1-(2-Hydroxyethoxymethylene)-5-fluorouracil (IX). A 0.1-mole sample of VIII was dissolved in 10 ml of a methanol solution of ammonia, and the solution was allowed to stand at 20°C for 6 h. It was then evaporated *in vacuo*, and the residue was recrystallized from ethanol–ethyl acetate (1:1).

1-(2-Methoxyethoxymethylene)-5-fluorouracil (X) and 1-(2-Ethoxyethoxymethylene)-5-fluorouracil (XI). These compounds were obtained by method A and were purified by recrystallization from chloroform–hexane (1:1).

LITERATURE CITED

1. S. A. Giller, R. A. Zhuk, and M. Yu. Lidak, Dokl. Akad. Nauk SSSR, 176, 332 (1967).
2. N. G. Blokhina, A. M. Garin, E. K. Voznyi, A. M. Lipatov, N. I. Karev, and N. V. Burachevskaya, in: Experimental and Clinical Pharmacotherapy [in Russian], Vol. 7, Zinatne, Riga (1977), p. 224.
3. O. S. Stepanova, O. I. Tishchenko, A. I. Drozdovskaya, É. A. Kal'nitskaya, T. D. Pantsuk, and E. A. Yatsenko, Zh. Vsesoyuzn. Khim. Obshchestva, No. 5, 598 (1963).
4. M. F. Shostakovskii, Vinyl Ethers [in Russian], Moscow (1952), p. 108.
5. L. Yu. Tychinskaya and V. L. Florent'ev, Bioorg. Khim., 4, 1461 (1978).
6. H. J. Schaffer, L. Beauchamp, P. de Miranda, G. B. Elien, D. J. Bauer, and P. Collins, Nature, 272, 583 (1978).
7. R. A. Zhuk, M. Yu. Lidak, A. P. Gilev, A. A. Ziderman, A. S. Tsieminya, and A. N. Kozhukhov, Current Problems in the Experimental Chemotherapy of Tumors [in Russian], Part 1, Chernogolovka (1980), p. 40.
8. Yu. V. Pokonova, Halo Ethers [in Russian], Khimiya, Moscow–Leningrad (1966), p. 281.
9. L. T. Kaulinya, M. Yu. Lidak, and R. A. Zhuk, Khim. Geterotsikl. Soedin., No. 8, 1109 (1980).

SYNTHESIS OF 5-NITRO-N,N-DIPHENYLHYDRAZINOPYRIMIDINES AND INVESTIGATION OF THEIR FREE RADICALS

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UDC 547.853.7.07

A number of 5-nitro-N,N-diphenylhydrazinopyrimidines were synthesized. Free radicals were obtained by oxidation of these compounds with PbO_2. The stabilities of 5-nitro-4-pyrimidinylhydrazyl radicals are close to the stability of the α,α-diphenyl-β-2,4-dinitrophenylhydrazyl radical. The structures of the compounds obtained were confirmed by the UV, IR, PMR, and EPR spectra.

The introduction of heterocyclic substituents in stable radicals has a substantial effect on their electronic and three-dimensional structures, and this gives rise to a change in the spectral characteristics and reactivities and to the manifestation of the specific properties of these radicals [1].

No reports regarding the effect of a pyrimidine ring on the properties of free radicals have appeared in the literature. At the same time, information of this sort may be of value for obtaining quantitative data on the electronic nature and chemical peculiarities of pyrimidine derivatives.

The aim of the present research was to synthesize N,N-diphenyl-N'-pyrimidinylhydrazines that contain diverse substituents in the pyrimidine ring, to generate the corresponding hy-

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1545-1549, November, 1980. Original article submitted May 22, 1980.

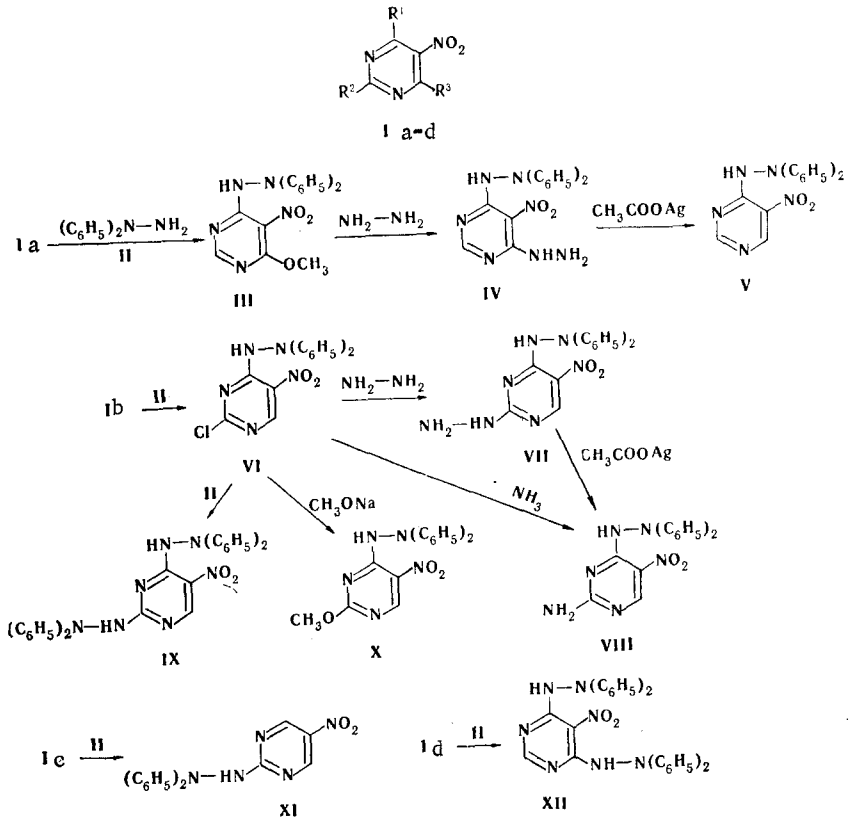
drazyl radicals from them, and to ascertain the stabilities of the latter as compared with the diphenylpicrylhydrazyl (DPPH) radical.

We synthesized such analogs of diphenylpicrylhydrazine in which the electron-acceptor picryl ring is substituted with 5-nitro-2- and 5-nitro-4-pyrimidinyl residues that contain various substituents. 5-Nitro-2(4)-diphenylhydrazinopyrimidines (III-XII) were obtained by reaction of 5-nitrochloropyrimidines (Ia-d) with N,N-diphenylhydrazine (II).

2,4-Dichloro-5-nitropyrimidine (Ib) and N,N-diphenylhydrazine react successively with the formation of mono- and disubstitution products. As in the reaction with amines [2], the chlorine atom in the 4 position of the pyrimidine ring is evidently replaced initially at 20°C, and hydrazinopyrimidine VI is formed. The chlorine atom attached to C_2 is replaced upon prolonged refluxing to give 5-nitro-2,4-bis(2,2-diphenylhydrazino)pyrimidine (IX). In the case of the reaction of 4,6-dichloro-5-nitropyrimidine (Id) with hydrazine II both chlorine atoms are so active that a monosubstitution product cannot be isolated, and 5-nitro-4,6-bis(2,2-diphenylhydrazino)pyrimidine (XII) is obtained.

The corresponding 2-aminopyrimidine VIII, the structure of which was proved by amination of chloropyrimidine VI, was obtained unexpectedly in an attempt to obtain diphenylhydrazine V by oxidation of 5-nitro-2-hydrazino-4-(2,2-diphenylhydrazino)pyrimidine (VII) with silver acetate by the method in [3]. It is known that hydrazine decomposes via two pathways during oxidation with the evolution of ammonia and nitrogen or only nitrogen [4]. The oxidation of 2-hydrazinopyrimidine VII probably takes place in the same way as the oxidation of unsubstituted hydrazine via the first pathway, as a result of which 2-aminopyrimidine VIII and nitrogen are formed. 5-Nitro-4-(2,2-diphenylhydrazino)pyrimidine (V) was obtained in the case of oxidation of hydrazine IV under the same conditions.

The synthesized mono- (III, V, VI, X, and XI) and bishydrazines (IX and XII) are crystalline substances that are stable in air. Compounds III, V, VI, and IX-XII absorb intensely (log ε 4.20-4.60) in the UV region of the spectrum at 276-290 nm (alcohol). A shoulder at 350-410 nm is observed in the visible part of the spectrum for III, V, VI, X, and XI. We



Ia R^1=Cl, R^2=H, R^3=OCH_3; b R^1=R^2=Cl, R^3=H; c R^1=R^3=H, R^2=Cl; d R^1=R^3=Cl, R^2=H

assigned the absorption bands in the IR spectra at 3300-3450 cm^{-1} to an associated NH bond. Two types of hydrogen bonds, viz., associated and nonassociated, are observed in the IR spectra of VII-IX (see the experimental sections).

Solutions of 5-nitro-N,N-diphenylhydrazinopyrimidines (III, V, VI, X, and XI) in benzene, from which the oxygen had been removed, upon oxidation with lead dioxide readily form free radicals with the bluish-violet color (λ_{max} 580-600 nm) that is typical for hydrazyl radicals. An hfs that is associated with coupling of the unpaired electron with the nuclei of the α- and β-^{14}N atoms (J = 1) of N,N-diphenylhydrazine is observed in the EPR spectra of the investigated radicals. The EPR spectrum of the radicals obtained consists of five lines (1:2:3:2:1) and constitutes evidence for the approximate equivalence of both hydrazyl nitrogen atoms. The hyperfine coupling constant (a_N) is ∿9 Oe and depends very little on the nature of the substituent attached to the pyrimidine ring. The g factor of the radicals obtained corresponds to the g factor of the DPPH radical. We were unable to observe splitting by the nitrogen atoms of the pyrimidine ring in a single case.

The biradicals obtained in the oxidation of IX and XII, in which spin–spin exchange through the conjugated system is realized, are of particular interest. In the case of treatment of solutions of IX and XII in benzene with PbO_2 we recorded EPR signals of weak intensity that have five well-resolved lines that are characteristic for a monoradical.

A qualitative comparison of the stabilities of the free radicals obtained by oxidation of leuco compounds III, V, VI, X, and XI shows that the presence of an NO_2 group in the ortho position relative to the N,N-diphenylhydrazyl substituent plays a substantial role in stabilization of the radical. In fact, the free radicals obtained in the oxidation of III, V, VI, and X proved to be more stable than the free radical obtained from leuco compound XI. This is associated with the fact that the NO_2 group in the ortho position, in addition to the purely electronic effect, has a stabilizing steric effect. We were unable to isolate the free radicals in the crystalline state, since they disappear completely in the course of a few dozen hours.

It is known [5] that the exceptional stability of the DPPH radical is associated in many respects with the presence at the β-nitrogen atom of a strong electron-acceptor trinitrophenyl group. A qualitative comparison of the lifetimes of the free radicals makes it possible to conclude that the stabilities of the synthesized 5-nitro-4-pyrimidinylhydrazyl radicals considerably exceed the stability of the triphenylhydrazyl radical [1] and are close to the stability of the α,α-diphenyl-β-2,4-dinitrophenylhydrazyl radical [6]. The close values of the half-conversion times of the α,α-diphenyl-β-2,4-dinitrophenylhydrazyl radical and the radical obtained by oxidation of V make it possible to conclude that replacement of the phenyl residue by a pyrimidinyl residue increases the stability of the radical and is equivalent to the introduction of a nitro group in the para position of the phenyl ring.

Thus, despite the significant electron-acceptor properties of the pyrimidinyl residue, the 5-nitropyrimidinylhydrazyl radicals obtained are less stable than the DPPH radical. This emphasizes the great importance of steric shielding in stabilization of hydrazyl radicals.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in d_6-DMSO were recorded on the δ scale at 20°C with a Tesla BS 467 spectrometer (60 MHz) with hexamethyldisiloxane as the external standard. The EPR spectra were recorded with an RE-1306 radiospectrometer. The individuality of the synthesized compounds was monitored by thin-layer chromatography (TLC) on a fixed silica gel–gypsum layer in a chloroform–methanol system (80:1), the chromatograms were developed in a gaseous chloroform atmosphere, after which they were sprayed with a starch-iodide solution. The starting chloronitropyrimidines Ia-d were obtained by the methods in [7-10].

5-Nitro-4-methoxy-6-(2,2-diphenylhydrazino)pyrimidine (III). A 0.95-g (5 mmole) sample of Ia was stirred in 8 ml of chloroform with 1.85 g (10 mmole) of II in 4 ml of chloroform, after which the mixture was stirred at 20°C for 1 h and refluxed for 12 h. The N,N-diphenylhydrazine hydrochloride was removed by filtration, and the mother liquor was concentrated to 5 ml. Hot ethanol (20 ml) was added, and the precipitate was removed by filtration to give 1.34 g (79%) of III as shiny yellow plates with mp 152-155°C (from ethanol). IR spectrum:

3330 (NH); 1565, 1355 cm^{-1} (NO_2). Found: C 60.9; H 4.4; N 20.7%. $C_{17}H_{15}N_5O_3$. Calculated: C 60.5; H 4.5; N 20.8%.

5-Nitro-4-hydrazino-6-(2,2-diphenylhydrazino)pyrimidine (IV). A 1.05-g sample of 98% hydrazine hydrate was stirred in 5 ml of absolute ethanol with a warm solution of 1.5 g (4.45) mmole) of III in 135 ml of absolute ethanol, and the mixture was then heated at 47-50°C for 1 h. The precipitate was removed by filtration and washed with ethanol to give 1.39 g (93%) of hydrazine IV as bright-orange acicular crystals with mp 168-170°C (dec., from ethanol). IR spectrum: 3355, 3325, 3250-3270 (NH_2, NH), 1565, 1350 cm^{-1} (NO_2). PMR spectrum: 8.27 (s, 1H, 2-H) and 6.83-7.83 ppm (10H, m, phenyl groups). Found: C 57.1; H 4.3; N 28.4%. $C_{16}H_{15}N_7O_2$. Calculated: C 57.0; H 4.5; N 29.1%.

5-Nitro-4-(2,2-diphenylhydrazino)pyrimidine (V). A 2-g (5.94 mmole) sample of hydrazine IV was suspended in 25 ml of water, 4.1 g (24.5 mmole) of freshly prepared silver acetate was added, and the mixture was stirred at 20°C for 5 min. Chloroform (100 ml) was added, and the mixture was stirred for another 1.5 h. The mixture was neutralized with Na_2CO_3, stirred for 15 min, and filtered. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (50 ml). The chloroform extract was dried over $MgSO_4$ and concentrated to 15 ml, and 30 ml of hot ethanol was added to the residue. The solution was separated from the dark suspension by filtration, and the oily product that remained after removal of the solvent by distillation was crystallized from petroleum ether (40-70°C) to give 1.18 g (65%) of dark-red prisms with mp 87-90°C. IR spectrum: 3355 (NH), 1570, 1360 cm^{-1} (NO_2). PMR spectrum: 8.93 (s, 1H, 2-H), 9.40 (s, 1H, 6-H), and 6.83-7.83 ppm (10H, m, phenyl groups).

2-Chloro-5-nitro-4-(2,2-diphenylhydrazino)pyrimidine (VI). A solution of 3.68 g (0.02 mole) of II in 10 ml of chloroform was added to a solution of 1.94 g (0.01 mole) of Ib in 15 ml of chloroform, and the mixture was stirred at 20°C for 3 h. It was then worked up as in the synthesis of pyrimidine III to give 3.17 g (92.7%) of dark-cherry-red prisms with mp 138-140.5°C (from petroleum ether, 70-100°C). IR spectrum: 3340 (NH); 1595, 1370 cm^{-1} (NO_2). Found: C 56.2; H 3.3; Cl 10.4; N 20.6%. $C_{16}H_{12}ClN_5O_2$. Calculated: C 56.2; H 3.5; Cl 10.4; N 20.5%.

5-Nitro-2-hydrazino-4(2,2-diphenylhydrazino)pyrimidine (VII). A 1-g (2.93 mmole) sample of pyrimidine VI was stirred in 40 ml of methanol with a solution of 0.4 ml of 98% hydrazine hydrate in 10 ml of methanol, and the reaction mixture was stirred at 20°C for 30 min. The precipitate was removed by filtration and washed with water to give 0.89 g (90%) of yellow prisms with mp 200-201°C (dec., from ethanol). IR spectrum: 3360, 3310, 3270 (NH_2, NH); 1540, 1370 cm^{-1} (NO_2). PMR spectrum: 9.07 (s, 1H, 6-H) and 6.83-7.83 ppm (10H, m, phenyl groups). Found: C 57.1; H 4.9; N 29.2%. $C_{16}H_{15}N_7O_2$. Calculated: C 57.0; H 4.5; N 29.1%.

5-Nitro-2-amino-4-(2,2-diphenylhydrazino)pyrimidine (VIII). A) This compound obtained from 2 g (5.94 mmole) of pyrimidine VII in 25 ml of water and 4.1 g (24.5 mmole) of silver acetate by a method similar to that used to obtain V. After removal of the solvent by distillation, the residue was crystallized from petroleum ether (70-100°C) to give 0.91 g (47.7%) of orange prisms with mp 156-159°C. No melting-point depression was observed for a mixture of this product with a genuine sample obtained by method B. IR spectrum: 3445, 3280, 3150-3170 (NH_2, NH), 1550, 1375 cm^{-1} (NO_2). Found: C 59.5; H 4.6; N 26.2%. $C_{16}H_{14}N_6O_2$. Calculated: C 59.6; H 4.4; N 26.1%.

B) A 1.71-g (5 mmole) sample of VI and 40 ml of cold absolute ethanol containing 13 g of gaseous ammonia were placed in a metal test tube, and the mixture was heated at 50°C for 4 h. It was then evaporated, and the residue was treated with 50 ml of water. The water-insoluble precipitate was removed by filtration to give 1.56 g (97%) of a product with mp 156-158°C (from ethanol). IR spectrum: 3445, 3280, 3150-3170 (NH_2, NH); 1550, 1375 cm^{-} (NO_2). Found: C 59.7; H 4.7; N 26.3%. $C_{16}H_{14}N_6O_2$. Calculated: C 59.6, H 4.4, N 26.1%.

5-Nitro-2,4-bis(2,2)diphenylhydrazino)pyrimidine (IX). A solution of 1.84 g (10 mmole) of II in 10 ml of chloroform was added to a solution of 1.71 g (5 mmole) of VI in 10 ml of chloroform, and the mixture was refluxed for 17 h. It was then worked up as in the preparation of III to give 1.53 g (62.7%) of fine yellow-brown crystals with mp 189-191°C (from ethanol). IR spectrum: 3300, 3190 (NH); 1550, 1370 cm^{-1} (NO_2). Found: C 68.9; H 4.8; N 20.2%. $C_{28}H_{23}N_7O_2$. Calculated: C 68.7; H 4.7; N 20.0%.

5-Nitro-2-methoxy-4(2,2-diphenylhydrazino)pyrimidine (X). A 1.39-g (4.07 mmole) sample of VI in 50 ml of methanol was added to a solution of sodium methoxide [from 0.1 g (4.35 mg-atom) of sodium and 10 ml of methanol], and the mixture was heated at 80-85°C for 1 h. It was then cooled and treated with several chunks of dry ice, and the resulting precipitate was removed by filtration and washed with water to give 1.17 g (85.5%) of bright-orange prisms with mp 137-139.5°C [from petroleum ether (70-100°C) and from ethanol]. IR spectrum: 3295 (NH); 1550, 1360 cm^{-1} (NO_2). Found: C 60.1; H 4.5; N 20.5%. $C_{17}H_{15}N_5O_3$. Calculated: C 60.5; H 4.5; N 20.8%.

5-Nitro-2-(2,2-diphenylhydrazino)pyrimidine (XI). A solution of 4.5 g (24.5 mmole) of II in 15 ml of chloroform was added to a solution of 1.95 g (12.2 mmole) of Ic in 15 ml of chloroform, and the mixture was refluxed for 3 h. The precipitate was removed by filtration and treated with 100 ml of hot water, and the water-insoluble product was removed by filtration. The chloroform mother liquor was concentrated to 10 ml, 30 ml of hot ethanol was added to the residue, and the resulting precipitate was removed by filtration. The two precipitates were combined and crystallized from ethanol to give 3.34 g (89%) of yellow needles with mp 231-232.5°C (dec.). IR spectrum: 3170 (NH), 1545, 1345 cm^{-1} (NO_2). Found: C 62.4; H 4.8; N 22.8%. $C_{16}H_{13}N_5O_2$. Calculated: C 62.5; H 4.3; N 22.8%.

5-Nitro-4,6-bis(2,2-diphenylhydrazino)pyrimidine (XII). A 1.2-g (6.18 mmole) sample of Id was stirred in 15 ml of chloroform with 4.6 g (25 mmole) of II in 15 ml of chloroform, and the mixture was refluxed for 1.5 h and worked up as in the preparation of III to give 2.37 g (78.5%) of pinkish-red fluffy needles with mp 184-186°C (from ethanol). IR spectrum: 3345 (NH), 1550, 1350 cm^{-1} (NO_2). Found: C 68.0; H 5.0; N 20.2%. $C_{28}H_{23}N_7O_2$. Calculated: C 68.7; H 4.7; N 20.0%.

LITERATURE CITED

1. É. G. Rozantsev and V. D. Sholle, The Organic Chemistry of Free Radicals [in Russian], Khimiya, Moscow (1979).
2. V. M. Cherkasov, G. S. Tret'yakova, and N. N. Aleksandrova, Ukr. Khim. Zh., 36, 694 (1970).
3. H. C. van der Plas, H. Jongejan, and A. Koudijs, J. Heterocycl. Chem., 15, 485 (1978).
4. T. A. Turney, Mechanisms of Redox Reactions [Russian translation], Mir, Moscow (1968), p. 66.
5. R. W. Baldock, P. Hudson, A. R. Katritzky, and F. Soti, J. Chem. Soc., Perkin I, 1422 (1974).
6. A. T. Balaban, P. T. Frangopol, M. Marculescu, and J. Bally, Tetrahedron, 13, 258 (1961).
7. E. C. Taylor, J. W. Barton, and W. W. Paudler, J. Org. Chem., 26, 4961 (1961).
8. N. Whittaker, J. Chem. Soc., 1565 (1951).
9. R. O. Robbin, P. S. Winnek, and J. P. English, J. Am. Chem. Soc., 64, 567 (1942).
10. W. R. Boon, W. G. M. Jones, and G. R. Ramage, J. Chem. Soc., 96 (1951).