# SYNTHESIS AND NEURTROPIC ACTIVITY OF 2-AMINOPERIMIDINES*

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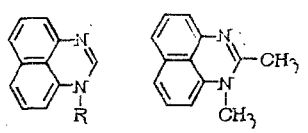
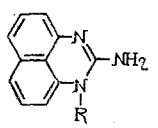
According to Szent-Gyorgi's hypothesis, the action of many natural products and drugs on the central nervous system (CNS) is connected with their ability to act as strong electron donors [1]. Such substances include, for example, the catecholamines, indole derivatives, phenothiazine derivatives, et al. Their electron-donating character shows up particularly in their ability to readily form deeply colored charge-transfer complexes with many π acceptors. It has already been shown [2] that perimidine [1] and its derivatives [2] are very strong π donors, superior in this respect even to the phenothiazines. In view of this, it seems very promising to look among the derivatives of perimidine for new drugs with CNS activity. Indeed, several 2-alkyl- and 2-heteroarylperimidine derivatives have recently been patented as active CNS depressants [3].

In the present work we have synthesized a number of 2-aminoperimidines and studied their action of the CNS. For comparison, we have also studied the biological activity of 1-substituted perimidines II-VI not containing an amino group. It should be emphasized that the π-donor power of 2-aminoperimidines is considerably greater than that of simple perimidines with alkyl or aryl substituents in the 2 position [2], so their effect on the CNS might differ considerably from that of the compounds studied in [3]. This has been confirmed in the present work.



I: R=H; II: R=CH$_3$
III: R=CH$_2$CH$_2$N(C$_2$H$_5$)$_2$
IV: R=CH$_2$CH$_2$N⟨⟩
V: R=CH$_2$CH$_2$N⟨O⟩



VII: R=H
VIII: R=CH$_3$
IX: R=(CH$_2$)$_3$N(CH$_3$)$_2$
X: R=C$_6$H$_5$CH$_2$
XI: R=C$_6$H$_5$

We chose to investigate the following compounds: the progenitor of the series, i.e., unsubstituted 2-aminoperimidine (VII); its 1-substituted derivatives with substituents of different types (alkyl, aralkyl and aryl); derivatives with one substituent on the amino group (XII-XVII); and tertiary amines XVIII and XXI.

We prepared compound VII somewhat unexpectedly in a yield of 40% by fusing 1,8-naphthylenediamine dihydrochloride with thiourea. The main product of this reaction is 2-mercaptoperimidine. As is known, fusion of other aromatic ortho-diamines with thiourea normally leads exclusively to 2-mercaptoimidazoles [4].

Compounds VIII-XI were synthesized by direct amination of the corresponding 1-substituted perimidines with sodamide. Secondary amines XII-XVII were prepared by reacting 1-methyl-2-chloroperimidine with the corresponding alkyl-, aralkyl-, and arylamines, and 1-methyl-2-piperidinoperimidine (XVIII) was prepared analogously. The chlorine atom in the 2 position of the perimidine system is highly labile, and its substitution by various nucleophiles generally proceeds readily and with good yields.

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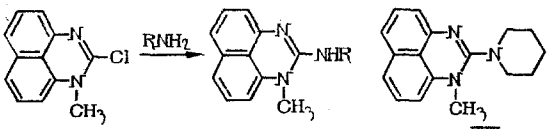
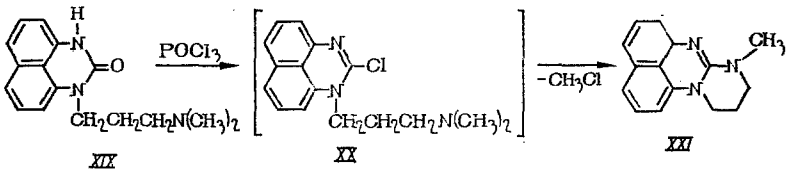


XII: R = $CH_3$; XIV: R = $C_6H_5$
XIII: R = $CH(CH_3)CH_2C_6H_5$; XV: R = 3,4-$(CH_3O)_2C_6H_3$
XVI: R = $C_6H_5CH_2$; XVII: R = 2-$ClC_6H_4$

We observed an interesting reaction when we tried to synthesize 1-(3-dimethylaminopropyl)-2-chloroperimidine (XX). It was found that heating 1-(3-dimethylaminopropyl)-perimidone (XIX) with phosphorus oxychloride leads to the formation of aminoperimidine XXI as well as XX. The stimulus for this reaction is evidently the high positive charge in the 2 position of the perimidine [5], which results, with the intercession of the chlorine atom, in intramolecular nucleophilic amination accompanied by elimination of methyl chloride. A similar reaction has been described for 1-(3-diethylaminoethyl)benzimidazolone [6], although this takes place under considerably more severe conditions.



XIX XX XXI

We evaluated the intraperitoneal toxicity of the compounds and their action on the CNS in experiments on $F_1$ mice. The CNS activity was assessed on the basis of an analysis of the acute intoxication pattern of the animals and on the basis of the effect of the compounds on motor activity (actometric method), exploratory reflex (Boissier's method [7]), on the narcotic effect of hexenal (60 mg/kg), and the spasmogenic action of corazole (Swineyard's method [8]). The effect of the compounds on the cerebral cholinergic and adrenergic systems was assessed from the ability of the test compounds to alter the duration of tremors induced by arecoline (20 mg/kg), spasms induced by nicotine (5 mg/kg), and stereotypy due to the administration of apomorphine (40 mg/kg) to the mice. The test compounds were injected intraperitoneally in a dose of 0.02 mmole 25-30 min after injecting the analysis substances.

In acute tests on narcotized (urethane, 1.2 g/kg) rats, we studied the effect of the compounds on the arterial pressure (recorded by mercury manometry from the carotid artery), electrocardiogram, and respiration.

It was found that the $LD_{50}$ values of the test compounds varied over a very wide range; from 23.8 mg/kg (XXI) to more than 600 mg/kg (Table 1).

Perimidine (I) and 2-aminoperimidine (VII) are CNS depressants. When they were administered in toxic doses, the animals were found to have limited mobility, disturbed coordination, and to adopt a prone position. In sublethal doses, both compounds cause tremors and weak periodic spasms, which are probably due to metabolites of these poisons, since they develop no sooner than 1-1.5 h after administration.

On the other hand, 1-methylperimidine (II) and especially 1-methyl-2-aminoperimidine (VIII) are CNS stimulants. In toxic doses, their stimulating action shows up in camphor-like (epileptiform) spasms. Introduction of a phenyl (XI), benzyl (X), or aminoalkyl (IX) substituent in the 1 position of 2-aminoperimidine also gives substances with a stimulant-type action, but less active.

Methylation of perimidine in the 2 position or of the amino group of 1-methyl-2-aminoperimidine has no significant effect on the spasmogenic activity of VI and XII, but substitution of the amino group by phenyl (XV-XVII) or phenylalkyl radicals (XIV, XIII) decreases the spasmogenic activity of the compounds or gives them CNS depressant properties (XIII and XVI).

In accordance with the character of their pharmacological activity, the test compounds decrease the duration of hexenal narcosis in mice, but there is not complete parallelism between the stimulant activity and toxicity of the compounds on the one hand and their antinarcotic activity on the other. The compounds with depressant activity either have no influence on the effect of hexenal (III, IV, XVI) or prolong hexenal narcosis (V), but they may

TABLE 1. Pharmacological Activity Parameters of Perimidine and 2-Aminoperimidine Derivatives

| Compound | Action at toxic doses | $LD_{50}$ (mg/kg) | Influence on effect of hexenal ($\Delta_t$, min) | Influence on effect of arecoline ($\Delta_t$, sec) | Influence on effect of nicotine ($\Delta_t$, sec) | Influence on effect of apomorphine ($\Delta_t$, min) |
|---|---|---|---|---|---|---|
| I | d | 160±23 | —8,9* | —30* | +36* | +22* |
| II | st | 103±38 | —10,2* | —21* | +30* | —2 |
| III | d | 271±60 | —0,7 | +20* | +11* | +11* |
| IV | d | 217±21 | —3,2 | +434* | +17* | —2 |
| V | d | 266±29 | +6,3* | +122* | +3 | +3 |
| VI | st, sp | 98±16 | —3,2 | +81* | +8 | +18 |
| VII | d | 27,5±5,2 | —14,3* | +113* | +74* | —1 |
| VIII | st, sp | 25,3±3,7 | —15,2* | —28* | +20* | 0 |
| IX | st, sp | 182±39 | +7 | +6 | Fatal | 0 |
| X | st, sp | 115±26 | —3 | +4 | +98* | —410* |
| XI | st, sp | 57,5±13,5 | —5 | +4 | +110* | —180* |
| XII | st, sp | 25±9,6 | —17* | —4 | —50* | —10 |
| XIII | d | 232±45 | —13,3* | +1 | +57* | —1 |
| XIV | st, sp | 191±26 | —14,7* | —29* | —37* | —16* |
| XV | st, sp | 311±69 | —21,8* | —37* | —43* | —17* |
| XVI | d | 600 | —4,4 | +111* | +71* | —14* |
| XVII | st, sp | 388±32 | —5 | +4 | +130 | —230* |
| XVIII | st, sp | 100±18 | +8 | +44* | +133* | —15 |
| XXI | st, sp | 23,8±4,3 | —7 | +42* | +132* | —4 |

Note. d) Depressant; st) stimulant; sp) spasmogenic.
*Statistically significant difference from control.

TABLE 2. 2-Aminoperimidines

| Compound | Yield (%) | Melting point (deg)* | Melting point of hydrochloride (deg)† | $\nu_{NH}$ ($cm^{-1}$) | Found (%) | | | Empirical formula | Calculated (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | | C | H | N |
| IX | 41 | 196—7 | 273 | 3450<br>3310 | 71,8 | 7,6 | 20,6 | $C_{16}H_{20}N_4$ | 71,6 | 7,5 | 20,9 |
| XI | 95 | 210 | 275 | 3510<br>3400 | 78,9 | 4,9 | 16,4 | $C_{17}H_{13}N_3$ | 78,7 | 5,1 | 16,2 |
| XII | 70 | 151 | 288 | 3460 | 74,1 | 6,1 | 20,0 | $C_{13}H_{13}N_3$ | 73,9 | 6,2 | 19,9 |
| XIII | 75 | 135 | 200 | 3450 | 79,3 | 7,1 | 13,0 | $C_{21}H_{22}N_3$ | 79,7 | 7,0 | 13,3 |
| XIV | 80 | 126—7 | 245 | 3440 | 79,1 | 5,8 | 14,9 | $C_{19}H_{17}N_3$ | 79,4 | 6,0 | 14,6 |
| XV | 95 | 117 | 260 | 3400 | 78,8 | 5,3 | 15,3 | $C_{18}H_{15}N_3$ | 79,1 | 5,5 | 15,4 |
| XVI | 80 | 229—230 | 250 | 3390 | 72,3 | 5,8 | 13,0 | $C_{20}H_{19}N_3O_2$ | 72,0 | 5,8 | 12,6 |
| XVII | 90 | 215 | 250 | 3400 | 69,9 | 4,8 | 14,0 | $C_{18}H_{14}ClN_3$ | 70,2 | 4,6 | 13,6 |
| XXI | 50 | 137 | 265 | — | 75,8 | 6,3 | 17,4 | $C_{15}H_{15}N_3$ | 75,9 | 6,4 | 17,7 |

*Compound IX was crystallized from toluene, all the others were crystallized from octane.
†With decomposition.

also have antinarcotic activity (I, VII). At the investigated dose (0.02 mmole/kg), however, none of these compounds inhibit the spasmogenic action of corazole. Neither do they have a significant effect on the exploratory reflex or motor activity of the animals at this dose.

The test compounds display a central, primarily cholinosensitizing, action, potentiating the effects of nicotine and arecoline even at low doses (0.02 mmole/kg) (see Table 1). In the apomorphine stereotypy test, the 1-phenyl and 1-benzyl derivatives of 2-aminoperimidine (X and XI) show significant central adrenonegative activity. This type of activity is also displayed by 2-aminoperimidines having a phenyl or benzyl substituent on the amino group (XIV-XVII). At the same time, these compounds do not alter the pressor effects of adrenaline or noradrenaline, as registered in experiments on narcotized rats.

When administered intravenously to narcotized rats, all the compounds give rise to a short-lived (1-5 min) decrease in arterial pressure (by 20-30%), and to bradycardia and tachypnea. This effect is probably a reflex effect.

Thus, in contrast to perimidine and its many 1- and 2-substituted derivatives with hydrocarbon or heteroaromatic substituents, the 2-aminoperimidines possess pronounced CNS stimulant activity. This effect can be ascribed to the high π-donating power of the 2-aminoperimidines. Indeed, when electron-accepting (phenyl or benzyl) or bulky substituents (as, for example, in compound XIII), which generally reduce the tendency to form donor–acceptor complexes, are introduced into the 1 position or the amino group of the 2-aminoperimidines, their stimulant action decreases. The only exception proved to be 2-aminoperimidine itself. This required special investigation, and especially a quantitative evaluation of the π-donor characteristics of the compounds investigated.

Although these pharmacological investigations did not reveal any compound which could be recommended for practical use, we think that a further study of the action of perimidine and 2-aminoperimidine derivatives on the CNS might be very promising.

## EXPERIMENTAL

Compounds I, II, and VI were prepared by the methods described in [9, 10], compounds III-V and XVIII were prepared as described in [11], and amines VIII and X were prepared as described in [12]. The IR spectra were recorded in chloroform solution, except for VII, the spectrum of which was measured in mineral oil. The properties, yields, and analysis data of the novel 2-aminoperimidines are given in Table 2.

2-Aminoperimidine (VII). A mixture of 2.3 g of 1,8-naphthylenediamine dihydrochloride and 7.6 g of thiourea was heated at 200-210° for 1.5 h. On cooling, the melt was treated with 500 ml of hot water and crude 2-mercaptoperimidine was filtered off. The filtrate was cooled to precipitate pale-yellow crystals of 2-aminoperimidine hydrochloride. These were separated and dried at 100°. The yield was 0.87 g (40%). They were crystallized from water to give colorless crystals melting at 274° with decomposition. The base was isolated by adding dilute ammonia solution to an aqueous solution of the hydrochloride. The colorless needles had an mp of 240° (from water or alcohol), which corresponds to the literature data [13], $\nu_{NH}$ 3440, 3350 $cm^{-1}$.

1-(3-Dimethylaminopropyl)perimidine. A mixture of 10.08 g of perimidine, 13.4 g of potassium hydroxide, and 18.8 g of 3-dimethylaminopropyl chloride hydrochloride in 154 ml toluene and 46 ml chlorobenzene was stirred and boiled in a nitrogen atmosphere for 3 h. On cooling, the mixture was treated with 50 ml water, filtered, and the organic layer carefully washed with water, dried, and distilled under reduced pressure to remove the solvent. The residue was dissolved in the minimum amount of chloroform and passed through a column of alumina, eluting with chloroform. The first yellow-colored fraction was collected, the chloroform was distilled off, and the residue was dissolved in benzene. A stream of dry hydrogen chloride was passed through the solution. The precipitated yellowish-green crystals of the dihydrochloride (8.8 g, 45%) were filtered off and crystallized from alcohol; mp 244-245°. Found, %: C 58.6; H 6.0; Cl 22.1; N 12.5. $C_{16}N_{19}N_3 \cdot 2HCl$. Calculated, %: C 58.9; H 5.9; Cl 22.3; N 12.9. The base was isolated in the form of a dark-yellow oil by adding concentrated ammonia solution to an aqueous solution of the dihydrochloride; yield 5.2 g (33%). The dipicrate was obtained in the form of golden-yellow platelets, mp 228° (decomp., from alcohol).

1-(3-Dimethylaminopropyl)-2-aminoperimidine (IX). A suspension of 1.1 g of finely divided sodamide in 3 ml absolute dimethylaniline was treated with 2.2 g of 1-(3-dimethylaminopropyl)perimidine. The mixture was stirred and heated at 140-145° in an atmosphere of dry nitrogen for 3 h. While continuing to pass nitrogen, the mixture was cooled and treated with 10 ml water. The precipitated amine IX was filtered off; washed with water, petroleum ether, and benzene; and dried. The yield was 0.95 g (41%) of light-grey fine crystals, mp 196-197° (from toluene).

1-Phenylperimidine. A solution of 5 g of N-phenyl-1,8-naphthylenediamine [14] in 20 ml of formic acid was boiled for 3 h, and then treated with 20 ml water and twice boiled with activated carbon. The cooled filtrate was neutralized with ammonia, and the precipitated crystals filtered off and dried in a vacuum desiccator over potash, to give a quantitative yield of yellow crystals, mp 110° (from octane). Found, %: C 83.2; H 5.0; N 10.8. $C_{17}N_{12}N_2$. Calculated, %: C 83.5; H 5.0; N 11.4.

1-Phenyl-2-aminoperimidine (XI). A solution of 2 g of 1-phenylperimidine in 6 ml of absolute dimethylaniline was treated with 1.56 g of finely divided sodamide. The mixture was stirred at 120-130° in a nitrogen atmosphere for 1.5 h. Vigorous hydrogen evolution was ob-

served and a voluminous precipitate was formed. The mixture was cooled under nitrogen and carefully treated with 10 ml water. After distilling off the dimethylaniline with steam, dark-grey crystals of crude amine XI remained in the residue. The yield was 2.1 g, which is close to quantitative. The colorless fine needles melted at 210° (from isooctane).

General Method for Chlorine Exchange in 1-Methyl-2-chloroperimidine. A. A solution of 0.01 mole 1-methyl-2-chloroperimidine [12] and 0.02 mole of amine in 20 ml dimethylformamide is stirred at 100-120° for 2-2.5 h, after which it is cooled and slowly added to water (200-300 ml). The resulting solution is neutralized with concentrated aqueous ammonia, and the precipitated 2-aminoperimidine is filtered off, dried, and crystallized. If the excess amine also precipitates during neutralization, as occurs in the case of the arylamines, it can be extracted with ether.

B. A mixture of 1-methyl-2-chloroperimidine and a fivefold excess of the amine is stirred at 110-120° for 2 h. The excess amine is then removed by steam distillation, and the remaining crystals are filtered off, dried, and recrystallized from a suitable solvent. This method is advisable in the case of arylamines.

C. When gaseous methylamine is used, the synthesis is best carried out by passing a stream of dry methylamine for 2 h into a solution of 1-methyl-2-chloroperimidine in dimethylformamide heated to 110-120°.

1-(3-Dimethylaminopropyl)perimidone (XIX). A mixture of 5 g of 1-(3-dimethylaminopropyl)-perimidine and 5.6 g of powdered anhydrous potassium hydroxide was fused at 200-210° for 1.5 h until hydrogen evolution ceased. On cooling, the mixture was treated with water (100 ml), and the dark precipitate (5 g) filtered off, washed with water, dried, and recrystallized from a mixture of octane and benzene using activated carbon, to give colorless needles, mp 134°. Found, %: C 71.5; H 7.1; N 15.9. $C_{16}H_{19}N_3O$. Calculated, %: C 71.3; H 7.1; N 15.6.

4-Methyl-1,2,3,4-tetrahydropyrimidino[1,2-a]perimidine (XXI). A mixture of 2.7 g XIX and 10 ml phosphorus oxychloride was boiled for 5 h. The solution was cooled, poured onto ice (100 g), and carefully neutralized with concentrated aqueous ammonia. The light-yellow crystals of XXI were filtered off, washed with water, and dried in a vacuum desiccator over potash. Yield 1.2 g (50%), mp 137° (from isooctane).

Preparation of Hydrochlorides. A stream of dry hydrogen chloride is passed through a solution of 0.01 mole of the 2-aminoperimidine in 50 ml benzene until precipitation ceases. The suspension of the hydrochloride is heated to remove excess HCl, cooled, and the colorless hydrochloride precipitate crystallized from alcohol or alcohol and ether.

The hydrochlorides of compounds I-VI and XVIII are described in [9, 11].

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