SEARCH FOR MEDICINAL PREPARATIONS IN THE SERIES OF 1,3,5-TRIAZINES (REVIEW)

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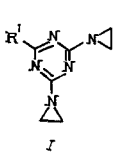
Since the fifties, a large number of publications have appeared in periodical journals on the varied biological activity of 1,3,5-triazine compounds. Among the compounds of this class were found antitumorigenic agents, chemotherapeutical preparations, active against viruses, pathogenic bacteria, protozoa, helminths, pharmacologically effective compounds used to treat cardiovascular, neuropsychotic disorders, or inflammatory processes, diuretics, antidiabetic agents, etc. A considerable number of 1,3,5-triazine derivatives were introduced abroad into medicinal practice as medicinal and disinfecting agents. Unfortunately, there are no attempts described in the literature to generalize the numerous individual publications on this problem, and by using this generalization, to reveal the characteristic features of the relationship between the structure and the biological activity in this series of compounds. The aim of the present review is to fill this gap and to show the prospects of further investigations in the chemically achieveable series of 1,3,5-triazine derivatives in a search for new medicinal preparations.

Compounds with Antitumorigenic Activity. One of the most widely studied fields of application of 1,3,5-triazine derivatives in medicine is the use of various ethyleneimino-1,3,5-triazines as antitumorigenic agents. 2,4,6-Triethyleneimino-1,3,5-triazine (triethylenemelamine, TEM, TET; Ia), which appreciably suppresses the growth of various recurring tumors, is one of the first heterocyclic derivatives containing ethyleneimine residues, which was independently selected by scientists in the U.S.A. [1] and in England [2] for more comprehensive study. The high experimental antitumorigenic activity of Ia was later confirmed by many authors [3-6], and clinical tests [7, 8] showed that (Ia) gives the best effect during chronic lympholeucosis [9, 10]. The medical results in lymphogranulomatosis differ, depending on the stage of the disease preceding the treatment of the state of hemogenesis, etc. During chronic myeloleucosis, most of the authors obtained a relatively weak effect. However, during arrhythmia, the preparation usually exhibits a pronounced therapeutic action and induced prolonged remissions. The preparation acts weakly in lymphosarcoma, and is inactive in reticulosarcoma, multiple myelitis and fungoid mycosis. For solid tumors, a definite effect was obtained in some patients with ovary cancer [11, 13]. Some authors [14] observed subjective and objective improvements in bronchogenic carcinoma. Positive results were noticed in the case of a combination of the preparation with x-ray therapy in retinoblastoma [15].



I

Ia: $R^1 = -N$ (ethyleneimino)

Ib: $R^1 = NHCH(CH_3)COOR^2$, $NHCH_2CH_2COOR^2$, $NHCH(C_6H_5)CH_2COOR^2$, $NHCH(COOC_2H_5)-CH_2COOR^2$; $R^2 = CH_3$, C_2H_5, $CH_2C_6H_5$;

Ic: $R^1 = OR^3$;

Id: $R^1 = NHR^4$

In the study of biotransformation of (Ia) [16, 17], it was found that not less than 16 metabolites of this preparation are formed in the organism, the principal ones being cyanuric acid, urea, and creatine. However, because triethylenemelamine is highly toxic and has a narrow range of therapeutic applicability, in the USSR, after clinical tests were carried out, (Ia) was not medically applied [18]. In recent years, triethylenemelamine is less frequently used in medical practice abroad. Attempts to intensify the antitumorigenic activity of the preparation by combining it with centrophenoxine [19] or to use its certain antiinflammatory action [20] did not give positive results.

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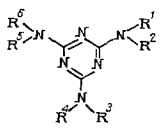
In a search for preparations with a broader range of therapeutic application, action selectivity and much lower toxicity, a large number of ethyleneimine derivatives of triazine, analogs of triethylenemelamine, have been synthesized [21-22]. In the paper by Soviet authors [4] it was shown that the antitumorigenic activity of compounds of this type depends on the number of ethyleneimine groups in the 1,3,5-triazine ring. Chemotherapeutic action is exhibited only by tri- and diethyleneimine derivatives of 1,3,5-triazine. Substitution of two or three ethylenemine groups in the ring by other residues led to almost complete loss of activity. 2,4-Diethyleneimino derivatives of 1,3,5-triazinylamino acids (Ib), though they had a lower toxicity, were also less active.

The same effect was obtained by the substitution of one of the ethyleneimino groups in the molecule of triethylenemelamine by heterocyclic residues (morpholinyl, piperidinyl, or piperazinyl). The best results were obtained with 6-alkoxy derivatives of 2,4-diethyleneimino-1,3,5-triazine (Ic), with not only a lower toxicity, but also antitumorigenic activity comparable with that of triethylenemelamine. Especially interesting in this respect was 6-benzyloxy-2,4-diethyleneimino-1,3,5-triazine (Ic, $R^3 = CH_2C_6H_5$), which was characterized by a fairly broad range of therapeutic applicability. This preparation, under the name of "Benzodet" [22], not only inhibited the growth of several recurring tumors in a tissue culture and had a therapeutic effect in experiments on mice with hemocytoblastic and lymphoblastic leucosis, but also had a therapeutic action in clinical practice on patients with metastases of skin and lung cancer.

From the correlation analysis between Taft constants of substituents and the distribution coefficients in the water–octanol system, it has been calculated [24] that in the series of 6-amino-2,4-diethyleneimino-1,3,5-triazines (Id), the most effective should be the hydrophilic compound Id with $R^4 = C(CH_2OH)_3$.

Abroad, trimethylolmelamine (IIa) has been used under the name of "Cealysin," "Cilag 61," "C61," as an alkylating cytostatic in the chemotherapy of malignant neoplasms. Its action was discovered already in 1959 on the Walker rat carcinoma [25], and was frequently confirmed in later investigations [26-29].



II

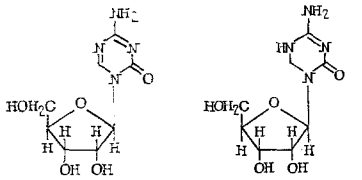
IIa: $R^1 = R^3 = R^5 = CH_2OH$; $R^2 = R^4 = R^6 = H$;
IIb: $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = CH_3$;
IIc: $R^1 = R^3 = CH_3$; $R^2 = R^4 = R^5 = R^6 = H$;
IId: $R^1 = R^3 = R^5 = CH_3$; $R^2 = R^4 = R^6 = H$;
IIe: $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$;
IIf: $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$; $R^6 = H$;
IIg: $R^1 = R^3 = R^5 = CH_2OH$; $R^2 = R^4 = R^6 = CH_3$.

In 1964, another derivative of melamine, hexamethylmelamine (IIb) was designated for clinical study; this compound is active toward Walker carcinoma 256 [25], sarcoma-180 [30], and several other tumors [31]. In clinical tests it had an inhibiting activity towards a large number of human tumors. The preparation is most effective in bronchogenic carcinoma, lymphoma, ovary adenocarcinoma, and breast cancer [32]. The mechanism of its action has not yet been established, but it apparently differs from that of alkylating agents of the triethylenemelamine type. During investigation, its metabolites, N^2,N^4-dimethylmelamine (IIc), N^2,N^4,N^6-trimethylmelamine (IId) and melamine (IIe) were identified. Unfortunately, because the preparation is sparingly soluble in water, its parenteral use is impossible. Therefore, further efforts [31, 33] were made to search for its chemotherapeutically active water-soluble analogs. However, investigations on increase in its solubility in water by removing the nonpolar methyl groups or by substituting one of these groups by a more polar residue, usually led to a decrease in the chemotherapeutic index. Of a large number of melamine derivatives, only two compounds, pentamethylmelamine (IIf) and N^2,N^4,N^6-trimethyl-N^2,N^4,N^6-tris(hydroxymethyl)-melamine (IIg) had a fairly high solubility in water and were found to be active in the experiment. These compounds have been recommended for clinical study.

Another trend in the search for new antitumorigenic agents in the series of 1,3,5-triazine derivatives was the synthesis and biological study of the aza analogs of natural nucleosides [34].

In the course of the investigations on the aza analogs of cytidine, in 1963, 4-amino-1-β-D-ribofuranosyl-1,3,5-triazine-2(1H)-OH-5-azacytidine (III) [35] was synthesized; the same

compound was later isolated from the filtrate of *Streptoverticillium ladakamus* culture [36]. 5-Azacitidine experimentally showed a high activity in different types of leukemia [37, 38] and Ehrlich ascites carcinoma [37]. It combines well with adriamycin, thioguanine and 5-aza-2'-desoxycytidine.

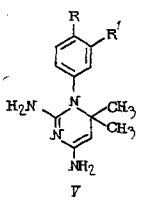


III IV

The best clinical results with 5-azacytidine were obtained in acute leukemia. The preparation was only slightly inferior in its effectiveness to cytosine-arabinoside and daunomycin [34]. The preparation is somewhat less active for solid tumors: breast and colon carcinoma and melanoma. It was suggested [34, 39, 40] that after it is introduced into the organism, 5-azacytidine converts into 5-azacytidine 5'-phosphate. At the same time spontaneous dissociation of 5-azacytidine takes place, and its deamination to 5-azauridine. 5-Azacytidine 5'-phosphate, included in the composition of RNA and DNA, effectively inhibits crotidine 5-phosphate decarboxylase and thus blocks the synthesis of RNA. The disturbance of the RNA and DNA synthesis explains the considerable anomalies induced by it in different types of cells, and also the broad spectrum of its biological activity; 5-azacytidine exhibits not only tumorigenic, but also cytotoxic, antimicrobial, abortive and mutagenic activity [39]. Because of the ease of hydrolysis of 5-azacytidine, 5,6-dihydro-5-azacytidine (IV) was prepared, which is a chemically more stable, readily soluble analog of 5-azacytidine, and is recommended for clinical use [41].

Potential antitumorigenic are also compounds which irreversibly inhibit dihydrofolate reductase of tumor tissue, and also inappreciably influence the dihydrofolate reductase of normal cells.

Of the large number of derivatives of 1-aryl-4,6-diamino-2,2-dimethyl-1,2-dihydro-1,3,5-triazines [42-45] of the general formula (V), tested in this direction, compounds (Va-Vh) were found to be the most active [45]. Compound (Vg) in the form of monoethanesulfonate, under the name of "Triazinate," has been successfully applied in the clinic for treating acute leucoses [46].



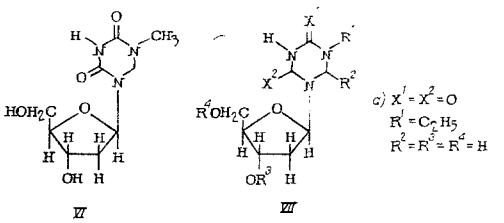
V

Va: $R = (CH_2)_2CONHC_6H_4SO_2F\text{-}4$, $R' = H$;
Vb: $R = CONHC_6H_4SO_2F\text{-}4$, $R' = H$;
Vc: $R = O(CH_2)_3OC_6H_5$, $R' = Cl$;
Vd: $R = OCH_2CONHC_6H_5$, $R' = Cl$;
Ve: $R = (CH_2)_2CONHC_6H_4CH_3\text{-}3$, $R' = H$;
Vf: $R = OCH_2CON(CH_2)_2OCH_2CH_2$, $R' = Cl$;
Vg: $R = OCH_2C_6H_4[CON(CH_3)_2]\text{-}3$, $R' = Cl$;
Vh: $R = OCH_2C_6H_4[CON(C_2H_5)_2]\text{-}3$, $R' = Cl$

Chemotherapeutically Active 1,3,5-Triazines. Analogs of natural nucleosides have in recent years occupied an important place in the searches not only for antitumorigenic, but also antiviral agents. A representative of this class of compounds, 5-iodo-2'-dexyuridine has been applied in medical practice as an antiherpetic agent [47]. Recently [48], in the fermentation broth obtained from the cultivation of *Streptomyces platensis* var. *clarensis*, a new 1,3,5-triazine nucleoside antibiotic has been discovered: 1-(2-deoxy-β-D-ribofuranosyl)-5-methyl-5,6-dihydro-1,3,5-triazine-2,4-(1H, 3H)-dione (5,6-dihydro-5-azathymidine) (VI). Experiments *in vitro* [48] showed that this preparation is active against herpes virus type 1. To a lesser extent, it acts on herpes virus type 2, slightly influences the smallpox virus, and is entirely inactive towards the pseudorabies virus. In its general antiviral action *in vitro*, this nucleoside was found to be less active than 5-iodo-2'-dexyuridine.

In experiments *in vivo*, (VI) protected mice infected with herpes virus type 1, if the virus was administered intravenously, and the preparation subcutaneously or perorally [49], and it also exhibited prophylactic and therapeutic activity towards the skin herpes virus [50].

Later [51], (VI) was obtained synthetically from trimethylsilyl derivatives of the corresponding substituted triazinyldione and ribofuranosyl chloride. It was thus possible to synthesize a large number of deoxyribofuranosyl-1,3,5-triazinyldiones of the general formula (VII).

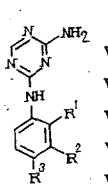


VI

VII

a) $X^1 = X^2 = O$, $R^1 = C_2H_5$, $R^2 = R^3 = R^4 = H$

In the experiment, one of the synthesized compounds (VIIa) had an antiherpetic activity comparable with that of (VI), and was less toxic. 2-Amino-4-arylamino-1,3,5-triazines (VIII) [52] were also found to be effective antiviral compounds.

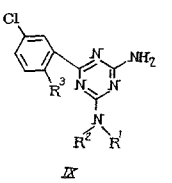


VIII

VIIIa: $R^1 = SCH_3$, $R^2 = R^3 = H$;
VIIIb: $R^1 = R^3 = H$, $R^2 = SCH_3$;
VIIIc: $R^1 = R^2 = H$, $R^3 = SCH_3$;
VIIId: $R^1 = R^3 = H$, $R^2 = COOC_2H_5$;
VIIIe: $R^1 = R^2 = H$, $R^3COOC_2H_5$;
VIIIf: $R^1 = R^2 = H$, $R^3 = OCH_3$;
VIIIg: $R^1 = OCH_3$, $R^2 = R^3 = H$

Compounds (VIII) having methylthio groups as substituents in o-, m- or p-positions of the phenyl residue (VIIIa, b, c), and especially those having carbethoxy groups (VIIId, e), were active toward herpes virus. An inhibiting action on the virus of the asiatic chicken pseudoplague was shown by compounds with a methoxy group in the aromatic ring. Of these compounds, (VIIIf) was most active, and (VIIIg) least active [53]. All these compounds had antifungal action [52].

A still broader spectrum of the biological activity was exhibited by 2,4-diamino-6-substituted-1,3,5-triazines [54] of general formula (IX).



IX

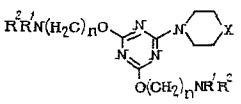
IXa: $R^1 = n\text{-}C_3H_7$, $R^2 = R^3 = H$;
IXb: $R^1 = CH_2C_6H_5$, $R^2 = R^3 = H$;
IXc: $R^1 = C_6H_4OCH_3 - 4$, $R^2 = R^3 = H$;
IXd: $R^1 = -N(CH_2)_4CH_2$, $R^2 = R^3 = H$;
IXe: $R^1 = CH_2CH_2C_6H_4$, $R^2 = H$, $R^3 = CH_3$;

Compounds (IXa-e) had a therapeutic action in experiments on mice infected with the A2/Hong-Kong influenza virus. Compounds (IX) also had antihelminthic action.

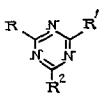
Derivatives of 1,3,5-triazine (X) containing piperazinyl or piperidyl, as well as aminoalkoxyl residues [55], showed an antiviral activity.

The influence of bacteriophages [56] on RNA and DNA was detected in certain derivatives of 1,3,5-triazines (XI), in which herbicidal properties have already been discovered. The most effective were compounds of (XI) containing methoxy or methylthio groups at position 2, and an isopropylamino group in combination with ethyl- or diethylamino groups at positions 4 and 6 of the triazine ring: the preparations ametryne (XIa), symmetrine (XIb), and ipathon (XIc). The activity markedly decreases when chlorine is introduced at position 2, or isopropylamino group is substituted by diethylamino. For example, preparations chlorazine (XId), and symazine (XIe) had a weaker action than ametrine and symetrine. (See top, following page.)

As known, active chlorine preparations (bleaching powder, chloramine B, pantocid, etc.) are widely used for disinfection, since they have a broad spectrum of action, i.e., bactericidal, fungicidal, virulicidal, andsporocidal activity [57].



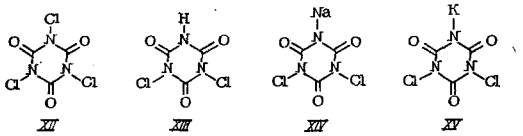
X



XI

XIa: $R^1 = SCH_3$, $R^2 = NHCH(CH_3)_2$, $R^3 = NHC_2H_5$;
XIb: $R^1 = SCH_3$, $R^2 = R^3 = NHC_2H_5$;
XIc: $R^1 = OCH_3$, $R^2 = NHCH(CH_3)_2$, $R^3 = N(C_2H_5)_2$;
XId: $R^1 = Cl$, $R^2 = R^3 = N(C_2H_5)_2$;
XIe: $R^1 = Cl$, $R^2 = R^3 = NHCH_2CH_3$

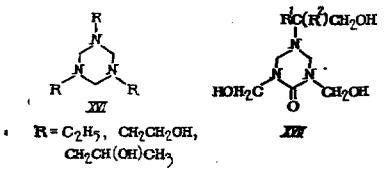
Active chlorine preparations obtained from cyanuric acid have received considerable attention in recent years as disinfectants.



XII XIII XIV XV

Their high and varied bactericidal activity had been noticed by several authors [58-62]. The sphere of application of chlorine active derivatives of cyanuric acid is very large. They are used for the disinfection of baths, toilets, equipment in the dairy and food industry, in households, in dishwashing machines, to disinfect swimming pools [58], for sterilization of linen, dishware, sputum of tubercular patients [61], etc.

The derivatives of 1,3,5-triazine of general formula (XVI) showed a bactericidal activity towards aerobic bacteria [63], and some 2-oxo analogs of these compounds (XVII) have been applied in practice as agents for preventing the development of bacteria in paints and oils [64].



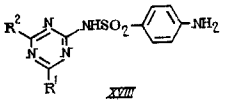
XVI

R = C_2H_5, CH_2CH_2OH, $CH_2CH(OH)CH_3$

XVII

Derivatives of 1,3,5-triazine with sulfanilamide residues are used as drugs in medicinal practice.

4,6-Dimethoxy-2-sulfanilamido-1,3,5-triazine (XVIIIa), used under the name of "Sulfatriazine," is active towards several bacteria including the tuberculosis bacillus [65].

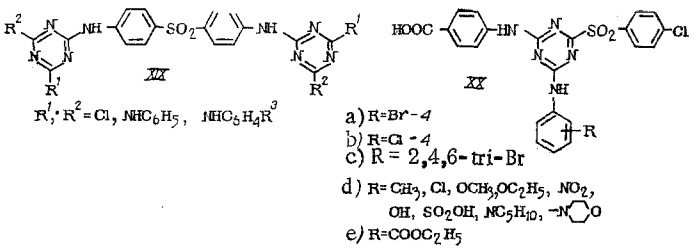


XVIII

XVIIIa: $R^1 = R^2 = OCH_3$;
XVIIIb: $R^1 = R^2 = C_2H_5$;
XVIIIc: $R^1 = R^2 = CH_3$;
XVIIId: $R^1 = R^2 = n\text{-}C_3H_7$;
XVIIIe: $R^1 = OCH_3$, $R^2 = C_2H_5$;
XVIIIf: $R^1 = CH_3$, $R^2 = C_2H_5$;
XVIIIg: $R^1 = R^2 = NH_2$

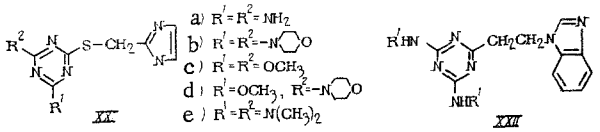
Its diethyl analog (XVIIIb), named sulfasymazine, eksulf, prosul, etc., is characterized by a still higher antibacterial activity, and high solubility in water [66]. On transition to 4,6-dimethyl (XVIIIc) and 4,6-di-n-propyl (XVIIId) analogs, the antibacterial activity decreases. The corresponding 4-methoxy-6-ethyl- (XVIIIe) and 5-methyl-6-ethyl- (XVIIIf) 2-sulfanilamido-1,3,5-triazines are only 1/16 as active as sulfasymazine; 4,6-diamino-2-sulfanilamido-1,3,5-triazine (XVIIIg) [66] is completely devoid of antibacterial properties.

bis-(1,3,5-Triazinylaminophenyl) sulfones of the general formula (XIX) [67], and also triazinylaryl(alkyl) sulfones (XX) [68] have a broad spectrum of chemotherapeutic activity towards gram-positive and gram-negative bacteria.



Of 31 compounds of type (XX) tested, the most active were found to be compounds (XXa-c). The introduction of methyl, methoxy, ethoxy, nitro, hydroxy, or sulfo groups, morpholine, piperidine rings, or chlorine atoms into the phenylamino group (XXd) decreases the antibacterial activity somewhat; o-, m- and p-carbethoxyaniline derivatives (XXe) are still less active.

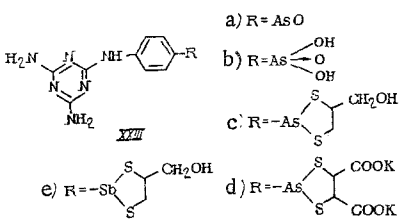
Of other derivatives of 1,3,5-triazine with chemotherapeutic activity, compounds containing imidazole substituents (XXI) [69] deserve attention.



Compound (XXIa) was the most effective for protozoa: trichomonads, amoebae and tripanosomes. Compounds (XXIb-d) were active only toward trichomonads.

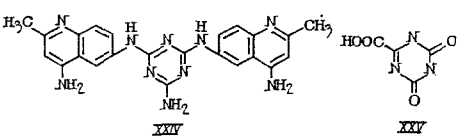
The activity decreased appreciably or completely disappeared when dimethylamino groups were introduced as R^1 and R^2 substituents (XXIe), and on transition from 2-substituted imidazole derivatives to 1-substituted benzimidazoles (XXII) [70].

Effective agents for treating protozoan infections are known among the arsenic-containing derivatives of melamine. Preparations of melanoarsenoxide (XXIIIa) and melarsene (XXIIIb) have been applied in practice for infection by trichomonads and spirochetes [71].



Melamine derivatives containing sulfur as well as arsenic or antimony, such as Mel B (XXIIIc), Mel W (XXIIId), MSb B (XXIIIe) have a high trypanocidal activity in combination with low toxicity [72-74].

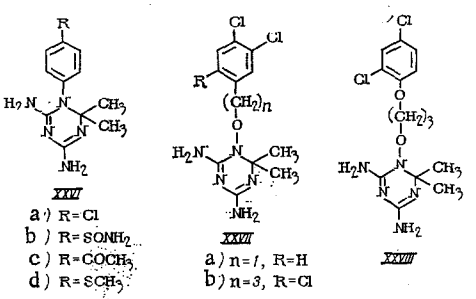
In diseases caused by protozoa and bacteria, a dicholine derivative of melamine (XXIV) is used under the name of "Surfen C" and "Congazine" [75, 76].



In the course of a search for antimetabolites of orotic acid, which plays an important role in the biosynthesis of pyrimidine bases, its aza analog has been obtained, 6-carboxy-2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazine (XXV). Experiments *in vitro* [7] have shown that 5-azaorotic acid influences the enzymatic system for the biosynthesis of uridine nucleotides. The ability of 5-azaorotic acid to suppress the biosynthesis of pyrimidine nucleotides apparently also leads to the antibacterial properties of this compound [78]. It is possible

that the inhibition of the synthesis of uric acid is the main factor of the antipodagric action of the potassium salt of this acid [79].

Derivatives of 4,6-diamino-1-phenyl-1,2-dihydro-1,3,5-triazines (V) are effective not only as growth inhibitors of tumors. The ability of these compounds to disturb the folic metabolism served as a basis for their use in the chemotherapy of several infectious diseases. In laboratory study, many compounds of this class showed an activity towards plasmodia of malaria, pathogenic and nonpathogenic bacteria, cocci, stimulants of toxoplasmosis, leishmaniasis and various intestinal helminths [80-94]. 4,6-Diamino-2,2-dimethyl-1-(p-chlorophenyl)-1,2-dihydro-1,3,5-triazine pamoate has been used in medical practice under the name "cycloguanyl pamoate," "Chlorazine," etc., (XXVIa), for treating malaria. Compound (XXVIa) was first obtained [57] from animal and human urine, as an active metabolite of the antimalarial preparation chloroguanide— 1-(p-chlorophenyl)-5-isopropylbiguanide; its structure was confirmed by an alternative synthesis [81, 82]. When administered intramuscularly, chlorazine protects human beings for a long time from malaria. It is effective in leishmaniasis [83]. It is very important that this preparation stimulates cardiac activity, since antimalarial agents usually depress the cardiac muscle [84].



A sulfamoyl analog of chlorazine, supazine (XXVIb) is used in clinical practice as an antimalarial preparation [85]. The substitution of a chlorine atom in the molecule of chlorazine by acetyl group (XXVIc) leads to a decrease in activity. The methylthio analog of chlorazine (XXVId) is active toward protozoa, and is comparable with chlorazine, but is more toxic [85]. At the same time, because of its considerably higher anticoccus activity, it has been practically applied under the name of "Methiotriazamine" to combat coccus infections [86, 87]. The same compound enters the composition of the coccidiostat trithiadol, used for treating growing chicks [88].

The introduction of the oxymethylene chain between the phenyl and triazine residue in compounds (XXVIIa) and (XXVIIb) does not decrease the antimalarial properties. These compounds also have a pharmacological activity [89]: compound (XXVIIb) induces an increase in the arterial pressure and tachycardia, compound (XXVIa) stimulates the cardiac activity and has antiarrhythmic properties. A combination of antimalarial and cardiostimulating properties, and also the low toxicity served as a basis for using 4,6-diamino-2,2-dimethyl-1-(3,4-dichlorobenzyloxy)-1,2-dihydro-1,3,5-triazine (XXVIIa) in medicinal practice as an antimalarial agent under the name of "Clociguanyl."

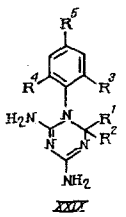
The introduction of the oxymethylene chain also affects the change in the antibacterial properties in the series of derivatives of 4,6-diamino-2,2-dimethyl-1,2-dihydro-1,3,5-triazines. Chloroazine does not act against *Escherichia coli* and resistant strains of *S. faecium* and *L. casei*. Compounds (XXVIIa) and (XXVIIb) were also found to be highly active towards the above bacteria [87].

Clociguanyl, like chlorazine, does not have an appreciable action on the preerythrocytic forms of the resistant strain of *P. falciparum* [87], but in combination with sulfadiazine it can reliably protect human beings from infection with this strain of plasmodium [90].

The antileishmaniasis activity, detected in the case of chlorazine, stimulated research workers to search for antileishmaniasis preparations among various antimalarial 1,3,5-triazine compounds [91]. It was assumed that these compounds, which inhibit dihydrofolate reductase and disturb the metabolism of compounds in mitochondria of malarial plasmodia, will correspondingly also influence the intracellular processes of leishmaniasis inducers. Among 2,4-diamino-2,2-dimethyl-1,2-dihydro-1,3,5-triazine derivatives, compound (XXVIII) has a high antileishmaniasis activity in tissue culture. Elongation of the methylene chain or acetylation of the amino groups led to a loss of activity.

Derivatives of 4,6-diamino-1,2-dihydro-1,3,5-triazines were found to be effective not only for combating bacterial and protozoan infection inducers, but also for more complex parasites, the helminths.

The antihelminthic properties of dihydro-1,3,5-triazine compounds were first discovered in (XXVId) and 4,6-diamino-1-[p-(methylthio)phenyl]2-propyl-1,2-dihydro-1,3,5-triazine [85]. However, attempts [63, 70] to find a correlation between the antihelminthic and antimicrobial activity and the structure of the compounds were unsuccessful [83]. For example, the active antimalarial preparations chlorazine (XXVIa) and Clociguanyl (XXVIIa) have no antihelminthic properties [83], while some compounds [92] containing bulky substituents at position 2 of the dihydro-1,3,5-triazine ring (XXIXb, c) or at the o-position of the phenyl residue (XXIXd, e) exhibited high antihelminthic activity with inappreciable suppression of the growth of microorganisms. The structurally similar compounds (XXIXf, g) did not act on helminths.



XXIX

XXIXa: $R^1R^2 = -(CH_2)_2CH(CH_3)(CH_2)_2-$, $R^3 = R^4 = H$, $R^5 = Cl$;

XXIXb: $R^1R^2 = -CH_2CH(CH_3)(CH_2)_3-$, $R^3 = R^4 = H$, $R^5 = Cl$;

XXIXc: $R^1R^2 = -(CH_2)_2CH(CH_3)(CH_2)_2-$, $R^3 = R^4 = R^5 = H$;

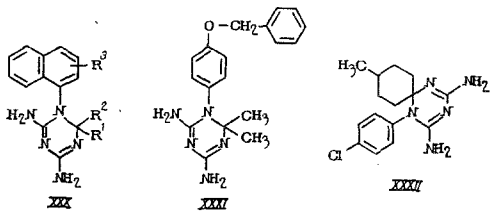
XXIXd: $R^1 = R^2 = CH_3$, $R^4 = R^5 = H$, $R^3 = n\text{-}C_4H_9$;

XXIXe: $R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = R^4 = CH_3$, $R^5 = H$;

XXIXf: $R^1 = R^2 = CH_3R^3\text{---}C(CH_3)_3$, $R^4 = R^5 = H$;

XXIXg: $R^1 = R^2 = CH_3$, $R^3 = OCH(CH_3)_2$, $R^4 = R^5 = H$

Compounds with naphthyl substituents at position 1, irrespective of the character of substituents at position 2 of the triazine ring and the character of the residues in the naphthyl substituent (XXX), are strong antihelminthic preparations.



XXX XXXI XXXII

Compound (XXXI) has a high antihelminthic and antibacterial activity, and also has an inhibiting action of dihydrofolate reductase [83].

2,4-Diamino-9-methyl-5-(p-chlorophenyl)-1,3,5-triazaspiro[5,5]undeca-1,3-diene (XXXII) has pronounced antihelminthic properties towards *Entrobius vermicularis* and *S. oboelata*. This compound is slightly toxic, and under the names of "Spirazine" and "Spirotriazine" is used in practical medicine. Removal of chlorine from the spirazine molecule appreciably weakens the antihelminthic activity.

It is probable that further studies on the mechanism of action and generalization of data on the biological activity and physicochemical parameters [93, 94] will help to develop more rational approaches for searching for new drugs in this undoubtfully interesting class of compounds.

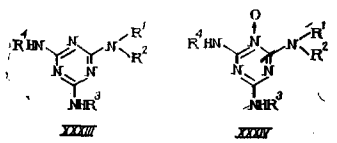
Pharmacologically Active 1,3,5-Triazines. In the description in the preceding section of antimalarial 1,3,5-triazine preparations, we noted their high pharmacological activity (stimulation of cardiac activity), which in combination with antimalarial properties was very valuable in the practical utilization of these medicaments.

A comprehensive study of 1,3,5-triazine derivatives made it possible to observe their varied pharmacological activity also without connection with the chemotherapeutic properties of these compounds.

In the course of the investigations it was shown that the melamine derivative, N^2,N^2-diallylmelamine (XXXIIIa), has a pronounced vasodilating action on rats and dogs [95]. However, in human beings, this preparation is practically inactive. In the study of the biotransformation features of N^2,N^2-diallylmelamine in the organisms of human beings and animals, 10 metab-

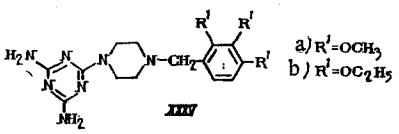
olites of this preparation were found in the urine of rats and dogs, but only eight in the urine of human beings. One of the biotransformation products absent in human beings (XXXIVa) was found to be responsible for the vasodilating action of the preparation.

The vasodilating activity of synthetically obtained N^2,N^2-diallylmelamine N^1-oxide (XXXIVa) exceeded that of the nonoxidized product by a factor of 21. Under the name "Oxonazine," ithas been clinically used as a hypotensive agent [96]. Oxonazine, as well as a large number of similar derivatives with general formula (XXXIV), obtained by oxidizing the corresponding triazines (XXXIII) with perbenzoic acid [96], had a considerable vasodilating and hypotensive action.



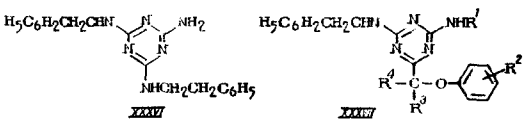
XXXIII XXXIV

A benzylpiperazinyl derivative of melamine (XXXVa) has a vasodilating and antiarrhythmic action [97]. In this compound, substitution of methoxy groups by ethoxy groups (XXXVb) does not change the activity.



XXXV

2-Amino-4,6-bis-(phenylethylamino)-1,3,5-triazine (XXXVI) has been suggested for treating atherosclerosis [98].

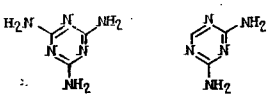


XXXVI XXXVII

This preparation inhibits biosynthesis in liver and decreases the cholesterol level in blood serum [98, 99].

Compounds of the general formula (XXXVII) [100, 101] also have an anticholesterol activity. The most active are compounds containing residues of lower alkylcarboxylic acids as R^1, halogen atoms as R^2, and methyl groups as R^3 and R^4.

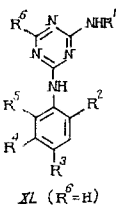
Already in 1944 [102], among compounds with a =N–C–N= group in their structure and with diuretic properties, derivatives of 1,3,5-triazine, melamine (XXXVIII) and formoguanamine (XXXIX) were found, whose diuretic effect has frequently been confirmed, first in the laboratory [103, 104], and then clinically [105].



XXXVIII XXXIX

Later, the diuretic activity was also found in a series of other derivatives of 2,4-diamino-1,3,5-triazine [106, 107], two of which, 2-amino-4-(p-chlorophenylamino)-1,3,5-triazine (chloraminosine, chlorazanil) (XLa) and 2-amino-4-phenylamino-1,3,5-triazine (amanosine, amenosine) (XLb) have been practically applied. (scheme, top, following page.) It was found that these two preparations also have antihistaminic activity [107].

The introduction into compound (XLa) of electron-donor substituents (alkyl, alkoxy-, dialkylamino groups) (XLf) instead of the chlorine atom, did not lower its diuretic activity [108]. An m-chloro substituted analog of (XLa), compound (XLc), is characterized by diuretic,



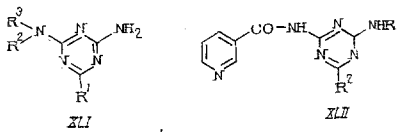
XL (R^6=H)

XLa: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Cl$;
XIb: $R^1 = R^2 = R^3 = R^4 = R^5 = H$;
XIc: $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = Cl$;
XId: $R^1 = R^4 = R^5 = H$, $R^2 = CF_3$, $R^3 = F$;
XIe: $R^1 = C_2H_5$, $R^2 = R^4 = Cl$, $R^3 = R^5 = H$;
XIf: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$, OC_2H_5, $N(C_2H_5)_2$, etc.

saluretic and antikaluretic activity [109] with a somewhat general decrease in the diuretic effect. The derivatives of formoguanamine (XLd) and (XLe) have diuretic and antiulcerous action [110].

The introduction of mercapto, hydroxy and alkylthio groups into the 1,3,5-triazine ring leads to a considerable weakening of the diuretic properties [109]. The activity also decreases for R^6 in the series H > alkyl-S > OH > SH. The activity also decreases in the case of the corresponding 6-ethoxycarbonyl- and 6-dimethylaminomethyl derivatives [111]. A transition to 6-allylthio-6-β-hydroxyethylthio- or 6-benzylthio compounds intensifies the saluretic action [108].

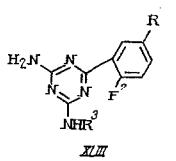
Of the 50 derivatives of 2,6-diamino-1,3,5-triazine with general formula (XLI), tested in experiments on animals, 2-amino-4-(2,3-dimethoxyphenyl)-6-p-chlorophenylamino-1,3,5-triazine and 2-amino-4-(2-isopropyl-5-methylphenyloxymethyl)-6-p-chlorophenylamino-1,3,5-triazine have the highest diuretic effect [108].



XLI XLII

R^1 = H, COC_5H_4N-3
R^2 = NH_2, C_6H_5, $NHCOC_5H_4N$-3

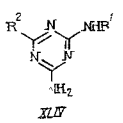
Nicotinoylamine derivatives of 1,3,5-triazine of formula (XLII) combine diuretic activity with a strong antiulcerous action [112]. The preparations were also found to be slightly toxic. The antiulcerous and diuretic effects are observed in compounds with formula (XLIII) [113, 114].



XLIII

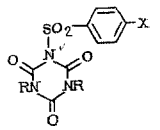
R^1 = H, SCF_3, SCH_3, SO_2CH_3, $SO_2N(CH_3)_2$, SO_2NH_2, CF_3, Br;
R^2 = H, Cl, $OCH_2CH_2OCH_3$, OCH_3;
R^3 = $NHCONH_2$, NH_2, OH

In benzyl (XLIVa) and phenylethyl (XLIVb) derivatives of formoguanamine (XLIV), hypoglycemic properties have been detected [115].



XLIV

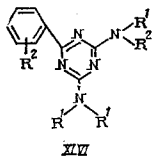
XLIVa: $R^1 = CH_2C_6H_5$, $R^2 = H$;
XLIVb: $R^1 = CH_2CH_2C_6H_5$, $R^2 = H$;
XLIVc: $R^1 = CH_2C_6H_4Br$-2, $R^2 = H$;
XLIVd: $R^1 = CH_2C_6H_4OCH_3$—4, $R^2 = H$;
XLIVe: $R^2 = NHCH_2CH(C_6H_5)OH$, R^1=H



XLV

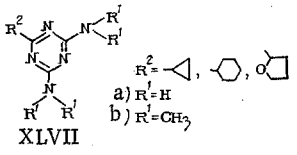
Since the sympatholytic action of these compounds is inappreciable, the concept of a disturbance of the carbohydrate metabolism as a primary action mechanism of the sympatholytics of the guanidine series is negated. The introduction of a bromine atom (XLIVc) into the o-position of the phenyl group of (XLIVa) or methoxy group into the p-position (XLIVd), leads to the disappearance of the hypoglycemic activity. 1,3,5-Triazine sulfones with the general formula (XLV) had a weak antidiabetic action [116].

A derivative of melamine, 2'-hydroxy-2'-phenylethylmelamine (XLIVd), is used under the name of "Trimazinol" in medical practice as an antiinflammatory agent [117]. 2,4-Diamino-6-aryl-1,3,5-triazines (XLVI), obtained from benzonitriles and dicyanodiamides [118], and 2,4-diamino-6-cycloalkyl-1,3,5-triazines (XLVII) [119] also have antiinflammatory activity.



XLVI

a) $R^1=R^2=H$
b) $R^1=CH_3$, $R^2=H$
c) $R^1=CH_3$, $R^2=F$-4

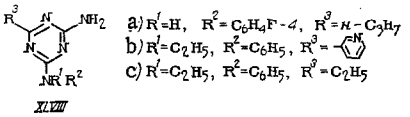


XLVII

a) $R^1=H$
b) $R^1=CH_3$

2,4-Diamino-6-phenyl-1,3,5-triazine (XLVa) has been studied clinically, but was found to be highly toxic [120]. N-Methyl derivatives of 2,4-diamino-6-phenyl-1,3,5-triazine (XLVIb) and 2,4-diamino-6-cycloalkyl-1,3,5-trizine (XLVIIb) were less toxic and retained the anti-inflammatory properties [120]. The most effective of these compounds was 2,4-bis-(dimethyl-amino)-6-(p-fluorophenyl)-1,3,5-triazine (XLVIc).

Compounds with the general formula (XLVII) are able to stimulate the secretion of ACTH and glucocorticoids. These compounds also have antiinflammatory activity [121].



XLVIII

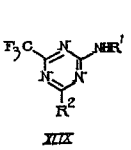
a) $R^1=H$, $R^2=C_6H_4F$-4, $R^3=N-C_3H_7$
b) $R^1=C_2H_5$, $R^2=C_6H_5$, $R^3=$
c) $R^1=C_2H_5$, $R^2=C_6H_5$, $R^3=C_2H_5$

2-Amino-6-propyl-4-(p-fluorophenylamino)-1,3,5-triazine (M1704; XLVIIIa) is used in medical practice as an antiinflammatory agent. This preparation increases the activity of cortisone and stimulates the separation of corticosterone. Its thymolytic action has also been noted [122].

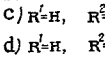
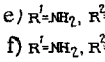
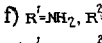
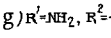
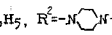
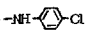
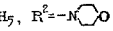
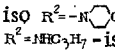
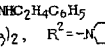
2-Amino-6-(3-pyridyl)-4-(N-phenyl-N-ethylamino)-1,3,5-triazine (XLVIIIb) and 2-amino-4-(N-phenyl-N-ethylamino)-6-ethyl-1,3,5-triazine (XLVIIIc) stimulate the functions of the pituitary and adrenal glands, increase the secretion of corticosteroids, in particular, glucocorticoids [123].

Some 1,3,5-triazine derivatives regulating the functions of the central nervous system have both depressant and stimulating type of action.

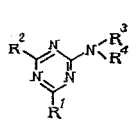
The different substituted 2,4-diamino-6-trifluoromethyl-1,3,5-triazines with the general formula (XLIX) are characterized by analgesic, sedative, antispasmodic, andtranquilizing properties [124-128]. Several of the compounds weaken the spontaneous motor activity. The inhib-



XLIX

a) $R^1=H$, $R^2=NHC_3H_7$-iso
b) $R^1=H$, $R^2=NHC_6H_{11}$
c) $R^1=H$, $R^2=$ 
d) $R^1=H$, $R^2=$
e) $R^1=NH_2$, $R^2=$ 
f) $R^1=NH_2$, $R^2=$ 
g) $R^1=NH_2$, $R^2=$ 
h) $R^1=-N=CHC_6H_5$, $R^2=$ 
i) $R^1=H$, $R^2=-NH-$ 
j) $R^1=N=CHC_6H_5$, $R^2=$ 
k) $R^1=C_3H_7$-iso $R^2=$ 
l) $R^1=CH_3$, $R^2=NHC_3H_7$-iso
m) $R^1=H$, $R^2=NHC_2H_4C_6H_5$
n) $NHR^1=N(CH_3)_2$, $R^2=$ 

iting effect of compounds (XLIXa-d) is noticeable in doses much lower than those at which muscle relaxation is observed. Experiments showed that compounds (XLIXb,d,e) were morphine antagonists, and compounds (XLIXb,e,f,g) considerably increased the duration of a hexabarbital-induced sleep. The depressant action of the 1,3,5-triazine derivatives on the central nervous system is mainly characterized by a sedative effect, and is accompanied by weak antispasomodic action. Compounds (XLIXc,d,e) have cataleptic activity, typical of neuroleptics, and compounds (XLIXc,d) also have analeptic activity. Compounds (XLIXg,i,j) are characterized by a moderate hypotensive activity and compounds (XLIXa,b,g,k, l) by adrenolytic properties. Compounds (XLIX l,m,n) show an antiserotonin action.

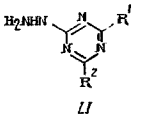


L

La: $R^1 = C_6H_3Cl_2$-2,4, $R^2 = R^3 = R^4 = H$;
Lb: $R^1 = C_2H_5$, $R^2 = R^3 = R^4 = H$;
Lc: $R^1 = C_6H_5$, $R^2 = R^3 = R^4 = H$;
Ld: $R^1 = R^2 = SCH_2CO_2C_2H_5$, OC_2H_5, $R^3 = C_6H_3(CH_3)_2$-2,3, $CH_2C_6H_4Cl-4$, $R^4 = H$, CH_3

Substituted 2-amino-1,3,5-triazines with general formula (L) have a strong depressant influence on the central nervous system [129-130].

2,4-Disubstituted-6-hydrazino-1,3,5-triazines (LI), obtained by the reaction of 6-trihalomethyl-1,3,5-triazines with hydrazine, have a neuroleptic action [131, 132].

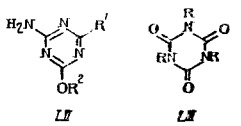


LI

R^1 = alkyl, haloalkyl
$R^2 = CH_3$, C_2H_5, NHC_2H_5, $N(C_2H_5)_2$,  , $NHNH_2$, etc.
a) $R^1 = R^2 = N(C_2H_5)_2$

Of compounds with the general formula (LI), 6-hydrazino-2,4-bis-(diethylamino)-1,3,5-triazine tartrate (LIa) has been used in practice under the name "Meladrazine tartrate," "Hydrometrazine," etc., as a muscle relaxant and spasmolytic [134].

2-Alkyl-4-alkoxy-6-amino-1,3,5-triazines (LII) also have sedative and antispasmodic activity [135].

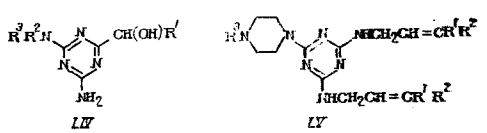


LII LIII

R = CH_3, C_3H_7, C_4H_9, $CH{-}CH{=}CH_2$, $C_6H_4(OCH_3)_2$, etc.
a) R = H

Substitution of the alkoxy group in compounds (LII) by an alkylthio or benzylthio residue is not accompanied by a change in activity [136]. N^1,N^3-Disubstituted isocyanuric acids (LIII) and their salts [137] are characterized experimentally by antispasmodic and spasmolytic properties. The most active compounds are those with lower alkyl substituents. In contrast to N^1,N^3-disubstituted derivatives (LIII), unsubstituted cyanuric acid (LIIIa) has an inappreciable antispasmodic action and is toxic, while isocyanuric acids tri- and monosubstituted at the nitrogen atoms are pharmacologically slightly active [137].

Triazine derivatives with general formula (LIV), obtained by cyclization of diguanides with α-hydroxycarboxylic acids are used in medicine for treating certain psychotic disorders, and also as analeptics in depression of cardiac activity and respiration [138].



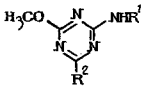
LIV LV

$R^1 = H$, $R^2 = H$, Cl, CH_3 or
$R^1 = R^2 = CH_3$, R^3 = substituted phenyl;
LVa: $R^1 = R^2 = H$, $R^3 = CH(C_6H_4F\text{-}4)_2$

In experiments on animals, 2,4-bis-(allylamino)-6-(1-piperazinyl)-1,3,5-triazines with the general formula (LV) had sharply expressed properties of respiratory analeptics [139].

2,4-bis-(Allylamino)-6-[4-[bis-(p-fluorophenyl)methyl]-1-piperazinyl]-1,3,5-triazine (LVa) has an analeptic effect in experiments on animals in depression of respiration induced by pentabarbital [140] and morphine without suppressing the anesthetic effect of morphine [141,142]. Clinically, this compound was found to be effective in acute respiratory insufficiency, caused by chronic pulmonary emphysema and hypercapnia, and also by intoxication by barbiturates [143]. Under the name of "Almitrin" it has been used in practice as a respiratory analeptic. Its action mechanism is probably related to excitation of carotid chemoreceptors [144]. In experiments on pentabarbital-narcotized animals, a hypertensive action of Almitrin has also been observed [145].

In an electroencephalographic study, 2-amino-4-methyl-6-methoxy-1,3,5-triazine (LVIa) had a psychostimulating activity [146]. 6-Methoxy-4-ethyl-2-ethylamino-1,3,5-triazine (LVIb) had a stimulating effect on the sympathetic and parasympathetic nervous system.



LVI

a) R^1=H, R^2=CH_3
b) R^1=R^2=C_2H_5

From an analysis of the literature data, we can conclude that 1,3,5-triazine compounds have varied and high biological activity. Many compounds in this class have been used in practice as medicinal preparations.

Most of the 1,3,5-triazine derivatives studied up to the present time are compounds with different amine residues as substituents in the triazine ring. Of the aza analogs of pyrimidine and pyridine biologically active compounds, with the C–C bond between the substituent and the heterocyclic ring, only 5-azaorotic acid has been described. The results of studies on this compound show that research in this direction is very promising.

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QUATERNARY AMMONIUM SALTS WITH A LABILE $\overset{+}{N}$—C BOND AS PRECURSORS OF MEDICINAL COMPOUNDS.

II. COMPOUNDS WITH A LABILE $\overset{+}{N}$—CH_2—N GROUPING

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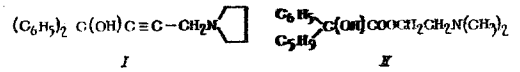
We have already reported on the reversible chemical modification of several pharmacologically active compounds, containing a tertiary amino group, by conversion into quaternary ammonium salts (QS).

We showed that because of the presence of this group, salts containing a $-CH_2OCOR$ grouping attached to a nitrogen atom can undergo a hydrolytic cleavage at the $\overset{+}{N}$—C bond with regeneration of a tertiary amine [1]. It was also found [2] that medicinal compounds modified in the form of their acyloxymethylates have a more prolonged action and are less toxic.

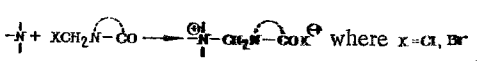
It could be assumed that, in analogy with the compounds already studied, quaternary salts with $\overset{+}{N}$—CH_2NHCOR or N—$CH_2\overset{+}{N}$—CO groupings can also be converted into the initial tertiary amines as the result of hydrolysis. But they should differ from their oxygen-containing analogs in the rate of hydrolysis, lipophilicity, and possibly in other properties, determining their pharmacokinetics. The present investigation deals with the development of methods of synthesis and study of certain properties of QS containing an acylamido(imido)methyl grouping.

For the investigation we used known pharmacologically active compounds containing a tertiary amino group: butynoline (azulone) (I) and cyclosil (II) [3].

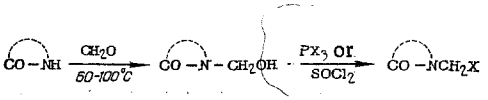


I II

To obtain the QS, we alkylated the free bases of these compounds by methyl halide derivatives of amides and imides.



The alkylating agents were synthesized by a two-stage method [4, 5].



By this method we obtained the halomethyl derivatives of benzamide, succinimide, phthalimide, benzoxazolone, benzimidazolone, hydantoin, andbarbituric acid. Because of the formation of a polymer at the last stage of the synthesis, we were unable to obtain bis-N-halomethylurea.

The amines were alkylated in acetone or in chloroform for 1-6 days at a temperature not above 55°C, since at a higher temperatre the halomethyl derivatives undergo a partial disproportionation [6].

All the synthesized QS (Table 1) are colorless crystalline compounds, readily soluble in alcohol, DMFA and DMSO, and somewhat less soluble in water, chloroform, acetone, and methylene

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