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SYNTHESIS OF ETHER-AMINES OF PROPANE-1,2-DIOL AND THEIR BIOLOGICAL ACTIVITY

B. Kh. Kimsanov and M. B. Karimov

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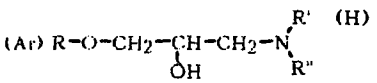
An account is given of various routes for the synthesis of ether-amines of propane-1,2-diol from glycerol derivatives. It has been established that this series of compounds exhibits pharmacological activity and also a stimulating or inhibiting effect on the germinating capacity and the energy of germination of the seeds of agricultural crops. A definite relationship has been revealed between the structure and biological activity of ether-amines of propane-1,2-diol. Ether-amines of propanediol and unsymmetrical 1,3-diaminopropan-2-ols, and also their sulfur-containing analogs, containing residues of primary amines or hydrazine are convenient synthons for passing to heterocyclic systems: derivatives of 1,3-oxazolidine, 1,3-thiazolidine, and 3-methyl-5-pyrazolone. The possibility of obtaining new polycyclic systems by diene synthesis from 1,3-oxazolidine and 1,3-thiazolidine derivatives including furfural residues and also from 1,3,4-thiadiazole derivatives, using cyano and thiocyano derivatives of glycerol and thiosemicarbazide is discussed.

At the present time, intensive investigations are being pursued throughout the world on the creation of new drugs having functional similarity to such important compounds as ephedrine, adrenaline, noradrenaline, dopamine, etc., which have found wide use in practical medicine as stimulators of α- and β-adrenoreceptors [1]. On this basis, importance is attached to investigations directed to the synthesis and detection of the biological activity of ether-amines of propane-1,2-diol, the presence of a secondary hydroxy group and of an aminomethyl residue in the molecules of which to some degree impart to them a similarity to the above-mentioned natural substances.

An analysis of voluminous literature material and of the experimental results that we have obtained in recent years shows that there is a definite relationship between the structure and the biological activity of the natural catecholamines and the closest of their synthetic analogs.

We have established that the presence of a combination of residues of various phenols (or alcohols), amines with a branched structure, and a 2-hydroxypropyl group in the molecules of ether-amines of propane-1,2-diol leads to the appearance of pharmacological activity or of growth-regulating properties with respect to the germinating capacity and the germinative energy of the seeds of agricultural crops. The structure of such compounds, under the general name of "ether-amines of propane-1,2-diol," is represented in the following way



where R′ and R″ are hydrogen atoms or radicals of aliphatic, cyclic, aromatic or heterocyclic amines, and R(Ar) represents the radicals of alcohols or phenols with various structures.

By varying the fragments of such a combination it is possible to regulate the degree of activity and toxicity of the compounds or to impart predetermined useful properties to them [2].

Various methods have been developed for the synthesis of ether-amines of propane-1,2-diol in which the starting materials are usually glycerol and its functional derivatives: epichlorohydrin, glycidol, α-mono- and α,γ-dichlorohydrins of glycerol, etc. Epichlorohydrin has found wide use for these purposes thanks to the presence in its molecule of two extremely reactive centers (an oxirane ring and a chlorine atom) and also to its availability and relatively low cost price [3].

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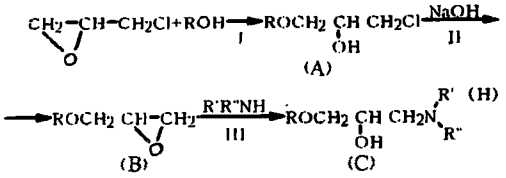
At the present time, the synthesis of ether-amines of propane-1,2-diol is carried out mainly by the following scheme [4]:



where R represents a C_1-C_{10} alkyl or an aryl (C_6H_5, $C_6H_5CH_2$, *o*-, *m*-, or *p*-$CH_3C_6H_4$- or *m*-$CH_3OC_6H_4$-) radical, R′ and R″ are H and H, CH_3 and CH_3, C_2H_5 and C_2H_5, H and $CH_2=CHCH_2$, H and $(CH_3)_3C$, H and $C_6H_5CH_2$, H and C_6H_{11}, H and NH, $-(CH_2)_5-(CH_2)_4O-$, or *iso*-C_5H_{11} and *iso*-C_5H_{11}.

A series of compounds of this class containing residues of various amines (isopropylamine, *tert*-butylamine, etc.) has been created using this transformation. It includes a whole series of β-blockers: anapriline — (±)-1-isopropylamino-3-(1′-naphthyloxy)propan-2-ol hydrochloride; oxyprenolol — 1-[(*ortho*-allyloxyphenoxy)-3-isopropylaminopropan-2-ol hydrochloride; talinolol — (±)-1-[*para*-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]cyclohexylurea; benzodixine — 5-(γ-isopropylamino-β-hydroxypropoxy)benzodioxane maleate; pindolol — 1-(indol-4′-yloxy)-3-isopropylaminopropan-2-ol; nadolol — 2,3-*cis*-1,2,3,4-tetrahydro-5-[2′-hydroxy-3′-(*tert*-butylamino)propoxy]naphthalene-2,3-diol; thymolol — (−)-1-(*tert*-butylamino)-3-(4′-morpholino-1′,2′,5′-thiadiazol-3′-yloxy)propan-2-ol, etc., which are widely used for the treatment of arrhythmia, stenocardia, tachycardia, arterial hypertension, and glaucoma [1].

When alcohols are used in reaction (I), catalysts for the process are protonic or aprotic Lewis acids (H_2SO_4, $SnCl_4$, boron fluoride ethyl etherate, etc., while when phenols are used their reaction is accelerated by substances of basic nature (pyridine).

By raising the temperature parameter of reaction (I) in proportion to an increase in the length of the carbon chain of an alcohol (C_1-C_{10}) in the temperature interval of 20-100°C we achieve a 90% yield of the intermediate product (A) with a considerable shortening of the reaction time.

We have developed a variant of the synthesis of ether-amines of propane-1,2-diol (III) by the direct interaction of 1-aryloxy(alkoxy)-3-chloropropan-2-ols with a mixture of the appropriate amine and alkali, which enables the desired product (III) to be obtained with a yield of about 90% of theoretical. This variant of the synthesis makes it possible to shorten stage (II), which considerably raises the yield of the final product (C) and substantially decreases the duration of this transformation [5, 6].

Using this variant, we have synthesized a large number of ether-amines of propanediol containing in the ether part of the molecule residues of phenol, the isomeric cresols, *m*-methoxyphenol, alcohols with C_1-C_{10} alkyl radicals, and phenylcarbinol, with, as the amine fragments, residues of dimethylamine, diethylamine, morpholine, piperidine, allylamine, *tert*-butylamine, cyclohexylamine, hydrazine, etc., [7, 8], and have studied their biological activity.

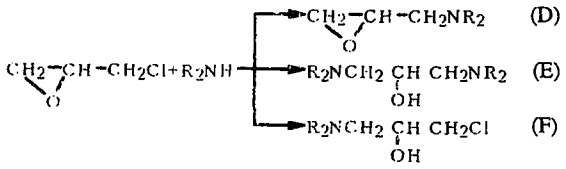
It has been found that ether-amines of propane-1,2-diol containing residues of various phenols and morpholine possess a hypotensive and spasmolytic activity. When residues of acetic acid and its homologs and diethylamine are combined in the molecules of such ether-amines, these compounds exhibit pronounced cholagogic, spasmolytic, cholinolytic, anticonvulsant, and sympathologic activity [2, 9].

It has been found that compounds having residues of *m*-methoxyphenol, benzyl alcohol, and amines of various structures possess the property of selectively inhibiting the germinating capacity and the germinative energy of agricultural crops. At low concentrations (0.1-0.001%) a series of 1-alkoxy-3-piperidinopropan-2-ols exhibits a stimulating action on the capacity for germination and the germinative energy of wheat, pea, and cotton seeds, while at high concentrations (0.2%) they exert an inhibiting action.

Compounds of the 1-alkoxy-3-diethylaminopropan-2-ol series also possess a powerful inhibiting effect. Such activity depends essentially on the degree of elongation of the carbon chain of the alkyl part of the molecule. A particularly strong effect is possessed by compounds of this series with C_7-C_{10} radical, which have shown a selective inhibitory action on the capacity for germination and the germinative energy of wheat, peas, and cotton at all the concentrations tested (0.001-0.2%) [2].

On the basis of a study of the physiological activity of a wide range of ether-amines of propane-1,2-diol we have revealed the presence in all these compounds of a stimulating or inhibiting effect on the capacity for germination and the germinative energy of agricultural crops.

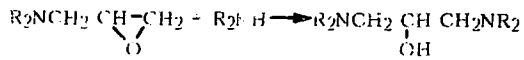
We have carried out a series of investigations connected with the replacement of the ether parts of ether-amines of propane-1,2-diol by various amine functions, with the aim of obtaining new representatives of symmetrical and unsymmetrical 1,3-diaminopropanols. The synthesis of such compounds started from epichlorohydrin by the following scheme:



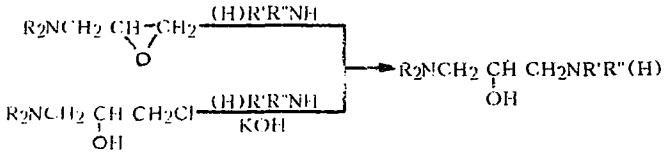
This led to the formation of a mixture of three products in each case; a N,N-dialkylaminomethyloxirane (D), a 1,3-bis(dialkylamino)propan-2-ol (E), and a 1-chloro-3-dialkylaminopropan-2-ol (F).

The amounts of these compounds in the mixture depends on the ratio of the reactants, the temperature, and the nature of the amines used [10, 11].

Symmetrical 1,3-diaminopropanols are also obtained by condensing product (D) with the appropriate amine:



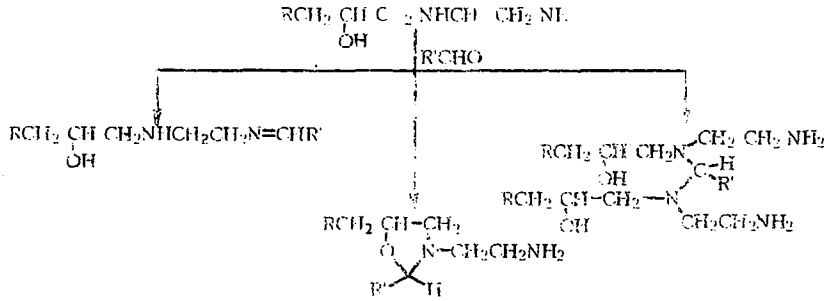
Unsymmetrical 1,3-diaminopropan-2-ols are obtained by the following transformations [12]:



It must be mentioned that this class of organic compounds possesses pronounced biological activity [13, 14].

The results of investigations of the pharmacological activities of the new representatives of such compounds that have been synthesized showed that they possess hypotensive and curaremimetic activities with low toxicity [2].

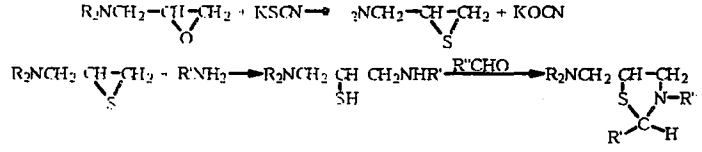
Ether-amines of propane-1,2-diol and unsymmetrical 1,3-diaminopropan-2-ols having residues of primary amines or hydrazine are convenient synthons for passing to heterocyclic systems. In particular, their condensation with oxo compounds leads to 1,3-oxazolidine derivatives [15]:



where R = RO or R_2N.

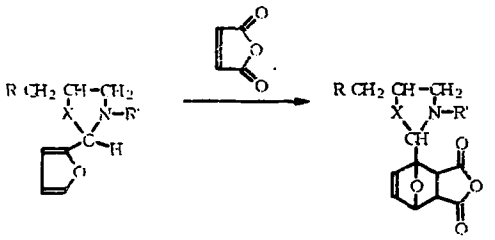
It has been found that this series of heterocyclic compounds possesses hypotensive and spasmolytic activity [2].

Extremely promising for the directed synthesis of new biologically active compounds is the production of sulfur-containing analogs of 1,3-diaminopropan-2-ols from the corresponding 2-dialkylaminomethylthiiranes:



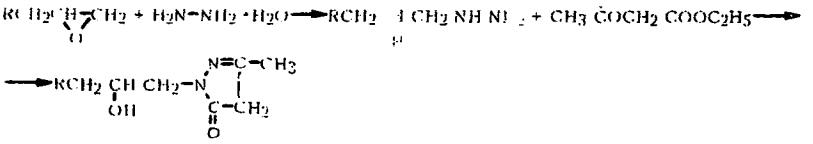
Using such thiol compounds, methods have been developed for the synthesis of 1,3-thiazolidine derivatives [16].

Particular interest is presented by 1,3-oxazolidine and 1,3-thiazolidine derivatives the synthesis of which involves furfural. By means of the diene synthesis, it is possible to pass from such compounds to new polycyclic systems [17]:



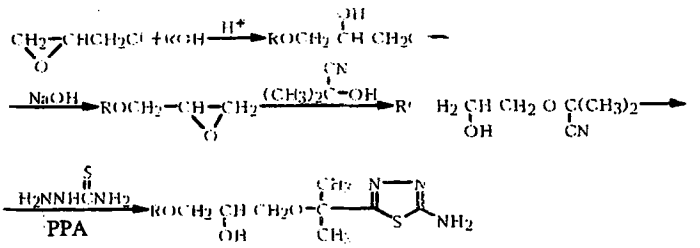
where X = O or S; R′ = C_6H_{11} or $C(CH_3)_3$; R = RO or R_2N.

Another interesting route for obtaining heterocyclic systems from epichlorohydrin is the creation of heterocyclic nitrogen-containing fragments in the amine parts of ether-amines of propane-1,2-diol and 1,3-diaminopropan-2-ols using acetoacetic ester [18] by the following scheme:

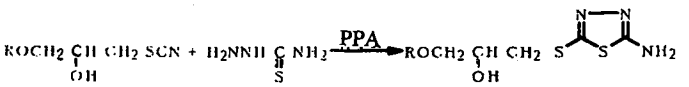


The new pyrazolone derivatives so obtained are potentially biologically active compounds.

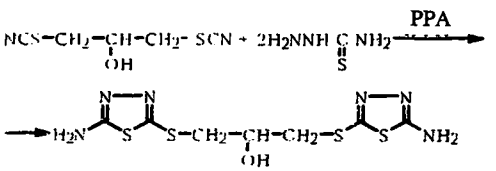
A promising direction for the synthesis of polycyclic sulfur- and nitrogen-containing systems is passage to new glycerol derivatives including a 1,3,4-thiadiazole fragment by the following transformation:



Analogous systems can also be obtained from thiocyano derivatives of glycerol by the scheme



The use of propan-2-ol derivatives with two thiocyano groups in this reaction leads to systems with two thiadiazole rings:



The study of such systems is permitting the revelation of changes in the biological activity of synthetic analogs of ephedrine and catecholamines and also the detection of new, previously unknown, useful properties of these substances [19].

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