substituted nitrogen atom of arylhydrazines is deprotonated, and the resulting anion adds to nitrile XV. The products are cyanoethylhydrazines XVI, the subsequent cyclization of which leads to XIII [25, 27, 28]. β-Cyanoethylhydrazine XXXIII is obtained from 1 mole of hydrazine and 1 mole of acrylonitrile (H_2O, 0-20°C); in the presence of hydrochloric or sulfuric acid it undergoes cyclization to acid salts of 3-iminopyrazolidines XXXIV [30, 31] (Scheme 3). The synthesis of 1-substituted 3-iminopyrazolidines XIII and 3-pyrazolidones X without the use of monosubstituted hydrazines VI is examined in Section 1.3.

1.2. Alkylation, Acylation, and Arylsulfonylation (Schemes 2 and 3). N,N'-Unsubstituted pyrazolidones IV are alkylated ambiguously; at the same time, the alkylation of 1-alkyl(1-aryl)- and 1-acyl-substituted compounds (X, XII), as well as 1-(arylsulfonyl)pyrazolidones are of great interest from a synthetic point of view. 1-Arylpyrazolidones X react with ω-bromo carboxylic acid esters [NaH, dimethylformamide (DMF)] to give 1,2-substituted pyrazolidones XXVI and 2-(ω-ethoxycarbonylalkoxy)-2-pyrazolines [32]. 1,2-Disubstituted pyrazolidones XXI (R^5 = alkyl, aryl, and acyl) were obtained in almost quantitative yields as a result of the Mannich reaction [33]. On the other hand, the alkylation of 1-alkyl(1-aralkyl)pyrazolidones X with alkyl halides, alkyl sulfates, alkyl tosylates, and benzyl chloride in alcohols, acetone, benzene, and in the absence of a solvent at 270°C gives cyclic hydrazinium salts XXII [7, 12, 34], which can also be obtained from unsaturated acid chlorides XXIV and N,N-disubstituted hydrazines [7, 12]. When they are treated with NaOH (MeOH) or are passed through an anion-exchange resin (H_2O), they are converted to 1,1-disubstituted pyrazolidone-N,N-betaines XXV [7, 12, 34] ("pyrazolinium 3-oxides" [7], "aminimides" [35]). Delocalization of the negative charge in compounds of the XXV type leads to a decrease in νCO (~1590 cm^{-1} [7, 34]) as compared with pyrazolidones (~1700 cm^{-1}). Betaines XXV are also formed in aqueous or alcohol

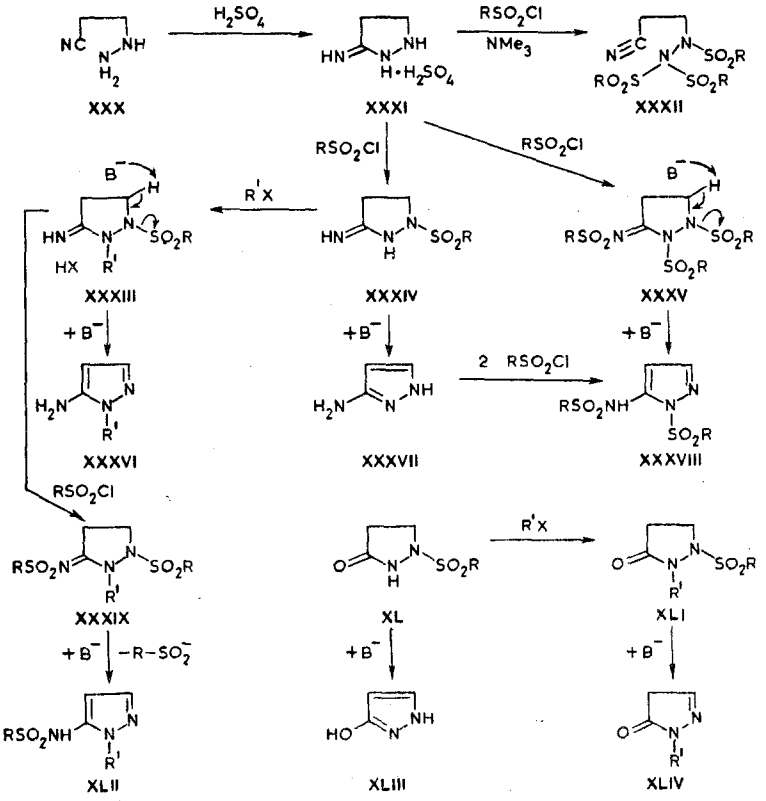
Scheme 2



solutions from unsaturated esters V and 1,1-dimethylhydrazine [36]. 1,2-Disubstituted pyrazolidones XXVI (R^5 = alkyl, R^6 = benzyl; Wawzonek rearrangement) [12, 34] or 2-acyl-1,1-dialkylhydrazines XXIX (R^5 = R^6 = alkyl; Hofmann cleavage) [12, 37] are obtained at 160-260°C from betaines XXV. The Wawzonek rearrangement (the aza analog of the Stevens rearrangement) proceeds via a radical dissociation—recombination mechanism [38]. A mixture consisting of 86% E- and 14% Z-1-phenylpropene is also obtained in addition to pyrazolidones XXVII at 200°C from betaines of the XXVIII type (the aza analog of ylid cleavage) [34].

1-Acylpyrazolidones XVIII are formed in the reaction of pyrazolidones IV with 1 mole of the acid chloride or with 0.5 mole of the anhydride (in an alkaline medium; benzene, triethylamine) [4, 18, 19, 39]; pyrazolidone derivatives XVIII, synthesized from α,β-unsaturated acid chlorides XXIV, are converted to two-ring systems II at 170-200°C [4]. The reaction of acid chlorides (tetrahydrofuran, triethylamine) with XVIII gives N,O-diacyl-3-hydroxy-2-pyrazolines (XIX), which at 110°C undergo rearrangement to 1,2-diacylpyrazolidones XX [39]. 1-Acylaminoazetidinones XXIII are formed in the photochemical decomposition of 1-acylpyrazolidones XVIII and 2-acylpyrazolidones [39]. 1,2-Bis(carbamoyl)pyrazolidones XX (R^4 = R^5 = NHR') were obtained as a result of the exothermic reaction of pyrazolidones IV with 2 moles of isocyanate [40]. Under the influence of dimethyl sulfate (water or DMF) of benzyl chloride (alcohols or MeCOEt), 1-acylpyrazolidones XVIII (R^4 = Ph or Me) are alkylated in the 2 position to give compounds of the XII type; however, 3-ethoxy-2-pyrazoline XVII was isolated when diethyl sulfate (MeCOEt, MeOH, or DMF) was used as the alkylating agent in a similar reaction with pyrazolidone XVIII (R^4 = Ph) [18, 19]. The synthesis of 3-hydroxy-1-pyrazolines was described in [41]. The reaction of pyrazolidones of the X type with substituents in the 1 position with acid chlorides (benzene, triethylamine) leads to 2-acylpyrazolidones XXVI (R^6 = acyl) in quantitative yields [19]. In the latter, the nitrogen atom in the 2 position has a higher positive charge as compared with isomers XII, as a consequence of which the order of the 3-(CO) bond increases, and ν(3-CO) undergoes an ~30-40 cm^{-1} increase; a similar regularity was established for isomeric 2- and 1-arylsulfonyl-3-pyrazolidones [18-20].

Scheme 3

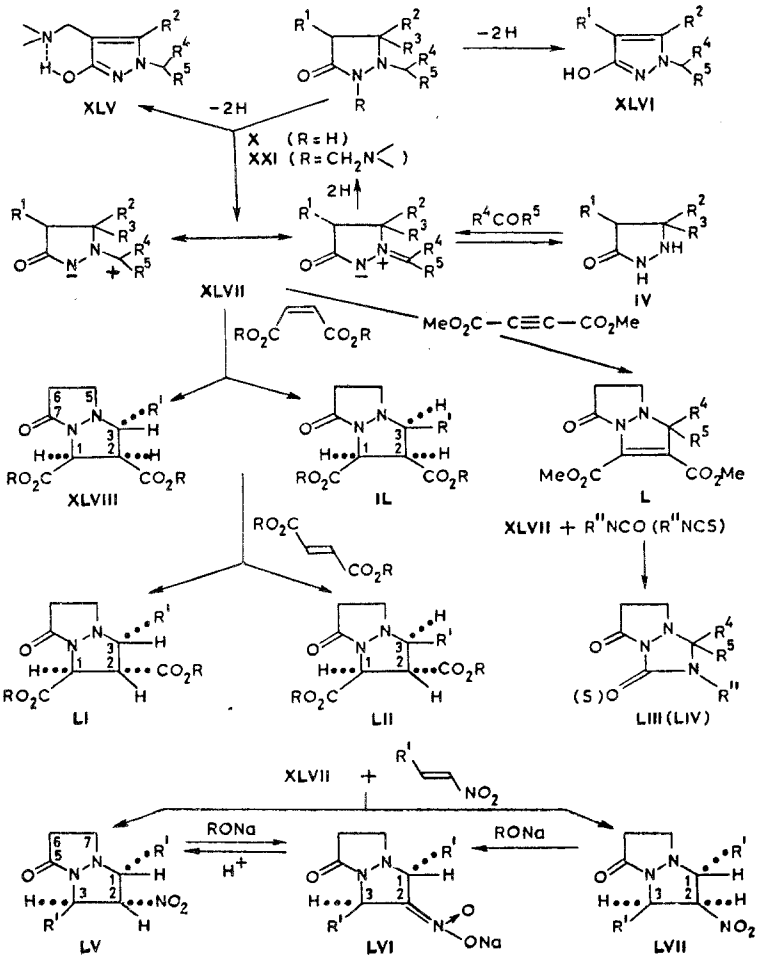


1-Sulfonyl- (XL, XLI) and 2-sulfonyl-3-pyrazolidones are formed as a result of the reaction of arenesulfonyl chlorides with pyrazolidones IV, IX, and X (pyridine or triethylamine, methylene chloride) [18, 20]. In aprotic media (K_3PO_4 in MeCN or NaH in dioxane) XL and XLI split out an arenesulfinate; this reaction is a convenient method for the synthesis of 3-hydroxypyrazole (XLIII) [42] and is the only method for the synthesis of 1-methyl-2-pyrazolin-5-one (XLIV, R' = Me) [42, 43]. The β cleavage of sulfinate ion (NaOH or an anion-exchange resin in water, RONa in alcohols) from 3-imino-1-sulfonylpyrazolidines XXXIV, XXXIII, XXXIX, and XXXV, which leads to the formation of 3-aminopyrazole (XXXVII) [30, 44], 1-alkyl-5-aminopyrazoles XXXVI [30], 1-substituted 5-(sulfonamido)pyrazoles (XLII, R' = alkyl [30], aryl [45]), and 1-sulfonyl-5-(sulfonamido)pyrazoles XXXVIII [46], proceeds in somewhat simpler fashion and quantitatively. This important exothermic reaction becomes possible owing to the formation of a stable heteroaromatic system [47]. Disulfonyl compounds XXXVIII are also obtained by the action of 2 moles of sulfonyl chloride on 3-aminopyrazole XXXVII (see Section 2.2). The acid cleavage of sulfinic acids from XXXIX (R' = aryl) and subsequent reactions are discussed in [45].

1-Sulfonyl derivatives XXXIV (NEt_3 in CH_2Cl_2 or $NaHCO_3$ in H_2O–C_6H_6) [30, 44], trisulfonyl derivatives XXXV (pyridine in CH_2Cl_2 [46], or 1-(2-cyanoethyl)-1,2,2-trisulfonylhydrazines XXXII (NMe_3 in CH_2Cl_2–benzene) [48] are formed by the action of arenesulfonyl chlorides on 3-iminopyrazolidine XXXI. 2-Alkyl-3-imino-1-sulfonylpyrazolidine salts XXXIII [30], which react with arenesulfonyl chlorides (pyridine in CH_2Cl_2 or an alkaline aqueous medium to give 3-sulfonimidopyrazolidines XXXIX, are obtained from 3-amino-1-sulfonylpyrazolidones XXXIV and alkyl tosylates or dimethyl sulfate in DMF. Phenyl-substituted XLIII (R' = Ph) can be isolated as a result of the reaction of 3-imino-2-phenylpyrazolidine with a twofold quantity of an arenesulfonyl chloride [45].

1.3. Reaction with Carbonyl Compounds — Chemistry of Pyrazolidine-(3)-azomethineimines (Schemes 4 and 5). Crystalline betaines XLVII are formed in the reaction of pyrazolidones IV with carbonyl compounds (aldehydes, ketones [14, 49, 50], keto acids and their esters [51], and monosaccharides [52]). These betaines attracted attention as interesting reagents for organic synthesis after it was established [14, 49] that they are stable dipoles of the allyl anion type (azomethineimines). Some representatives of betaines XLVII (R^3 = R^5 = Ph) were

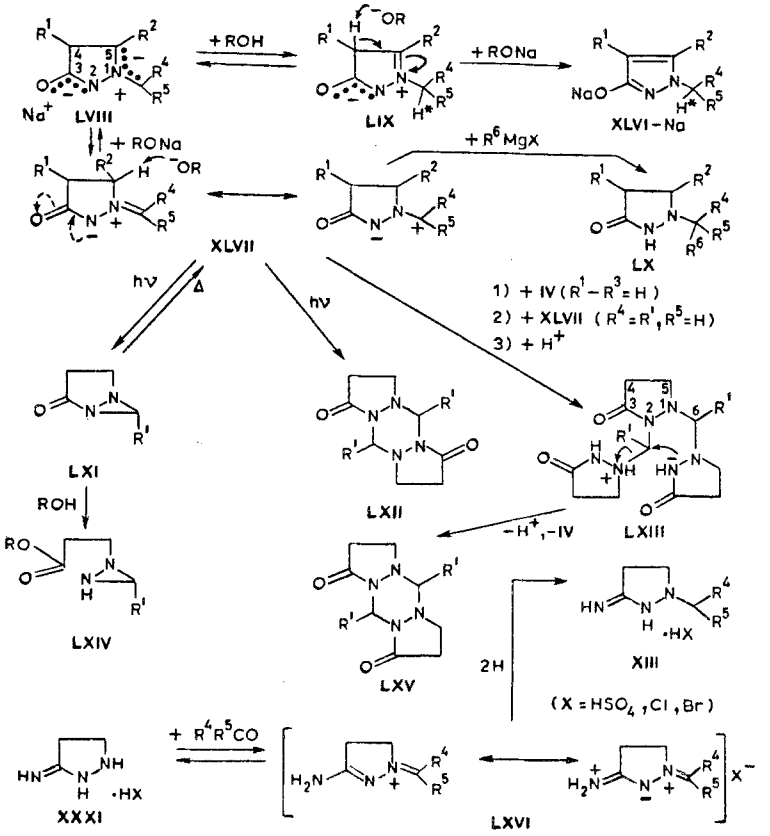
Scheme 4



described [53-55] prior to the establishment of their true structures; reviews dealing with azomethineimines have been published [56, 57]. The formation of azomethineimines XLVII is reversible in the presence of water. Compounds XLVII are obtained in quantitative yields when the product is precipitated or when the water is removed by azeotropic distillation. 1-Substituted pyrazolidones X are obtained by hydrogenation (Pt, alcohol or water) of azomethineimines XLVII or equimolar amounts of pyrazolidones IV and carbonyl compounds [14, 49-52]. The exothermic dehydrogenation of X (R^3 = H) (HgO, $MgSO_4$, $CHCl_3$ [58]; I_2, $NaHCO_3$, MeOH [59]) leads to 3-hydroxypyrazoles XLVI and azomethineimines XLVII; the percentage of the latter in the reaction mixtures increases when R^4 = H [59]. Mannich compounds XXI (R^3 = H) do not react with mercuric oxide or sulfur, while azomethineimines XLVII and 4-aminomethyl-3-hydroxypyrazoles XLV are formed with iodine (MeOH, H_2O) [59], and N-iodines of X (R^3 = H, R = I) are formed as intermediates. Extremely stable Mannich compounds with the XLV structure are obtained from 3-hydroxypyrazoles XLVI, formaldehyde, and secondary amines [59].

The dipolarophilic esters of acetylenedicarboxylic acid and isocyanates (isothiocyanates) add to XLVII to give two-ring systems L and LIII (LIV) [14, 40]. The primary products of the addition of singlet oxygen ($^1\Delta g$) to the XLVII dipole (R^5 = aryl, R^4 = R^1 = H, R^2 = R^3 = H or Me) undergo decomposition to R^5CHO, N_2, and ethylene or isobutylene, CO_2, and β-propiolactone [60]. Dimethyl maleate (Z) and, correspondingly, dimethyl fumarate (E), which have dipolarophilic natures, add in a "cisoid" manner upon heating to pyrazolidone-(3)-azomethineimine XLVII with retention of their configuration and the formation of 7-oxoperhydropyrazolo[1,2-a]-pyrazoles in the form of mixtures of isomers, viz., XLVIII and L (2:1) in the first case, and LI and LII (1:1) in the second case [61], as required by a concerted [$_\pi4_s + _\pi2_s$] mechanism [62, 63]. It should be noted that "noncisoid" 1,3-dipolar cycloaddition reactions were not described prior to 1977 [64]. Each of the four stereoisomers undergoes epimerization under basic catalysis conditions to give mixtures of all of the isomers [61]. The thermal stereospecific addition of E-β-nitrostyrenes to azomethineimines XLVII [65], which gives two of the

Scheme 5



four possible pairs of enantiomers, viz., LVI ("cisoid") and LVII ("noncisoid") (in a ratio of 7:3 when R' = Ph) [65], is of great theoretical significance. The formation of LVII is the first instance of "noncisoid" thermal addition of a 1,3-dipole. The structures of LV and LVII, as well as of the corresponding 2-amino-5-oxoperhydropyrazolo[1,2-a]pyrazoles (R^1 = aryl), were confirmed by ^1H and ^{13}C NMR spectroscopy [61, 65], while the structures of LV and LVII ($R^1 = C_6H_4Cl$-p) were confirmed by the results of x-ray diffraction analysis [66]. The product of "noncisoid" addition of the LVII 1,3-dipole is not the result of E ⇌ Z isomerization of nitrostyrenes, elimination and addition reactions, or epimerization at the 2-C atom of LV [65]. Epimers LV and LVII form the same sodium salt LVI, which, however, gives only LV upon reaction with acids.

1-Substituted 3-hydroxypyrazoles XLVI are formed in quantitative yields by the action of 1 mole of an alcohol solution of alkoxide on pyrazolidone-(3)-azomethineimines XLVII (R^3 = H) (the Dorn rearrangement) [67, 68]. The product of the first step is azomethine ylid LVIII, which then adds reversibly one proton from a solvent molecule (H*) to the 5-C atom (to give XLVII) and to the 6-C atom (to give LIX), during which RONa is liberated. The latter promotes deprotonation of azomethineimine LIX, and XLVI-Na is formed as a result of this latter irreversible step [67].

The formal 1,3-dipolar structure of azomethineimines XLVII in Schemes 4 and 5 evidently reflects to the greatest degree the actual state of polarization of the bonds in molecules of this type. This assumption is also confirmed by the specific addition to nitrostyrenes [65] and to Grignard reagents (R^6 = alkyl, aralkyl, and aryl) in tetrahydrofuran, as a result of which 1-substituted pyrazolidones LX are formed exothermally [69]. In general, the reaction of compounds of the H—Y type such as alcohols [70-72] with azomethineimines involves attack by Y^- on the nucleophilic carbon atom (6-C). Thus pyrazolidone IV also may add to azomethineimine XLVII to give 1-substituted 3-pyrazolidone, which upon treatment with 1 mole of azomethineimine XLVII may undergo "thorough alkylation" at the 2-N atom, as in the Mannich reaction [33]. In the presence of hydrogen ions, 1 mole of pyrazolidone IV is split out from N-monoacylaminal LXIII to give stable N,N'-bisacylaminal LXV, the first mirror-symmetrical hexahydrotetrazine [73, 74]. The mechanism of this reaction clearly demonstrates that the thermal dimerization of azomethineimines is a multistep catalytic (H—Y/H^+) reaction [73]

rather than a Woodward–Hoffmann-prohibited [62] concerted "head-to-tail" dimerization. The photochemically allowed [$\pi 4_s + \pi 4_s$] dimerization of pyrazolidone-(3)-azomethineimines XLVII leads to the formation of centrosymmetric hexahydrotetrazine LXII (R^1 = aryl) [75] in 1-6% yield. The principal products of the photochemical process (UV, dioxane) with the participation of azomethineimines XLVII are two-ring diaziridines LXI (R^1 = aryl, CH=CH–Ph) (see [76] and the literature cited therein). The latter readily undergoes rearrangement to stable azomethineimines XLVII ($R^1 = R^2 = R^4 = H$; $R^5 = R^1$) and are cleaved by nucleophiles, as is characteristic of acid amides (νCO 1750 cm^{-1}) that are not mesomerically stabilized. As a consequence of the information set forth above, UV irradiation of XLVII in alcohol solutions leads to (2-alkoxycarbonylethyl)diaziridines LXIV [76]. The reversible character of the reaction XLVII [λ_{max} ~ 350 nm (ε ~ 4.2)] $\rightleftarrows$ LXI [R^1 = aryl; λ_{max} ~ 235 nm (ε ~ 3.7)] is the result of a pronounced photochromic effect. Stabilization of the negative charge on the 2-N atom in pyrazolidone-(3)-azomethineimines XLVII due to the carbonyl group is confirmed by the reduced νCO value (~1600 cm^{-1}), while the positive charge on the 1-N atom of XLVII (R^2 = H) is confirmed by the decrease in shielding of 5-CH_2 (δ ~ 4.4 ppm) as compared with 3-pyrazolidones (δ ~ 3.3 ppm) [14].

Stabilized imino forms of azomethineimine salts LVI can be readily obtained in methanol from 3-iminopyrazolidines XXXI and carbonyl compounds [23, 77]. These compounds are hydrogenated quantitatively to salts of 1-substituted 3-iminopyrazolidines XIII (Pt, CH_3OH) [23], so that the reaction is an elegant general method for the synthesis of XIII in which the need for monosubstituted hydrazines is obviated. Delocalization of the negative charge on the 2-N atom of LXVI is confirmed by the depressed ν(3-C=N) value (~1590 cm^{-1}), while the positive charge on the 1-N atom is confirmed by the decreased shielding of 5-CH_2 (δ ~ 4.6 ppm) as compared with 3-iminopyrazolidines (δ ~ 3 ppm) [23].

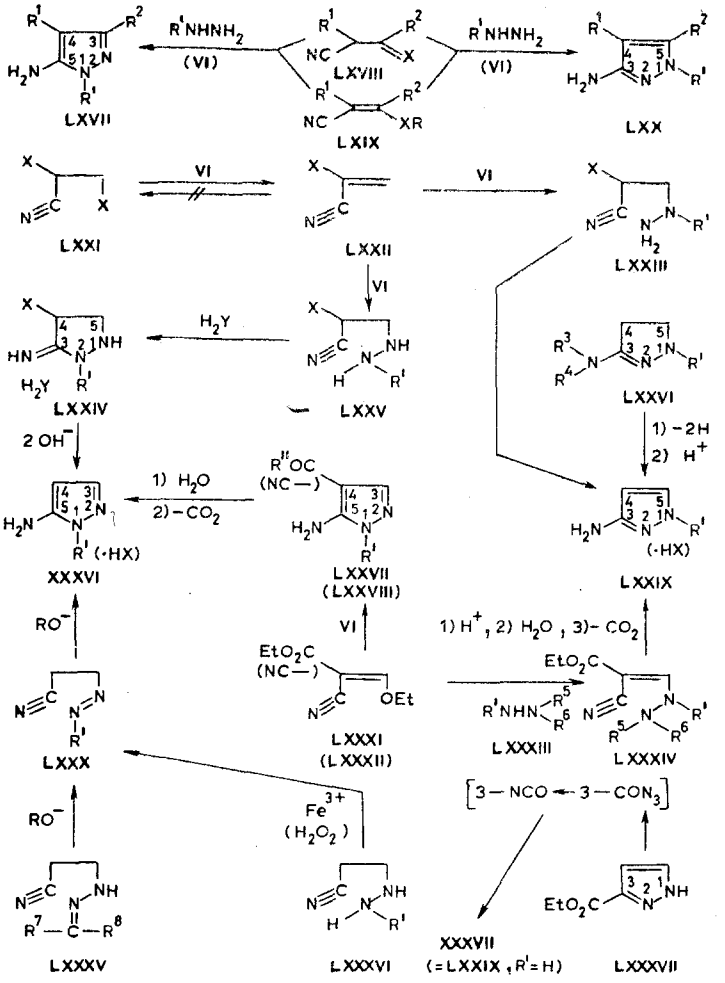
2. 3-Amino- and 5-Aminopyrazoles

2.1. Synthesis and Physical Properties (Schemes 6-8). The classical syntheses that are carried out under acid catalysis conditions are based on the reaction of β-oxo (LXVIII, X = O) [78-83] and β-imino nitriles (LXVIII, X = NH), β-cyano enamines (LXIX) [83-88], or enol ethers (LXIX, X = O) with hydrazine or monosubstituted hydrazines VI. However, in the case of alkylhydrazines the reaction proceeds ambiguously to give 5-aminopyrazoles LXVII, 3-aminopyrazoles LXX, or mixtures of them [82]. The reaction of monosubstituted hydrazine LXXXIII with a blocked amino group (R^5R^6 = CHPh or R^5 = H, R^6 = MeCO) with ethoxymethylenecyanoacetic ester (LXXXI) or -malononitrile (LXXXII) gives α-cyano-β-hydrazinoacrylic esters LXXXIV, the subsequent acid cyclization, saponification, and decarboxylation of which give exclusively 1-substituted 3-aminopyrazoles LXXIX (R' = alkyl, aralkyl [89-91], and Ph [92]). On the other hand, 5-amino-4-ethoxycarbonyl (or 4-cyano)pyrazoles LXXVII (LXXVIII), which can subsequently be converted to 1-substituted 5-aminopyrazoles XXXVI (R^1 = alkyl, cycloalkyl, aralkyl [30, 89, 90, 93, 94], aryl [24, 93, 95], and H [95, 96]), were synthesized from LXXXI or LXXXII and monosubstituted hydrazines. Thus analogs of the virostatic agent pyrazomycin [97] such as LXXVII (R' = ribosyl, R'' = NH_2) are similarly obtained from N-benzoylethoxymethylenecyanoacetamide and 2,3-O-isopropylidene-D-ribosylhydrazine [98]. One cyano group is replaced by the action of methylhydrazine on tetracyanoethylene to give 3-amino-4,5-dicyano-1-methylpyrazole LXX ($R^1 = R^2$ = CN; R' = Me) [99]. α,β-Unsaturated α-cyano-β-hydrazinocarboxylic acid esters LXIX (R^1 = CO_2Me, R^2 = alkyl, XR = $NHNH_2$) undergo cyclization under acid catalysis conditions to give 4-alkoxycarbonyl-5-alkyl-3-aminopyrazoles LXX (R' = H) [100] (cf. Section 3.1).

1-Aryl-3-aminopyrazoles LXXIX can also be obtained as a result of dehydrogenation of azomethine (R^3R^4 = ArCH=; $KMnO_4$, Me_2CO [101, 102]) or acyl derivatives (R^3 = H, R^4 = MeCO; sulfur [103]) of 3-aminopyrazolines LXXVI. 1-(2-Cyanoethyl)-2-phenylhydrazine (LXXXVI) is dehydrogenated by $Fe_2(SO_4)_3$ [24] and preferably by 3% H_2O_2 and catalysis by Fe^{3+} ions [104]; dilute H_2SO_4] to give azo compound LXXX (R' = Ph), which then undergoes cyclization in an alkaline medium to 5-amino-1-phenylpyrazole (XXXVI, R' = Ph).

A number of elegant specific methods based on α,β-unsaturated nitriles have thus far been proposed for the synthesis of 1-substituted 5-aminopyrazoles LXVII/XXXVI and 3-aminopyrazoles LXX/LXXIV. 5-Aminopyrazoles (R' = alkyl, cycloalkyl, and aralkyl) are obtained from β-cyanoalkylhydrazones such as LXXXV in butanol with sodium butoxide [105]. In my opinion, the intermediate step in this general method of synthesis is the formation of azo compounds LXXX (R' = CHR^7R^8) and β-hydrazono nitriles LXVIII (X = $NNHCHR^7R^8$); in principle, the hydrazone $\rightleftarrows$ azo compound rearrangement in the presence of alkalis is known [106]. 3-Aminopyrazoles

Scheme 6

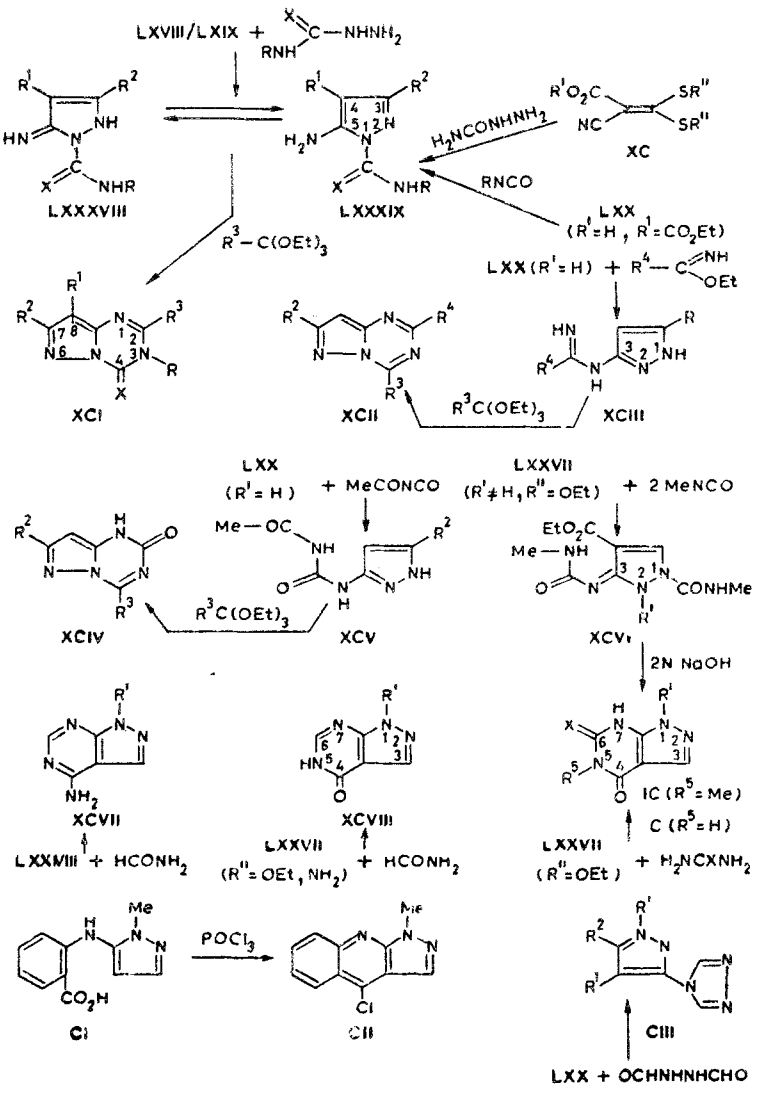


LXXIX (R' = alkyl, cycloalkyl, and aralkyl) and 5-aminopyrazoles XXXVI (R' = aryl) are obtained from α-haloacrylonitriles LXXII or α,β-dihalopropionitriles LXXI (X = Cl, Br) and hydrazines VI [107-109]. Hydrazines VI (R' = alkyl, cycloalkyl, and aralkyl) add at a rather high rate to LXXII (methanol, 0°C) to give 1-substituted 1-(2-cyano-2-haloethyl)-hydrazines LXXIII, which then undergo spontaneous conversion to LXXIX•HX (methanol, 20°C) [109]. Arylhydrazines VI add rapidly to LXXII (methanol, 20°C) to give 1-aryl-2-(2-cyano-2-haloethyl)hydrazines LXXV, which undergo cyclization with two equivalents of acids to 2-aryl-4-halo-3-iminopyrazolidine acid salts LXXIV (methanol, 20°C) [109]. Iminopyrazolidines LXXIV are converted spontaneously to XXXVI•HX [109]. The irreversible reaction of α,β-dihalopropionitriles LXXI with hydrazines VI proceeds rapidly to give α-haloacrylonitrile LXXII and VI•HX (methanol, 0°C). If one equivalent of a base such as Na_2CO_3 is added to the reaction mixture in the course of a few minutes, LXXI can thus also be used for the synthesis of aminopyrazoles [109].

Unsubstituted 3-aminopyrazoles are formed via a Curtius reaction in the decomposition of pyrazole-3-carboxylic acid esters (obtained from diazoacetic ester and acetylene); however, the elimination of sulfinates (see Section 1.2) and Lossen cleavage of 1-methyl- and 1-phenyl-4,5- and 3,4-dicarbohydroxamates [92] are preferred methods for the preparation of XXXVII. The action of nitric acid (sp. gr. 1.5) in acetic acid on pyrazoles gives 1-nitropyrazoles, which undergo thermal rearrangement to 3-nitropyrazoles; 3-aminopyrazoles can be obtained by hydrogenation of the latter (see [111] and the literature cited therein). A mixture of 1-methyl-3-nitro- and 1-methyl-5-nitropyrazoles (3:1), the subsequent hydrogenation of which makes it possible to isolate the corresponding aminopyrazoles [112], is formed by the action of methyl iodide on 3-nitropyrazole.

5-Aminopyrazoles XXXVI and 3-aminopyrazoles LXXIX are soluble in chloroform, acetonitrile, dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA), methanol, and water and crystallize in the tautomeric amino form [113]. The Bellamy equation (see Section 1.1) is

Scheme 7



satisfied for the νNH_2 frequencies of these compounds. The vicinal spin–spin coupling constants J_{34} (XXXVI) = 2.05 (D_2O), 1.90-1.95 (CDCN, $CDCl_3$), and 1.80-1.85 Hz [$(CD_3)_2SO$] and J_{45} (LXXIX) = 2.35-2.40 (D_2O, MeOH), 2.20-2.30 (CDCN, $CDCl_3$), and 2.15-2.20 Hz [$(CD_3)_2SO$] confirm the existence of the amino form [113, 114], as does the inertness of these compounds with respect to Raney nickel. Electron-acceptor substituents (RSO_2, RCO, and NO_2) attached to the ring nitrogen atom give rise to a 0.9-1.2 Hz increase in the J_{34} and J_{45} values [113]. The difference between J_{34} and J_{45} is too small for identification of 1-substituted 5- and 3-aminopyrazoles. A parameter of the PMR spectra, viz., $\Delta_{HMPT}^{CDCl_3} = CDCl_3 - \delta HMPT$ (for R^2 = H), is more suitable for this purpose. This parameter is greater than zero (> −0.4) for 5-aminopyrazoles LXVII, whereas it is less than zero (< −0.4) for 3-aminopyrazoles LXX; the values in parentheses pertain to those cases in which R' is an electron acceptor [115]. The reason for the specific ΔY^X effect is interaction of a specifically polarized pyrazole isomer with polar solvent (Y) molecules [115]. The dipole moments [115, 116], the enthalpies of formation in the gas phase [113, 117], and the pK_a values [118] have been calculated and measured.

5-Amino-1-(thio)carbamoyl- and, respectively, 5-amino-1-guanylpyrazoles LXXXIX [X = S(O) or NH] (tautomers LXXXVIII) are obtained under acid catalysis conditions from β-oxo nitriles LXVIII (X = O) or β-cyano enamines LXIX (X = NH) and (thio)semicarbazides and, respectively, aminoguanidines, while 5-amino-1-carbamoylpyrazoles LXXXIX (R = Co_2R'; R^2 = SR", X = O) are obtained from 2-cyano-3,3-bis(alkylmercapto)acrylic esters XC and semicarbazides in ethanol [122].

2.2. Substitution at the Ring Nitrogen Atoms and at the Exocyclic Amino Group (Schemes 7-9). Substitution in (3)5-aminopyrazoles LXX/LXVII may proceed at the ring nitrogen atoms (R' = H), at the exocyclic amino group, and at the 4-C atom (R' = H). Many syntheses of various interesting heterocyclic systems [cyclic adenosine monophosphate (CAMP)—phosphodiesterase inhibitors, antiphlogistic and psychopharmacological agents, and antimetabolites] are based on methodical and mechanistic advances in these reactions.

3-Aminopyrazoles LXX (R^1 = H) are converted to N-(3-pyrazolyl)-amidines XCIII upon reaction with imido esters (R^4 = Me, Et) [123]. These compounds, like 1-acyl-5-aminopyrazoles LXXXIX, undergo cyclization in the presence of ortho esters to pyrazolo[1,5-a]-sym-triazines XCII [123] or their 3,4-dihydro-4-oxo(thioxo) or 4-amino derivatives XCI [X = O(S) or NH] [120, 121, 123]. Acetyl isocyanate addes to the exocyclic nitrogen atom of 3-amino-5-methylpyrazole (LXX, R' = R^1 = H, R^2 = Me, Et_2O, 20°C) to give XCV. After removal of the acetyl group (NH_3, H_2O), 3-pyrazolylurea XCV undergoes cyclization with ortho esters to give 1,2-dihydro-2-oxopyrazolo[1,5-a]-sym-triazines XCIV [120]. In the absence of a solvent, 3-amino-4-ethoxycarbonylpyrazole (LXX, R' = R^2 = H, R^1 = CO_2Et) quantitatively adds methyl isocyanate to the ring 2-N atom to give 5-amino-1-methylcarbamoylpyrazole (LXXXIX, R = Me, R^1 = CO_2Me, R^2 = H) [124]. The reaction of other electrophilic partners (RSO_2^+, RCO^+) with 3-aminopyrazoles LXX (R' = H) takes place primarily at the nucleophilic nitrogen atom (2-N) (see below). 1-Substituted 5-aminopyrazoles LXXVII (R' ≠ H, R'' = OEt) add 2 moles of methyl isocyanate (in choloroform or benzene in the presence of triethylamine) to give bis(carbamoyl)-3-imino-4-pyrazolines XCVI (R' = Me [89], Mr, Ph [124]), which readily undergo cyclization to give 1,5-disubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidines IC (C=O) [89, 124]. Bis-(arylsulfonyl)-3-imino-4-pyrazolines CVII (R' = Me) are synthesized in acetone from 5-amino-1-methylpyrazole (XXXVI, R' = Me) and arenesulfonyl chlorides [47]. Upon heating or in the presence of trimethylamine (20°C), which promotes transfer of an RSO_2^+ group, they undergo rearrangement to the more stable 5-bis(arylsulfonamido)pyrazoles CIV (R' = Me) [47]. The latter are also formed as a result of the reaction of 1-substituted 5-aminopyrazoles XXXVI (R' = Me, Ph) with sulfonyl chlorides in pyridine [30, 125, 126].

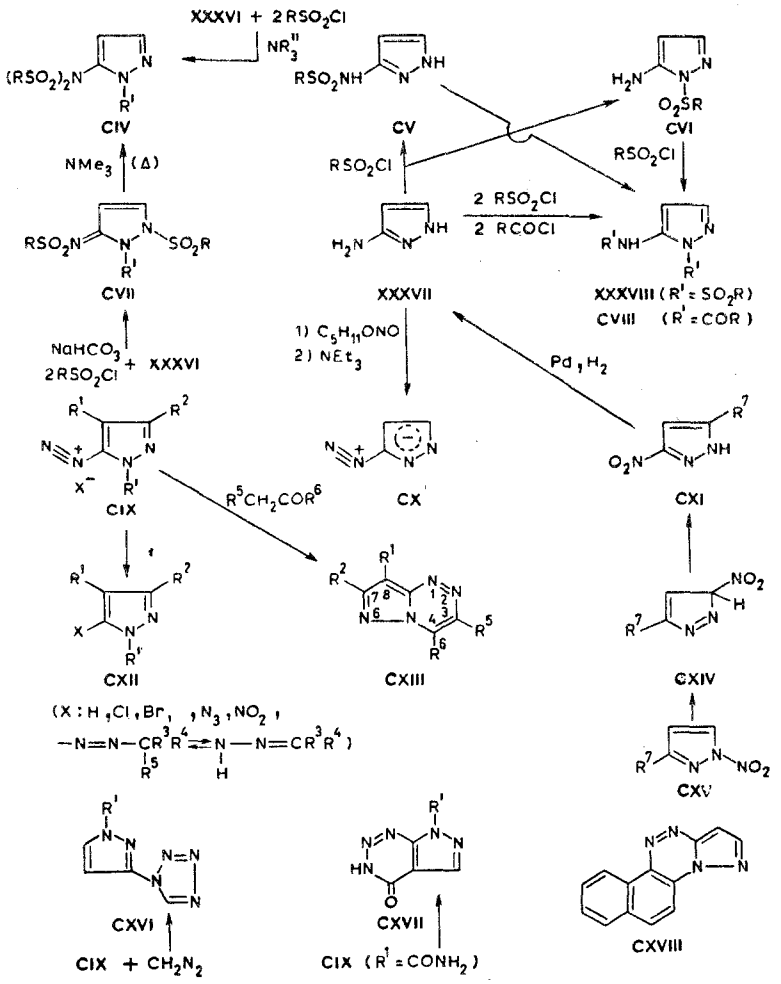
Derivatives of 5-amino- (LXXVII, R' = CO_2Et or $CONH_2$) and 3-aminopyrazole-4-carboxylic acids react with excess formamide (200°C) to give, respectively, 1-substituted (XCVIII, R' = alkyl, cycloalkyl [89], and Ph [95]) and 2-substituted (R' = H [95, 96], alkyl [89]) 4,5-dihydro-4-oxopyrazolo[3,4-d]pyrimidines. The reaction of the same starting compounds with urea (thiourea) (180-200°C) gave, respectively, 1-substituted (C, R' = alkyl [89, 93], CH_2Ph [89], and pH [92, 93]) and 2-substituted (R' = H [95], alkyl [89], and Ph [92]) 4,6-dioxo(4-oxo-6-thioxo)-4,5,6,7-tetrahyxropyrazolo[3,4-d]pyrimidines. 1(2)H-XCVIII (allopurinol) is a xanthine oxidase inhibitor (an antigout agent), while 1(2)H-C (X = O) is its natural metabolite. 3(5)-Amino-4-cyanopyrazoles such as LXXVIII react with formamide (200°C) to give 4-aminopyrazolo-[3,4-d]pyrimidines such as XCVII [89, 93, 96]. The condensation of 3-aminopyrazoles LXX (R' = R^2 = H, R^1 = Ph) with N,N'-diformylhydrazine ($HOCH_2CH_2OH$, 150-180°C) leads to pyrazolyl-4H-1,2,4-triazoles CIII (herbicides to combat chenopodium) [127].

The reactions of 3-aminopyrazole XXXVII with arenesulfonyl chlorides [46], acid chlorides [113, 128], and acetic anhydride [128, 129] take place at the hydrogen atom in the 2 position (the pyridinelike 2-N atom) and at the amino group. When 1 mole of $ArSO_2Cl$ (pyridine) is used, one obtains CVI (insoluble in 2 N NaOH, the principal product) and CV (soluble in 2 N NaOH), while XXXVIII is obtained with 2 moles of $ArSO_2Cl$, and trisulfonamidopyrazoles CIV (R' = RSO_2) are obtained with 3 moles of $ArSO_2Cl$; the sulfonyl and acrylic residues attached to the ring nitrogen atom in CVI, XXXVIII, and CVIII are readily split out as a result of hydrolysis [46, 113].

5-(2-Carboxyphenyl)amino-1-methylpyrazole CI is synthesized by means of the Ullmann reaction from 5-amino-1-methylpyrazole and 2-iodobenzoic acid (copper, alkali, aqueous or alcohol solution) [130], while 5-amino-1-(3-carboxy-2-chloro-5-sulfophenyl)pyrazole undergoes intramolecular conversion to the corresponding pyrazolo[1,5-a]benzimidazole [131]. 5-Dimethylamino-1-methyl(phenyl)pyrazole is synthesized from N-methyl(phenyl)hydrazones and dichloromethyleneiminium chloride ($Cl_2C{=}\overset{+}{N}Me_2Cl^-$) in chloroform [132].

All of the reactions that are peculiar to aromatic diazo compounds, except replacement of the diazo group by an OH group (the photochemical occurrence of this process is possible in the case of 4-diazopyrazoles [133], are characteristic for pyrazole-3(5)-diazonium salts CIX. 3(5)-Diazopyrazoles such as CX are formed by the action of bases on CIX (R' = H) [110].

Scheme 8



For simplification, only the (1H—5X) form of diazonium salts CIX and their conversion products CXII, CXVI, and CXVII (R' = H) are used in Scheme 8. The tautomeric (1H—3X) ⇌ (1H—5X) conversion in pyrazoles [113, 134, 135] can be observed by means of ^1H (below —100°C) and ^{13}C (20°C [135]) NMR spectroscopy; very rapid proton transfer occurs in inert solvents via an intramolecular process as a result of the formation of triple associates with hydrogen bridges.

3(5)-Chloro(bromo)pyrazole is obtained from CX via the Sandmeyer reaction [136]. 3(5)-Iodopyrazole is formed as a result of the action of concentrated hydriodic acid on pyrazole-3(5)-diazonium chloride CIX (R' = R^1 = R^2 = H) [110], while 3(5)-azidopyrazole is formed in the case of NaN_3 in water [137], and pyrazolyltetrazole CXVI (R' = H) is formed by the action of diazomethane in ether solutions [138]. In the synthesis of 3(5)-chloro(bromo)pyrazole CXII (R' = R^1 = R^2 = H, X = Cl or Br) preference should be given to the method based on the thermal cyclization of β,β-dichloro(dibromo)acrolein azine $(X_2C{=}CH{-}CH{=}N)_2$ to pyrazole CXII (R' = CHX—CH—CX_2; X = Cl or Br, R^1 = R^2 = H), which then undergoes acid hydrolysis [139]. It is possible to replace the amino group in 3-amino-4-methoxycarbonyl-1-methylpyrazole by a nitro group (HBF_4, H_2O, $NaNO_2$; Cu, 20°C) [140]. Pyrazoles CXII (R' = X = H) can be synthesized rather simply (methanol) starting from 3(5)-diazopyrazoles and the corresponding diazonium salts CIX under the condition that R^1 is an electron acceptor, as, for example, in CXII (R^1 = Ph, R^2 = COPh) [133] and 4-nitropyrazole CXII (R^1 = NO_2, R^2 = H) [141].

Azo compounds CXII (X = N=N—R") are formed as a result of coupling of 3(5)-diazopyrazoles with phenols, dimethylaniline, and 2-pyrazolin-5-ones, while naphthopyrazolo-1,2,4-triazines CXVIII are formed with β-naphthols [136, 142], and CXII [X = N=N—CH(CN)CO_2Et, R' = R^1 = R^2 = H) are formed with cyanoacetic ester [143]. Pyrazolo[5,1-c]-1,2,4-triazines CXIII (R^5 = COMe, R^6 = Ph [145] or R^5 = CO_2Et, R^6 = Me [143]) are formed in the reaction of 3(5)-diazopyrazoles or diazonium salts CIX (R' = H) with 1,3-diketones or with β-keto carboxylic acid esters; these results are correlated in [145, 146]. Compound CXII [R' = R^1 = R^2 = H, X = NHN=C(CO_2Et)-$(CH_2)_3CO_2$Et] was synthesized via the Japp—Klingemann reaction from pyrazole-3(5)-diazonium chloride CIX and 2-ethoxycarbonylcyclopentanone (ethanol) [146]. 4,5-Dihydro-4-oxopyrazolo-

[3,4-d]-1,2,3-triazines CXVII were obtained by diazotization of 3(5)-aminopyrazole-4-carboxamides [147, 148]. The synthesis of pyrazole-3(5)-diazonium salts CIX should be carried out in aqueous or alcohol solutions of concentrated acids in the presence of sodium nitrite or isoamyl nitrite, since dilute acids promote the occurrence of side reactions such as 4-C nitrosation (Section 2.3).

1,3-Diketones readily condense with 3-aminopyrazoles LXX [R' = H; $R^1 = R^2 = H$ [129, 149]; R^1 = Me, R^2 = Ph [150]; $R^1 = CO_2Et$, R^2 = H [129]; R^1 = Cl or Br, R^2 = H (see [151] and the literature cited therein)] to give pyrazolo[1,5-a]pyrimidines CXXXVII. A mixture of isomers is formed if $R^3 \neq R^4$. Enamino ketones of the CXIX type (R' = RSO_2 instead of OR:R^4), which undergoes cyclization to stable pyrazolo[1,5-a]pyrimidines CXXXVII (ethanol, 2 N NaOH), are synthesized under acid catalysis conditions (propanol) from 5-amino-1-arylsulfonylpyrazoles CVI and 1,3-diketones [149]. Compounds of the CXXXVII type (R' = halogen) are cyclic adenosine monophosphate (CAMP)—phosphodiesterase inhibitors and have a relaxing effect similar to that of tranquilizers [151]. Electrophilic substitution at the 3-C atom (halogenation [151], nitrosation [150], and the Mannich reaction [152]) is characteristic for pyrazolo[1,5-a]-pyrimidines CXXXVII (R^1 = H). The reaction of 3(5),4-diaminopyrazoles with diketones was examined in Section 2.3. Esters of β-keto carboxylic acids such as acetoacetic ester react with 3-amino- (LXX) and 5-aminopyrazoles (LXVII) to give 2-ethoxycarbonylvinylamines CXX (R^2 = H, R' = H [94, 129]; Me, CH_2Ph [153]; Ph [154]), CXIX (R^2 = H R' = Me, CH_2Ph [94], Ph [154]; R^2 = R' = Me [155], Ph [150]; R^2 = Me, R' = Ph [154]), or the corresponding acetamides CXXXIV and CXXXIII. The course of the reaction depends entirely on the temperature; thus at 20-80°C the corresponding vinylamines CXX or CXIX are formed (ethanol, benzene, or without a sample, with or without acid catalysis), whereas the corresponding amide is formed at 140-160°C (xylene) [153, 156]. 4,7-Dihydro-7-oxopyrazolo[1,5-a]pyrimidines CXXI were obtained by cyclization of 2-ethoxycarbonylvinylamine CXX (R' = H) (heating; an alcohol or aqueous solution of NaOH; acetic acid) [94, 129, 149]. These compounds can also be obtained by direct synthesis (acetic acid) from 3-aminopyrazoles LXX (R' = H) and β-keto acid esters. The reaction of 3-aminopyrazole XXXVII with R—C≡C—CO_2Me leads to the formation of 5-substituted (R = Me, CO_2Me) 4,7-dihydro-7-oxopyrazolo[1,5-a]pyrimidines (for example, CXXI) and their isomers, viz., 7-substituted (R = H, Me, Ph) 4,5-dihydropyrazolo[1,5-a]pyrimidines [157].

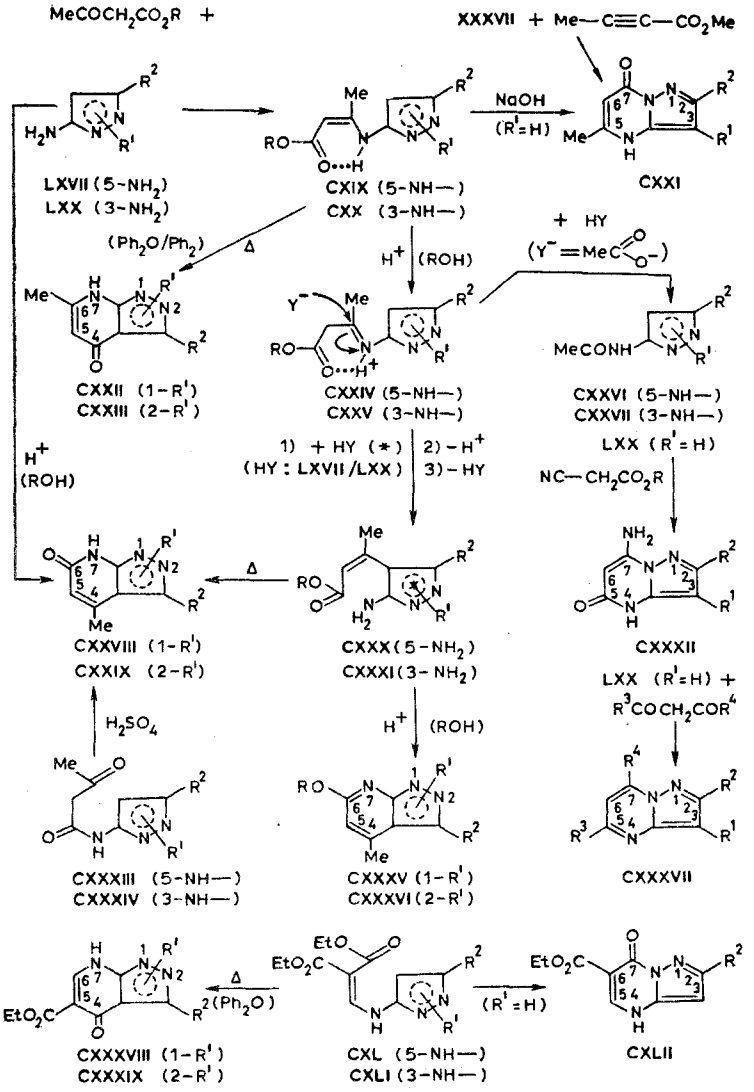
The reaction of 3-aminopyrazoles LXX (R^1 = H or CO_2Et) with cyanoacetic ester (160-170°C) gives 3-(2-cyanoacetamido)pyrazoles, which in acetic acid are capable of undergoing cyclization to 7-amino-4,5-dihydro-5-oxopyrazolo[1,5-a]pyrimidines CXXXVI; the latter can also be synthesized directly (ethanol, NaOEt) from LXX and cyanoacetic ester [129]. β-Keto nitriles react with 3-aminopyrazoles (R' = H) in the same way as β-keto acid esters; 5,6-disubstituted 7-aminopyrazolo[1,5-a]pyrimidines are formed under acid catalysis conditions [80]. 7-Amino-3,6-dicyanopyrazolo[1,5-a]pyrimidine was obtained by reaction of 3-amino-4-cyanopyrazole with ethoxymethylenemalonodinitrile [158].

5,7-Dihydroxypyrazolo[1,5-a]pyrimidines CXXXVII ($R^3 = R^4$ = OH; R^2 = H; R^1 = H, CO_2Et [129], Ph, Cl, Br, NO_2 [78, 79]) are formed in the cyclization of diethyl malonate with 3-aminopyrazoles LXX (R' = H). At elevated temperatures (100-140°C) the reactions of 3-amino- (LXX) and 5-aminopyrazoles LXVII with ethoxymethylenemalonic ester lead to the corresponding enamines CXLI or CXL [159-161]. When R' = H, 4,7-Dihydro-6-ethoxycarbonyl-7-oxopyrazolo-[1,5-a]pyrimidines CXLII are isolated (NaOH, H_2O) [157, 160, 162].

2.3. Substitution at the Ring Nitrogen Atoms and at the 4-C Atom (Schemes 9 and 10).

The monocyclic products that are formed from 3-amino- (LXX) or 5-aminopyrazoles (LXVII, R' ≠ H) and β-keto carbonyl compounds are capable of participating in intramolecular electrophilic substitution reactions at the 4-C atom of the pyrazole ring. 2-Ethoxycarbonylvinylamines CXX or CXIX, like CXLI or CXL, undergo cyclization in Dowtherm or diphenyl ether (240-260°C) (the Conrad—Limpach synthesis) to give 2- or 1-substituted 6,7-dihydro-7-oxopyrazolo-[3,4-h]pyridines CXXIII (R^2 = H, R' = Me, CH_2Ph [153], and Ph [154]) and CXXII (R^2 = H, R' = Me, CH_2Ph [153], R^2 = R' = Me [155], R^2 = H or Me, R' = Ph [154]) and CXXXIX and CXXXVIII [159-161, 163], respectively. Derivatives of CXXXIX and CXXXVIII are cyclic adenosine monophosphate (CAMP)—phosphodiesterase inhibitors; they have antipyretic action and, in addition, have a soothing effect (they eliminate apprehension). In $POCl_3$ 2-ethoxycarbonylvinylamines CXL undergo cyclization to give 1-substituted 4-chloro-5-ethoxycarbonylpyrazolo[3,4-b]pyridines [159, 161]. 1-Methyl-4-hydroxy-6,7-dihydro-6-oxopyrazolo[3,4-b]pyridine CXV is formed in the reaction of 5-amino-1-methylpyrazole LXVII (R' = Me, R^2 = H) with diethyl malonate (Ph_2O) [164]. Amides CXXIV and CXXIII (R' = Ph) [154, 156] undergo cyclization in concen-

Scheme 9

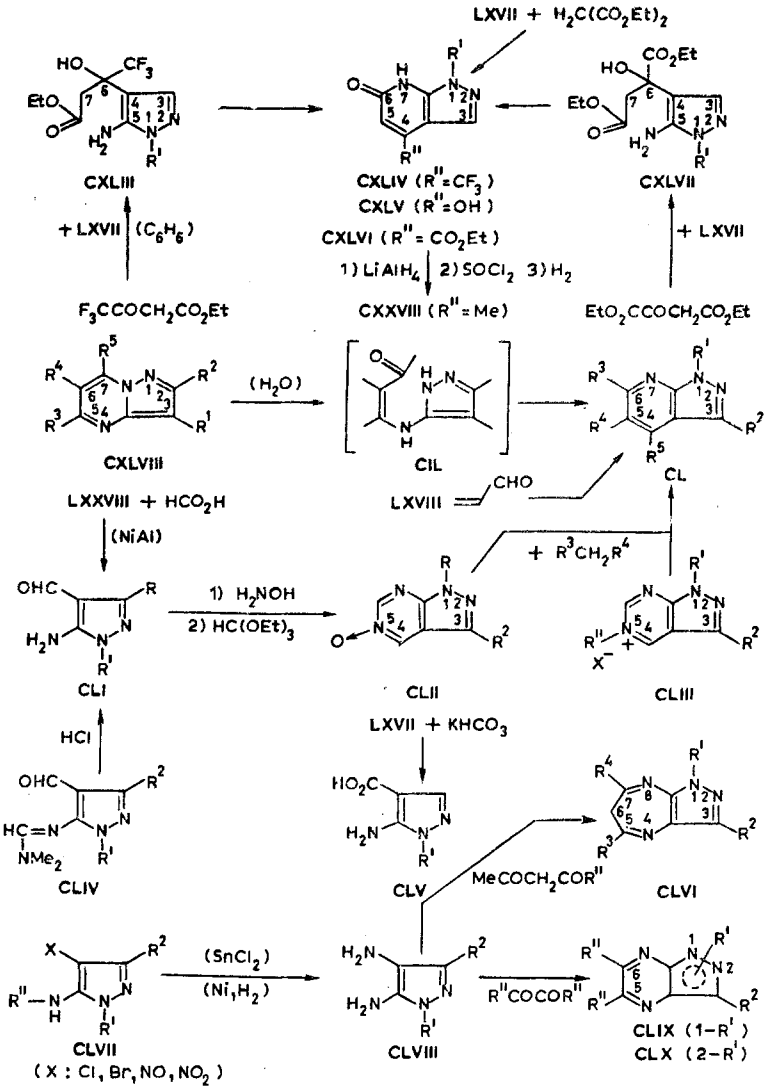


trated sulfuric acid (the Knorr synthesis) to give 2- and 1-substituted 6,7-dihydro-6-oxo-pyrazolo[3,4-b]pyridines CXXXIX and CXXVIII, respectively.

The preferred method for the synthesis of the latter is the cyclization of 2-ethoxycarbonylvinylamines CXX and CXIX (R' = alkyl, aralkyl, and aryl) [153] under acid catalysis conditions (ethanol or propanol); protonated enamine CXXV or CXXIV undergoes nucleophilic attack by catalytic amounts of 3-amino- (LXX) and 5-aminopyrazole LXVII [HY(*)], and LXX and LXVII (HY), respectively, are liberated. 3-Amino- (CXXXI) and 5-amino-4-(2-ethoxycarbonylvinyl)-pyrazoles (CXXX), which readily undergo cyclization to 6,7-dihydro-6-oxopyrazole[3,4-b]-pyridines CXXIX and CXXVIII, are formed in an intermediate step (they were isolated in [153]). When hydrogen ions are present, 5-8% 6-alkoxypyrazolo[3,4-b]pyridine CXXXVI or CXXXV (intramolecular formation of imido esters) is formed in addition to the latter products [153]. The increased electron density on the 4-C atom in the case of HY(*) (LXVII > LXX) promotes nucleophilic attack of protonated enamine CXXV and CXXIV just as in the Conrad–Limpach synthesis. 3-Acetamido- (primarily CXXVII) and, corresponding, 5-acetamidopyrazoles CXXVI are also formed in addition to the corresponding 6,7-dihydro-6-oxopyrazolo[3,4-b]pyridines CXXIX and CXXVIII in acetic acid from 2-ethoxycarbonylvinylamines CXX and CXIX; acetate ion (Y^-) begins to play a competitive role as a nucleophile [153]. Compounds CXXIX and CXXVIII are best synthesized under acid catalysis conditions (propanol) starting directly from 3-amino- (LXX) and 5-aminopyrazoles (LXVII) and β-keto carbocylic acid esters [153, 156].

The position of R' (alkyl, aryl, and glycosyl) in a condensed pyrazole system, as, for example, in CXXII and CXXIII, CXXVIII and CXXIX, and CLIX and CLX, is determined on the basis

Scheme 10



of the parameter (for R^2 = H) of the PMR spectra [153]. This value is greater than −0.65 ppm for compounds of the 1-R' type but lower than −0.65 ppm for compounds of the 2-R' type. The assignment of structures containing 4-oxo (CXXII/CXXIII, $\delta^{13}C{=}O$ 173-179 ppm) and 6-oxo (CXXVIII/CXXIX, $\delta^{13}C{=}O$ 163-167 ppm) groups was made by means of ^{13}C NMR spectroscopy with allowance for the effect of the solvent on the tautomeric oxo-hydroxy equilibrium [153].

In the reaction of 1-substituted 5-aminopyrazoles LXVII with strong electrophilic agents such as trifluoroacetic ester [165, 166] or oxalacetic ester [167] the process takes place directly at the 4-C atom (20°C) to give 5-amino-4-(2-ethoxycarbonyl-1-hydroxyethyl)pyrazoles CXLIII and CXLVII, respectively. The latter undergo cyclization in acetic acid to give 1,4-disubstituted 6,7-dihydro-6-oxopyrazolo[3,4-b]pyridines CXLIV and CXLVI. The conversion of the CO_2Et group in CXLVI to a methyl group leads to 6-oxo structure CXXVIII [167, 168].

In an alkaline medium pyrazolo[1,5-a]pyrimidines CXLVIII (R^1 = H) undergo rearrangement to pyrazolo[3,4-b]pyridines CL (R' = H) [169]. This reaction is an example of the Kost rearrangement [170], which involves opening of a heterocyclic ring as a consequence of cleavage of the C–N bond, as in the Dimroth rearrangement (compare with CIL [145]), and the subsequent rearrangement of the C–C bond as a result of electrophilic attack at, for example, the 4-C atom of the pyrazole ring (see above). The Kost rearrangement is promoted by electron-acceptor R^4 substituents (for example, NO_2) and electron-donor R^2 substituents (for example, OH). Compounds CL (R' = aralkyl, aryl) are synthesized from 5-aminopyrazoles LXVII, glycerol, and sulfuric acid (the Skraup synthesis) [171]. Numerous pyrazolo[3,4-d]pyrimidines are converted to pyrazolo[3,4-b]pyridines under the condition that favorable conditions for primary

nucleophilic attack at the 4-C atom exist in the starting compounds. The first step of this reaction is similar to the Dimroth reaction. N-Oxides CLII [172] and quaternary salts CLIII (R" = Me or H, X = I or HSO_4; R' = Me, Ph) [173] react with active methylene compounds (2 moles of malonodinitrile, cyanoacetic ester, acetoacetic ester, acetylacetone, etc.) in butanol or ethanol to give the corresponding pyrazolo[3,4-b]pyridines CL. The latter can also be obtained directly from 5-amino-4-formylpyrazole (CLI) and an active methylene compound (ethanol, EtONa; the Friedländer synthesis) [173, 174].

5-Amino-4-formylpyrazole is obtained from 5-aminopyrazoles LXVII by means of the Vilsmeier reaction ($POCl_3$, DMF) through an intermediate step involving dimethylaminomethylene derivatives CLIV (R' = Ph) [174] or from 5-amino-4-cyanopyrazoles LXXVIII, formic acid, and Raney nickel (R' = Me, Ph) [172]. In turn, their oximes undergo cyclization with orthoformic acid esters to give pyrazolo[3,4-d]pyrimidine 5-oxides CLII (R' = Me, Ph) [172]. Acetic anhydride and benzoyl chloride react with 1,3-dimethyl-5-aminopyrazole to give two- and three-ring systems; the intermediates are evidently the 4-acyl derivatives, which, however, could not be isolated [175]. 4-Carboxylic acid CLV was obtained by the action of $KHCO_3$ (H_2O, 100°C) on 5-aminopyrazole LXVII (R' = cyclohexyl) [176].

In the case of 3- and 5-aminopyrazoles one can carry out halogenation, nitration, and nitrosation in the 4-C position. Bromination is carried out in acetic acid [128, 177], whereas in the case of chlorination (SO_2Cl_2) and nitration (concentrated H_2SO_4, HNO_3) it is best to carry out the synthesis through an intermediate step involving N-acetyl derivatives CLVII (R" = MeCO; X = Cl, NO_2) [128]. In dilute acids (2-5N, HCl, H_2O, or EtOH; $NaNO_2$ or $C_5H_{11}ONO$) 2-substituted 5-amino- [178, 179] and 5-dialkylaminopyrazoles [180] yield 5-amino-4-nitrosopyrazoles CLVII (X = NO). The latter ($SnCl_2$, 2 N HCl) [178, 179], like 3(5)-amino-4-nitropyrazoles (H_2, Ni) [128], can be reduced to 3(5),4-diaminopyrazoles CLVIII, which undergo condensation with β-keto carbonyl compounds to give pyrazolo[3,4-b][1,4]-diazepines CLVI [181] and with 1,2-diketones to give pyrazolo[3,4-b]pyrazines CLX and CLIX [178]. 4-Bromopyrazoles CLVII (R' = Me, R" = PhCO, X = Br) react with aroyl chlorides through a step involving the lithio derivative (BuLi; tetrahydrofuran, −50°C) to give 5-amino-4-aroylpyrazoles CLVII (R' = R" = Me, X = ArCO), which are intermediates in the synthesis of pyrazolo[3,4-e][1,4]diazepines [177].

3. 3-Hydroxypyrazoles, 4-Pyrazolin-3-ones, and 2-Pyrazolin-5-ones

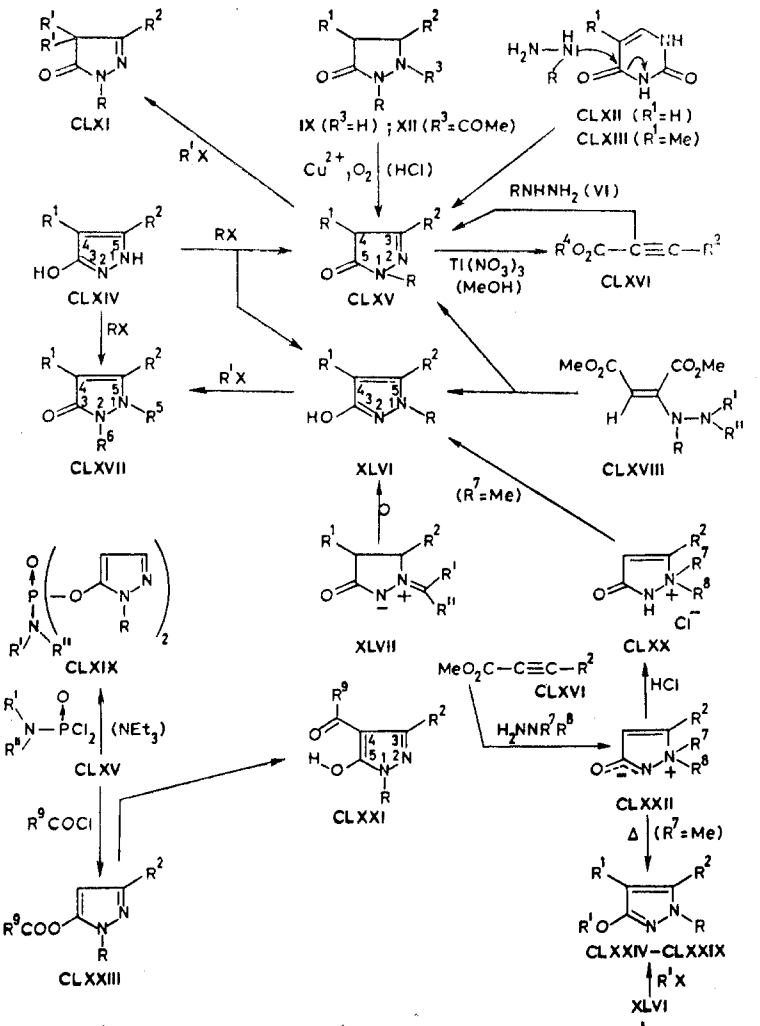
3.1. Synthesis, Alkylation, and Acylation. 3-Hydroxypyrazoles CLXIV and XLVI and the corresponding 2-pyrazolin-5-ones CLXV (R = H) are isomers, and the latter exist primarily in dilute nonpolar aprotic solutions [113]. Despite their practical value (as color-forming components of dyes and as analgesic and antipyretic agents) and the intensive research in this area up to 1964, significant methodical and structural-chemical problems that require solution have remained.

3-Hydroxypyrazoles CLXIV are readily accessible, since they can be synthesized from β-keto carboxylic acid esters and hydrazine [1]; unsubstituted 3-hydroxypyrazole XLIII [46] was examined in Section 1.2. In addition, CLXIV are formed by the action of $Li[PdCl_3]$ (NEt_3, MeCN; 20°C) [182] on α,β-unsaturated acid hydrazides. The latter are obtained by treatment of activated α,β-unsaturated esters [183], mixed anhydrides [6, 183], or methacryloyl chloride [184] with hydrazine (chloroform, 0°C). α,β-Unsaturated esters of α-cyano-β-hydrazino carboxylic acids undergo cyclization (NH_3 or K_2CO_3; H_2O) to 4-cyano-3-hydroxypyrazoles LXXXV (R^2 = alkyl, Ph) [100] (cf. Section 2.1).

A mixture of 1-substituted 2-pyrazolin-5-ones CLXV, 3-hydroxypyrazoles XLVI, and 1,2-disubstituted 4-pyrazolin-3-ones CLXVII is formed as a result of alkylation of 3-hydroxypyrazoles CLXIV. Pyrazolinones CLXV (R^1/R^2 = H or Me; R = Me [185, 186], Et; $CHMe_2$, CH_2Ph [187]) are formed in addition to CLXVII by the action of alkyl halides or benzyl chloride (in a refractory glass tube at 100-125°C in 20-40% yields), while LXVI (R = Me) are formed in the case of MeI $(MeO)_2SO_2$, or TosOMe (2 N NaOH, MeONa, MeOH, in 10-25% yields) [185, 188, 189].

2-Pyrazolin-5-ones such as CLXV (R^1 = H, R^2 = Me; R = Me [185, 190], $CHMe_2$ [187], CH_2Ph [187, 191-193], aryl [1]) are obtained from monosubstituted hydrazines VI and β-keto carboxylic acid esters such as acetoacetic ester. In the case of catalysis by Cu^{2+} ions 2-substituted 3-pyrazolidones IX or their 1-acetyl derivatives XII are dehydrogenated (O_2; 1 N HCl) to give CLXV (R = Me, CH_2Ph [19], Ph [21]). This general method of synthesis, like the

Scheme 11

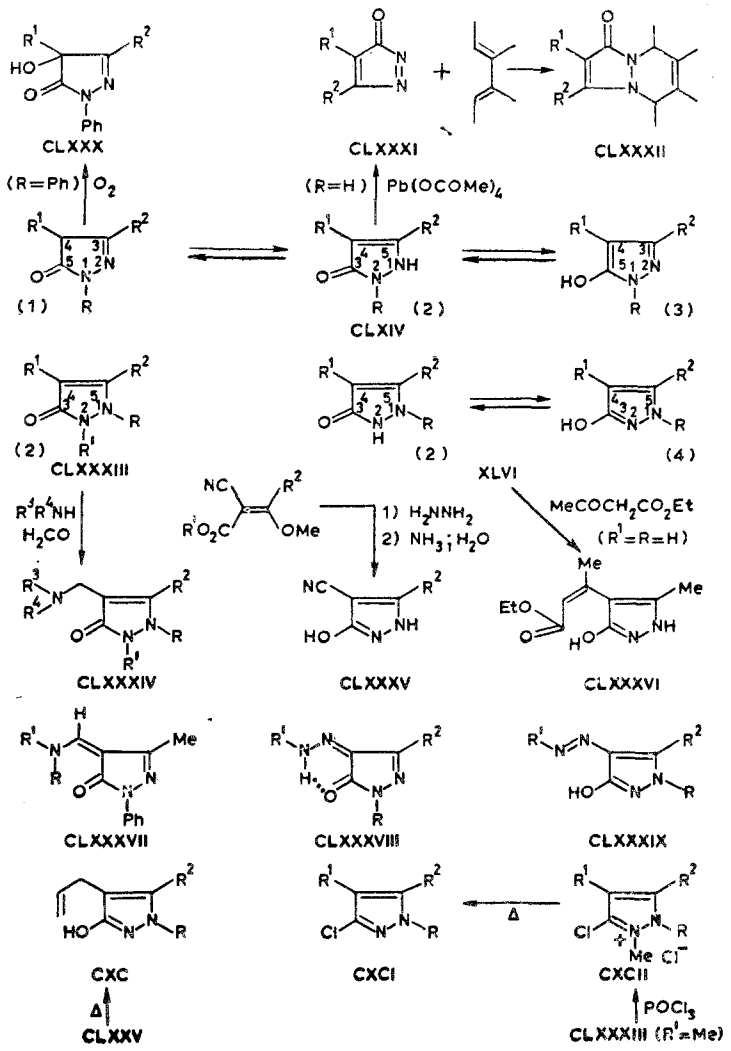


CLXXIV R'=Me, R=Me,Ph ; CLXXV R'=$CH_2CH{=}CH_2$, R=Ph ; CLXXVI R'=MeCO, R=Ph, R'=H ; CLXXVII R'=H, R=Ph, R'=MeCO ; CLXXVIII R'=CMe_2CO_2R''; CLXXIX R'=$CH_2CH(OH)CH_2NR''R'''$

elimination of sulfinates from 2-substituted 1-arylsulfonyl-3-pyrazolidones XLI [42, 43] (Section 1.2), makes it possible to unambiguously obtain 2-pyrazolin-5-ones CLXV. The nucleophilic attack (H_2O, 100°C) of methylhydrazine on uracil CLXII or thymine CLXIII leads to the formation of 1-methyl- and, correspondingly, 1,4-dimethyl-2-pyrazolin-5-one CLXV and urea [186]. 1,2-Disubstituted 4-pyrazolin-3-ones CLXVII are obtained in the reaction of 3-hydroxypyrazoles CLXIV ($R^1 = R^2 = H$; $R^1 = H$; $R^1 = H$, $R^2 = Me$) with 2 moles of TosOMe in DMF ($R^5 = R^6 = Me$ [42]), 1-substituted 3-hydroxypyrazoles XLVI with MeI (110°C) ($R^5 = Me$ [194], CH_2Ph [115], Ph [195]; $R^6 = Me$), 1-substituted 2-pyrazolin-5-ones CLXV with MeI or $(MeO)_2SO_2$ ($R^5 = Me$; $R^6 = Me$ [194], Ph [1, 113, 196]), or finally, N,N'-disubstituted hydrazine and acetoacetic ester ($R^2 = Me$, $R^5 = R^6 = CH_2Ph$ [193]). 4,4-Disubstituted 2-pyrazolin-5-ones such as CLXI ($R = R^1 = CH_2Ph$, $R^2 = Me$) are also formed when CLXV ($R^1 = H$) are used (EtOH, NaOH) [193].

The reaction of acetylenecarboxylic acids CLXVI with monosubstituted hydrazines VI proceeds ambiguously. Compounds VI and their hydrazones add to esters CLXVI ($R^2 = CO_2Me$) to give 2-hydrazinomaleates CLXVIII and the corresponding hydrazones, the subsequent cyclization of which yields mixtures of isomers consisting of 1-substituted 2-pyrazolin-5-ones CLXV ($R^1 =$ H, $R^2 = CO_2Me$; R = alkyl, cyclohexyl, CH_2Ph) (the principal product at 100°C without a solvent; benzene, see [197] and the literature cited therein; DMSO [198]) and 3-hydroxypyrazoles XLVI (the principal product in acetic acid [197]). The isolation of intermediate CLXVIII is not necessary [197]. 3-Hydroxypyrazole XLIII or the corresponding 1-substituted 2-pyrazolin-5-one CLXV is formed in the reaction of acetylenecarboxylic acid ester CLXVI ($R^2 = H$ [186], alkyl [199]) (Et_2O; MeOH) with anhydrous hydrazine VI (R = H or Me [186], alkyl [199]).

Scheme 12



Betaines CLXXII are formed (MeOH, H_2O; 0°C) by the action of 1,1-disubstituted hydrazines ($R^7 = R^8 =$ Me; R^7—R^8 = $(CH_2)_5$, $(CH_2CH_2)_2O$; R^7 = Me, R^8 + pH) on methyl propiolate or dimethyl acetylenedicarboxylate (R^2 = H or CO_2Me) [200]. These betaines undergo isomerization (190°C) to 1-substituted 3-methoxypyrazoles CXXIV (R^7 = Me) and tetrahydropyrazolo[1,2-a]diazepin-1-ones [R^7—R^8 = $(CH_2)_5$], respectively. They react with hydrochloric acid to form 1,1-disubstituted 2,3-dihydro-3-oxopyrazolinium chlorides CLXX, which are converted to 200°C to 1-substituted 3-oxopyrazoles XLVI [R^1 = H, R^2 = H, CO_2Me; R = Me, Ph, $(CH_2)_5Cl$] [200]. The Dorn rearrangement [67] proceeds unambiguously in the case of azomethineimines XLVII (see Section 1.3) and 1-substituted 3-hydroxypyrazoles such as XLVI (R^1/R^2 = H, alkyl, aryl; R = CH_2Ar, CH_2Het [68]). Hydrazides of β-keto carboxylic acids undergo cyclization (PCl_5 [194, 195]; concentrated HCl [201]) to give 1-substituted 3-hydroxypyrazoles XLVI (R = Me, aryl); N'-acetylated hydrazines VI (R = Me [194], aryl [195]) and β-keto carboxylic acid esters or phenylhydrazine and ketene [201] are used as the starting compounds. The synthesis of 1-aryl-3-hydroxypyrazoles XLVI (R = aryl) can be carried out more simply using the dehydrogenation ($FeCl_3$ or Cu^{2+}/O_2) of 1-aryl-3-pyrazolidones X [16], since the formation of azomethineimines XLVII is impossible in this case (see Section 1.3). 1-Phenyl-3-pyrazolidone (phenidone) is used as a developer [202, 203], and its electrochemical oxidation is described in [204].

The N-alkylation of 3-hydroxypyrazoles CLXIV and XLVI and the corresponding 2-pyrazolin-5-ones CLXV was examined in the section dealing with syntheses. O-Alkylation is carried out in polar aprotic media (acetone, DMF, and DMSO) using solutions of alkali salts of XLVI or CLXV [115, 197, 205-210]. The most frequently encountered side reaction in this synthesis is alkylation of XLVI in the 2-N position to give CLXVII and CLXV and in the 4-C position with the formation, for example, of CLXI (R = Me, R^2 = CO_2Me, R^1 = $CH_2CH{=}CH_2$) [197]. Alkali salts of 3-hydroxypyrazoles XLVI react (DMF) with epichlorohydrins to give 3-(2,3-epoxypropoxy)-

pyrazoles, the further reaction of which with amines yields amino alcohols CLXXIX [206-208]. 3-(1-Carboxyalkoxy)pyrazoles (hypolipemic and antipyretic agents) are obtained by the action of trichloro-tert-butyl alcohol (Me_2CO, NaOH) [209, 210].

The reaction of 3-hydroxypyrazoles XLVI and the corresponding 2-pyrazolin-5-ones CLXV with acetic anhydride (pyridine) or acid chlorides (dioxane, NEt_3; benzene—water, Na_2CO_3) is used for the synthesis of 1-substituted 3-acyloxy- (for example, CLXXVI [205]) and the corresponding 5-acyloxypyrazoles CLXXIII [197, 211-213]. These compounds are capable of undergoing the Fries rearrangement ($AlCl_3$) to give 4-acyl-3-hydroxy- (for example, CLXXVII) [205] and the corresponding 4-acyl-5-hydroxypyrazoles CLXXI [211]. 5-Hydroxypyrazole-4-carboxylic acid esters CLXXI (R = Ph, R^9 = OEt [214]) with a substituent in the 1 position can also be synthesized from monosubstituted hydrazines VI and ethoxymethylenemalonic ester, whereas 3-hydroxypyrazole-4-carboxylic acid ester CLXIV ($R^1 = CO_2Et$, R^2 = H) was isolated in the case of hydrazine itself [215]. This ester can also be obtained from malonic ester, chloroform, and hydrazine [216]. The preferred tautomers are the forms with a free OH group and forms in which the OH group is linked by a hydrogen bridge [217]. Phosphorylated 5-hydroxypyrazoles CLXIX were obtained by the reaction of 2-pyrazolin-5-ones CLXV (R = Me, Ph) with phosphoric acid dichlorodiamide (NEt_3; tetrahydrofuran or benzene) [218].

In the presence of lead tetraacetate (CH_2Cl_2; −10°C) 3-hydroxypyrazoles CLXIV (CLXV, R = H) undergo dehydrogenation to give 3-oxopyrazoles CLXXXI; the latter add to 1,3-dienes as azodienophiles with the formation of compounds of the CLXXXII type [219]. Compounds CLXXXI [$R^1 = Te(ONO_2)_2$; R^2 = alkyl, Ph] are similarly intermediates in the reaction of 3-hydroxypyrazoles CLXIV (CLXIV, R = H) with $Te(NO_3)_3$ (MeOH), while the final products are nitrogen and methyl acetylenecarboxylate CLXVI [220]. In the case of oxidation with air oxygen 1-aryl-2-pyrazolin-5-ones CLXV give, in addition to colorless 4,4'-bispyrazolones (2H-) and "pyrazole blue" (4H-), 4-hydroxy derivatives CLXXX (R^1 = Me, Et) [221].

3.2. Substitution of 3-Chloropyrazoles in the 4-C Position and Tautomerism (Scheme 12). As in the case of 2-pyrazolin-5-ones CLXV, in the case of 3-hydroxypyrazoles CLXIV and XLVI substitution in the ring 4-C position is realized quite readily. Thus the Claisen rearrangement makes it possible to convert 3-allyloxy-1-phenylpyrazole CLXXV ($R^1 = R^2$ = H) [205] and methyl 5-allyloxy-1-methylpyrazole-3-carboxylate [197] to the corresponding 4-allyl-3-hydroxy- (CXC) and 4-allyl-5-hydroxypyrazoles CLXV (R = Me, $R^1 = CH_2CH{=}CH_2$, $R^2 = CO_2Me$). The reaction of acetoacetic ester (NaOH, H_2O) with CLXIV (XLVI, R = R^1 = H, R^2 = Me) gives 4-(2-ethoxycarbonylvinyl)-3-hydroxypyrazole (CLXXXVI), which then undergoes thermal cyclization (—EtOH) [222]. 3-Hydroxypyrazoles XLVI (R^1 = H; R = alkyl, CH_2Ph [59, 152], Ph [205]) and 4-pyrazolin-3-ones CLXVII (CLXXXIII, R^1 = H, R^2 = H or Me; R = R' = Me [152], R^2 = R = Me, R' = Ph [223]) readily form Mannich bases XLV (see Section 1.3) and the corresponding CLXXXIV, including those formed under the influence of dichlorodiethylamine ($R^3 = R^4 = CH_2CH_2Cl$ [15]). Z-4-Aminomethylene-2-pyrazolin-5-ones CLXXXVII (R = R' = Me or R = Me, R' = Ph) are obtained via Vilsmeier formulation (DMF or PhMeNCHO; $POCl_3$) from 1-phenyl-2-pyrazolin-5-ones CLXV (R^2 = Me, Ph) [224]. These compounds are hydrolyzed in an alkaline medium to give 4-hydroxymethylene-2-pyrazolin-5-ones (CLXXXVII; in place of NRR':OH) [225, 226], whereas they give Z-4-aminomethylene-2-pyrazolin-5-ones CLXXXVII (R = H) in reactions with $R'NH_2$ (MeOH) [224]. Compounds CLXXXVII (R = H) are characterized by a strong intramolecular hydrogen bond. They exist in tuatomeric form CLXXXVIII in nonpolar and polar media [227, 228]. Photochemical Z/E isomerization is discussed in [229]. The products of coupling (at the heteroring 4 position) of 1-substituted 3-hydroxypyrazoles XLVI (R = alkyl, aralkyl [58], phenyl [205]) and 2-pyrazolin-5-ones CLXV (R = alkyl, aralkyl [19, 42], aryl [1]) with arenediazonium chlorides are 4-arylazo-3-hydroxypyrazoles CLXXXIX (in CCl_4 and $CHCl_3$ and in the crystalline state [113, 230]) and Z-4-arylhydrazono-2-pyrazolin-5-ones CLXXXVIII (in C_6H_{12}, CCl_4, $CHCl_3$, and EtOH and in the crystalline state [113, 230]), respectively.

When DMSO and pyridine are used as the solvents, the intramolecular hydrogen bond in CLXXXVIII are cleaved [230]. The products of diazo coupling of N-unsubstituted 3-hydroxypyrazoles CLXIV exist in the CLXXXVIII form (R = H) both in chloroform and in the crystalline state [113, 231]. The UV spectra of the products of oxidative coupling of CLXV (R^1 = H) with N,N-dialkyl-p-phenylenediamines (4-arylimino-1-aryl-2-pyrazolin-5-ones) have been investigated [232]. 3-Hydroxypyrazoles XLVI (R = alkyl, aralkyl [59, 197, 206-208], Ph [205]) undergo chlorination, bromination, and nitration in the ring C-4 position quite simply.

3(5)-Chloropyrazoles are quite easily obtained from "pyrazolones" under the condition that the tautomeric oxo structure predominates. Thus 1-alkyl, 1-aralkyl- [115, 233], and

1-aryl-5-chloropyrazoles [115, 234] were synthesized from 1-substituted 2-pyrazolin-5-ones CLXV and $POCl_3$ at 135-140°C (in an autoclave). 3(5)-Chloro-5(3)-methylpyrazole CXCI (R = R^1 = H, R^2 = Me) was obtained by the reaction of $POCl_3$ with hydroxy-5-methylpyrazole at 144°C [233]. 3-Chloro-1-phenylpyrazoles CXCI were first prepared at 205-210°C from $POCl_3$ and 3-hydroxy-1-phenylpyrazoles XLVI (R^1 = R^2 = H [235], R^1 = H, R^2 = Me [236]). However, the preferred method of synthesis is methylation of 3-hydroxypyrazoles CLXIV or XLVI with the formation of 1,2-disubstituted 4-pyrazolin-3-ones CLXXXIII (R' = Me), which react with refluxing $POCl_3$ to give pyrazolium chlorides. 3-Chloropyrazoles CXCI (R^1 = H; R^2 = H, R = Me, CH_2Ph [115], R^2 = Me, R = Ph [236]) are obtained when MeCl is split out from the latter (130 150°C).

After 1964, many problems in the tautomerism of pyrazolidones and hydroxypyrazoles (the effect of the solvent, the concentration dependences, and the effects of substituents) were solved by means of physical methods of investigation (PMR, IR, and UV spectroscopy and measurement of the pK_a values and dipole moments) and semiempirical calculations; the modern state of the problem has been critically reviewed [113, 230]. In the case of 1-substituted 2-pyrazolin-5-ones CLXV ($R \neq H$) there are three tautomeric forms, viz., (1) and (2) (2-substituted 4-pyrazolin-3-ones) and (3) (1-substituted 3-hydroxypyrazoles). Form (1) predominates in dilute solutions (less than 0.05 mole/liter) in nonpolar aprotic media, while form (3) predominates in polar aprotic media. The fraction of form (1) in the tautomeric equilibrium decreases linearly as the basicity of the solvent on the Agami scale increases, and the concentrations of forms (2) and (3) increase. Forms (2) and (3) predominate in polar protogenic solvents. The higher the basicity of the solvent, the higher the fraction of form (3). Thus the concentration of form (2) in aqueous solutions significantly surpasses that in alcoholic solutions. Electron-donor R^2 substituents (NH_2, OEt, Me) promote an increase in the fraction of form (1). The existence of associates that are linked by means of hydrogen bridges in the form of forms (2) and (3) has been established in crystals [113, 230].

Tautomeric forms (4) and (2) (1-substituted 4-pyrazolin-3-ones) exist in the case of 1-substituted 3-hydroxypyrazoles XLVI ($R \neq H$). Clear predominance of form (4) is noted in nonpolar and polar aprotic media; form (2), the amount of which is greater in water than in alcohols (see above), also appears in polar protogenic solvents in addition to form (4). The existence of associates with a dimeric structure that are linked by means of hydrogen bonds has been established in crystals and in solutions in carbon tetrachloride and chloroform [113, 230].

Tautomeric forms (1) (2-pyrazolin-5-ones), (2) (4-pyrazolin-3-ones), and (3) and (4) (5- and 3-hydroxypyrazoles) are formed in the case of 3-hydroxypyrazoles CLIV (CLXV and XLVI, R = H) (four other forms in virtually negligible amounts also appear). Form (4) predominates along with form (1) in nonpolar and polar aprotic media. The existence of structure (1) is favored when R^2 = Me. Forms (2) and (4) exist in polar protogenic solutions. The fraction of form (2) decreases as the basicity of the solvent increases; however, upon the whole it is nevertheless higher than in 1-substituted 3-hydroxypyrazoles [113, 230].

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STEREOCHEMISTRY OF THE IODOCYCLIZATION OF UNSATURATED ALCOHOLS

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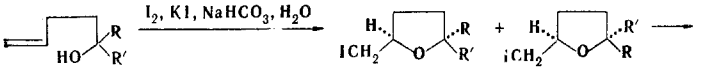
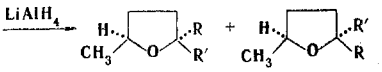
The corresponding tetrahydrofuran derivatives were obtained by iodination of δ,ε-unsaturated alcohols containing substituents attached to the α-carbon atom. The effect of substituents on the stereochemistry of the products and the rate of iodination of the unsaturated alcohols were studied.

Electrophilic heterocyclization of δ,ε-unsaturated alcohols is widely used for the synthesis of derivatives of tetrahydrofuran and tetrahydropyran [1, 2].

In a continuation of our research on electrophilic heterocyclization [3, 4] we have studied the effect of substituents attached to the α-carbon atom of δ,ε-unsaturated alcohols on the rate of their iodination and the stereochemistry of the cyclization products.



I a-c II a-c



III a, c

I-III a R = H, R′ = CH_3; I-II b R = C_2H_5, R′ = CH_3; I-III c R = C_6H_5, R′ = H

The cyclization of alcohol Ia may lead to derivatives of both tetrahydrofuran and tetrahydropyran. The PMR spectrum of the reaction product indicates the formation of only a five-membered heteroring. Two well-resolved doublets at 1.75 and 1.81 ppm (with an intensity ratio of 7:3) with J = 6 Hz, which are related to nonequivalent 2-CH_3 groups of cis- and trans-2-methyl-5-iodomethyltetrahydrofuran (IIa), are a characteristic feature of this spectrum.

Because of the development of chiral centers in the IIa molecule, the protons of the CH_2I substituent turn out to be diastereotopic and form a complex multiplet (2H) centered at

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