SYNTHESIS AND NEUROTROPIC ACTIVITY OF 1-ACETONYL- AND 1-PHENACYLPERIMIDINES*

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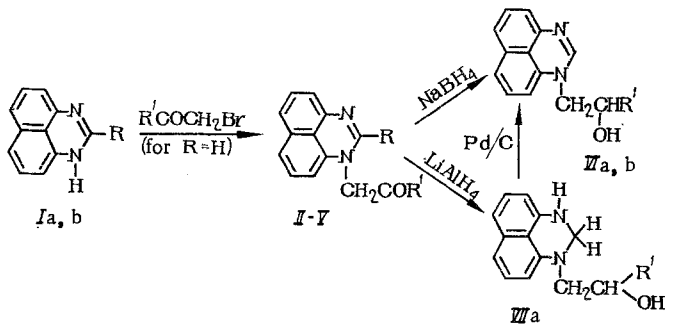
Recently in a patent [1] and in a series of our works [2-4], it was demonstrated that many perimidine derivatives have high neurotropic activity. However, in spite of the fact that the number of perimidine compounds tested probably now approaches 100, no preparation has yet been found which could be recommended for practical application. One of the possible paths of further searching for active substances, in analogy with the successes achieved in the benzimidazole series, is the synthesis of perimidine derivatives containing the butyrophenone radical and other ketoalkyl substituents. In this connection, our aim in the present paper is to synthesize a series of 1-ketoalkylperimidines, primarily 1-phenacyl-(II) and 1-acetonylperimidine (III) and to study certain of their chemical properties and their neurotropic activity.



Ia: R = H; Ib: R = C_6H_5; II: R′ = C_6H_5, R = H; III: R′ = CH_3, R=H; IV: R′ = CH_3, R = C_6H_5; V: R′ = R = C_6H_5; VIa: R′ = CH_3; VIb: R′ = C_6H_5; VIIa:R′ = CH_3.

In contrast to 1-alkylperimidines [5], compounds II-V could not be obtained via alkylation of perimidine (Ia) or 2-phenylperimidine (Ib) with bromoacetone and phenacyl bromide in the presence of a base. The initial perimidine was regenerated unchanged in this case. Compounds II and III were obtained by alkylation of Ia in a neutral medium at room temperature.

2-Methyl- and 2-phenylperimidine could not be alkylated with phenacyl bromide even in neutral medium. The initial compounds were separated from the reaction mixture in nearly quantitative amounts. The difficulty in alkylating 2-substituted perimidines with phenacyl bromide is probably caused by steric hindrance, which is more significant in the perimidine series than in the imidazole series due to the close proximity of the H_4 and H_9 protons to the nitrogen atom. 1-Ketoalkyl-2-phenylperimidines (IV, V) were synthesized by us previously using a recyclization reaction. The structure of the 1-ketoalkylperimidines was verified by PMR and IR spectra; the mass spectrum was used for compound III. The IR spectrum of 1-phenacylperimidine has one absorption band for $\nu_{C=O}$ at 1685 cm^{-1} in mineral oil and at 1690 cm^{-1} in chloroform, whereas 1-acetonylperimidine has one band for $\nu_{C=O}$ at 1720 cm^{-1} in mineral oil, which is resolved into two (1725 and 1750 cm^{-1}) in chloroform solution. The reason for this is not clear. The distinguishing property of the prepared 1-ketoalkylperimidines is their instability in alcoholic solutions of alkali and to some extent in neutral media; they decompose on heating in organic solvents. On the other hand, their acid solutions do not change, even during prolonged boiling.

In view of this, the quaternary salts VIII-X were synthesized for testing. They were prepared by quaternization of 1-ketoalkylperimidines with methyl iodide and by treating 1-methylperimidine with bromoacetone

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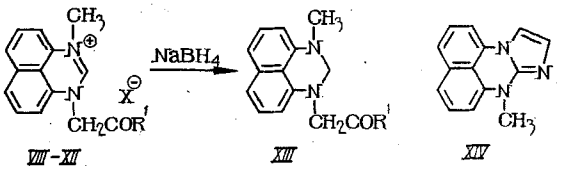
or phenacyl bromide. The salts VIII-XII are easily hydrogenated with sodium borohydride to 1-ketoalkyl-3-methyl-2,3-dihydroperimidines (XIII).

It is interesting to note that during the action of sodium borohydride on 1-ketoalkylperimidines, the C=O bond is hydrogenated and alcohols are formed in good yields; these were also tested with respect to their effect on the central nervous system. During the treatment of compounds II and III with lithium aluminum hydride, the C=N bond is reduced in addition to the C=O bond, leading to the formation of compounds of type VII. These can be converted to the alcohols VI by reduction with palladium over carbon.

1-Methylimidazo[1,2-a]perimidine (XIV), obtained previously [6] by treating 1-methyl-2-aminoperimidine with chloracetaldehyde, was also subjected to pharmacological testing.



VIII-XII XIII XIV

VIII: R′ = CH_3, X^- = Br; IX: R′ = C_6H_5, X^- = Br; X: R′ = C_6H_5, X^- = I;
XI: R′ = C_6H_5, X^- = ClO_4; XII: R′ = C_6H_5, X^- = NO_3; XIII: R′ = C_6H_5.

EXPERIMENTAL PHARMACOLOGICAL PART

The toxicity of the compounds during intraperitoneal administration and the nature of their action on the central nervous system were evaluated in tests on white mice. The test methods are described in previous reports [2, 3].

The LD_{50} of the investigated compounds varied from 141 mg/kg (VIa·HCl) to 275 mg/kg and more (V·HCl and VIb·HCl in doses of 400 mg/kg did not cause death in the animals).

All of the compounds have a depressive effect. With compounds containing the acetophenone radical and with XIV·HCl, general depression is accompanied by the development of tremors. Tremors develop 1-1.5 h after administration of the preparations and are probably caused by metabolites formed from the compound being studied. Although in appearance the tremors resemble those caused by arecoline, none of these substances increase the central cholinomimetic effects of arecoline. In subtoxic and toxic doses, V·HCl characteristically causes gastric evacuation of the intestines (defecation).

The depressant effect of all of the substances in toxic doses appears as restricted motion, disruption of coordination, and assumption of a lateral position. In doses of 0.02 mg/kg, all of the compounds, with the exception of IX·H_2O, prolong the narcotic effect of hexenal. Compounds containing acetonyl substituents are somewhat more active in this respect than compounds containing acetophenone radicals. However, potentiation of the narcotic effect of hexenal by the compounds is observed only on addition of them to the narcotic; the investigated compounds do not cause the "return phenomenon" of the narcotic effect of hexenal.

With the exception of VIa·HCl, which prolongs the apomorphine stereotypy and potentiates the central nervous effect of arecoline, the remaining compounds have no influence on the action of apomorphine and arecoline. All of the investigated compounds possess a definite ability to increase the influence of nicotine on the central nervous system.

All of the compounds decrease the arterial pressure in rats on a short-term basis.

Thus, 1-acetonyl- and 1-phenacylperimidines do not exhibit neurological activity. Their depressant action on the central nervous system appears only in subtoxic and in toxic doses.

EXPERIMENTAL CHEMICAL PART

The IR spectra were obtained on a UR-20 apparatus, the UV spectra on an SF-4A apparatus, and the PMR spectra on a Tesla BS-487C spectrometer. The chemical shifts are given on the scale δ, ppm, relative to tetramethylsilane. The mass spectra were taken at ionizing electron energy 70 eV.

The hydrochlorides IVa and Va were obtained by saturation of a benzene solutions of compounds IV and V with dry hydrogen chloride. Quantitative yields were obtained.

IVa Hydrochloride. Yellow crystals with mp 213°C (from alcohol). Found, %: N 8.4. $C_{20}H_{16}N_2O \cdot HCl$. Calculated, %: N 8.3.

Va Hydrochloride. Yellow crystals with mp 242-243°C (from alcohol). Found, %: N 6.9. $C_{25}H_{18}N_2O \cdot HCl$. Calculated, %: N 7.0.

Attempted Preparation of Compound V. A. A solution of 0.5 g (2.5 mmole) phenacyl bromide in 1 ml dimethylformamide (DMF) was added to 0.6 g (2.5 mmole) 2-phenylperimidine in 10 ml DMF. The mixture was heated for 20 min on a boiling water bath. It was then cooled and the precipitated 2-phenylperimidine hydrobromide was filtered off. Yield 0.7 g (87%). On treating with aqueous ammonia, 2-phenylperimidine was obtained.

B. A mixture of 0.6 g (2.5 mmole) 2-phenylperimidine, 0.22 g (4 mmole) finely divided sodium hydroxide, and 0.85 g (4 mmole) phenacyl bromide in 40 ml toluene was heated at boiling for 6 h in a nitrogen atmosphere. It was cooled and the precipitate filtered off. On cooling, 2-phenylperimidine was obtained in quantitative yield.

1-Phenacylperimidine (II). A solution of 1 g (0.005 mole) phenacyl bromide in 1 ml DMF was added to a solution of 1.7 g (0.01 mole) perimidine in 7 ml DMF. The reaction mixture was stirred for 15 h at room temperature. The precipitate was separated, dissolved in 150 ml water, and treated with aqueous ammonia. The product was filtered off, washed with water, and dried. It was then dissolved in 15 ml chloroform and separated from the initial perimidine by filtration. The filtrate was passed through a chromatography column filled with aluminum oxide, sorbing the first yellow fraction (eluent – chloroform). Yield 0.55 g (38%), as yellow crystals with mp 179-181°C (with decomposition). UV spectrum, λ_{max}, nm (log ε) (in methanol): 333 (4.18); 345 (inflection) (3.99); 395 (inflection) (3.05); 255 (inflection) (4.0); 237 (4.52). IR spectrum (chloroform), cm^{-1}: 1690 (C=O). PMR spectrum* (in DMSO): 4.37 (s, 2H, CH_2); 6.10 (q, 1H, H_9); 6.80 (q, 1H, H_4); 7.15 (m, 4H); 7.62 (m, 4H); 8.15 (q, 2H). Mass spectrum, m/e: 286 (M^+), 181 (M–PhCO). Found, %: N 9.6. $C_{19}H_{14}N_2O$. Calculated, %: N 9.8. On heating, compound II decomposed, therefore purification by crystallization was difficult. It was crystallized from alcohol and toluene, giving dark green crystals, which were chromatographically impure and had an IR absorption at 3540 cm^{-1} (mineral oil).

1-Acetonylperimidine (III). Compound III was prepared by treating I with bromoacetone analogously to the preparation of 1-phenacylperimidine, with 36% yield. Light-yellow crystals, mp 185-186°C (with decomposition). IR spectrum (chloroform), cm^{-1}: 1725, 1750 (C=O); (mineral oil), cm^{-1}: 1720 (C=O). PMR spectrum (CF_3COOH): 2.17 (s, 3H, CH_3); 4.67 (s, 2H, CH_2); 6.17 (q, 1H, H_9); 6.56 (q, 1H, H_4); 7.17 (m, 4H); 7.75 (d, 1H). Found, %: C 74.6, H 5.1, N 12.6. $C_{14}H_{12}N_2O$. Calculated, %: C 74.8, H 5.4, N 12.5.

1-Phenacyl-3-methylperimidinium iodide (X). Methyl iodide (0.27 ml, 4.2 mmole) was added to a solution of 0.6 g (2.1 mmole) 1-phenacylperimidine in 15 ml acetone. The mixture was heated at boiling for 4 h, cooled, and the precipitate filtered off. Yield 0.7 g (87%). Yellow needles, mp 223-225°C (from alcohol). UV spectrum, λ_{max}, nm (log ε) (methanol): 228 (4.77); 246 (4.41); 295 (4.00); 310 (4.10); 324 (4.10); 350-410 (3.32). IR spectrum (mineral oil), cm^{-1}: 1680 (C=O). Found, %: N 6.5. $C_{20}H_{17}IN_2O$. Calculated, %: N 6.5.

1-Phenacyl-3-methylperimidinium bromide (IX). A solution of 0.55 g (3 mmole) 1-methylperimidine and 0.6 g (3 mmole) phenacyl bromide in 5 ml acetone was heated at boiling for 30 min. The bright yellow precipitate was filtered off and washed with acetone. Yield 0.8 g (66%), mp 236-238°C (from alcohol). IR spectrum (mineral oil), cm^{-1}: 1700 (C=O); 3420, 3520 (OH). PMR spectrum (CF_3COOH): 3.25 (s, 3H, CH_3); 5.37 (s, 2H, CH_2); 6.20 (q, 1H, H_9); 6.47 (q, 1H, H_4); 7.37 (m, 9H); 8.92 (s, 1H). Found, %: C 60.4; H 4.5; Br 19.7; N 7.3. $C_{20}H_{17}BrN_2O \cdot H_2O$. Calculated, %: C 60.2; H 4.8; Br 20.0; N 7.0. The crystalline hydrate did not lose water on drying in a spray drier over phosphorous pentoxide (110°C) for 20 h.

The crystalline hydrate 1-acetonyl-3-methylperimidinium bromide (VIII), was obtained analogously, mp 245-247°C (from alcohol). IR spectrum (mineral oil), cm^{-1}: 1720 (C=O); 3400, 3600 (OH). Found, %: C 53.7; H 4.9; Br 23.5; N 8.2. $C_{15}H_{15}BrN_2O \cdot H_2O$. Calculated, %: C 53.4; H 5.1; Br 23.7; N 8.3.

1-Phenacyl-3-methylperimidinium Perchlorate (XI). A. Concentrated chloric acid (2 ml) was added to a hot solution of 0.38 g (1 mmole) compound IX in 1 ml water. The mixture was heated at boiling for 10 min. On cooling, the precipitate was filtered off and washed with water. The yield was quantitative, mp 246-247°C (from alcohol). IR spectrum (mineral oil), cm^{-1}: 1100 (ClO_4^-); 1710 (C=O). Found, %: C 59.6; H 4.1; Cl 8.8; N 7.3. $C_{20}H_{17}ClN_2O_5$. Calculated, %: C 59.9; H 4.3; Cl 8.9; N 7.0.

*Note: s = singlet, d = doublet, q = quartet, and m = multiplet.

B. Concentrated chloric acid (2 ml) was added to a hot solution of 0.2 g (0.44 mmole) compound X in 1 ml water, with further treatment as in method A. The melting point and IR spectrum were identical to that of the compound obtained by method A.

1-Phenacyl-3-methylperimidinium Nitrate (XII). Silver nitrate (0.48 g, 2.6 mmole) in 10 ml water was added to a solution of 1 g (2.6 mmole) compound IX in 150 ml water. The precipitate was filtered off and washed with hot water (150 ml). On cooling, 1-phenacyl-3-methylperimidinium nitrate precipitated from the filtrate. Gold flakes, mp 204°C (from water). IR spectrum (mineral oil), cm^{-1}: 1710 (C=O); 1370 (NO_3^-). Found, %: C 65.8; H 4.4; N 11.4. $C_{20}H_{17}N_3O_4$. Calculated, %: C 66.1; H 4.7; N 11.6.

1-(β-Hydroxypropyl)perimidine (VIa). Sodium borohydride (0.38 g, 10 mmole) was added to a solution of 1.1 g (5 mmole) 1-acetonylperimidine in 50 ml alcohol over 30 min. The mixture was stirred for another 30 min, 10 ml water added, and part of the solvent distilled off. On cooling, a precipitate was formed, which was filtered off. It was purified chromatographically, with sorption of the first yellow fraction (aluminum oxide, eluent – chloroform). The yield was quantitative. Yellow crystals, mp 170-171°C (from ethyl acetate). Found, %: C 74.4; H 5.9; N 12.6. $C_{14}H_{14}N_2O$. Calculated, %: C 74.3; H 6.2; N 12.4.

1-(β-Phenyl-β-hydroxyethyl)perimidine (VIb), mp 192-193°C (from ethyl acetate) was obtained analogously. IR spectrum (chloroform), cm^{-1}: 3610, 3690 (OH). Found, %: N 9.9. $C_{19}H_{19}N_2O$. Calculated, %: N 9.7. The hydrochlorides VIa and VIb were obtained by saturation of toluene solutions of compounds VIa, b with dry hydrogen chloride. The yield was quantitative. Yellow crystals, mp 288-289°C and 255-256°C (from alcohol with ether), respectively.

1-(β-Hydroxypropyl)-2,3-dihydroperimidine (VIIa). 1-Acetonylperimidine (2 g, 0.009 mole) was added to a solution of 1.3 g (0.0035 mole) lithium aluminum hydride in 70 ml absolute ether. The reaction mixture was heated at boiling with stirring for 1 h. The yellow solution was cooled, 15 ml water added, and the solution stirred for an additional 30 min. The ether layer separated out. After evaporation of the ether, the remaining oil was crystallized by trituration with petroleum ether. It was purified chromatographically (aluminum oxide, chloroform) with sorption of the first colorless fraction, mp 76°C (from benzene). Yield 1.8 g (90%). IR spectrum (chloroform), cm^{-1}: 3410 (NH); 3620 (OH). PMR spectrum (deuterochloroform): 1.05 (d, 3H, CH_3, I=6Hz); 2.97 (m, 1H); 3.67 (d, 2H); 4.20 (s, 2H, $N-CH_2-N$); 6.40 (m, 2H, H_4, H_9); 7.07 (s, H_{5-9}). Found, %: N 12.2. $C_{24}H_{16}N_2O$. Calculated, %: N 12.3.

Dehydrogenation of 1-(β-hydroxypropyl)-2,3-dihydroperimidine VIIa in boiling benzene over 6 h in the presence of 15% palladium on carbon gave 1-(β-hydroxypropyl)perimidine VIa in 40% yield.

1-Phenacyl-3-methyl-2,3-dihydroperimidine (XIII). XIII was obtained according to the general method [7], using sodium borohydride, in quantitative yield. Green flakes, mp 154-155°C (from ethyl acetate). IR spectrum (mineral oil), cm^{-1}: 1690 (C=O). Found, %: C 79.3; H 5.9; N 9.1. $C_{20}H_{18}N_2O$. Calculated, %: C 79.4; H 6.0; N 9.3.

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