HETEROCYCLIC ANALOGS OF PLEIADIENE.

60.* SYNTHESIS AND PROPERTIES OF 1-METHYL-2-CHLOROMETHYLPERIMIDINE

A. F. Pozharskii, E. V. Tsarevskaya, and M. I. Rudnev

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The previously unknown 1-methyl-2-chloromethylperimidine was synthesized. The chlorine atom in it has high lability and is readily exchanged under the influence of S, O, N, and C nucleophiles. It is shown that 1-methyl-2-cyanomethylperimidine exists in the methylidene form.

Many 2-substituted perimidines have significant biological (particularly neurotropic) activity [2]. The cyclization of 1,8-naphthalenediamine with carboxylic acids and their derivatives is a general method for their synthesis. However, some groups are conveniently introduced into the 2 position by functionalization of substituents already present. In order to develop such approaches, in the present research we accomplished the synthesis of 1-methyl-2-chloromethylperimidine. It could be hoped that exchange of the chlorine atom in this compound for various functional groups would occur very readily.

We used 2-hydroxymethylperimidine as the starting compound [3]. Its methylation with methyl iodide in the NaH–THF system previously led to the formation of two compounds — 1-methyl-2-hydroxymethylperimidine and 1-methyl-2-methoxymethylperimidine [4] — which is not surprising since the acidities of the protons of the OH and NH groups in perimidine are evidently commensurable [2]. We accomplished methylation under neutral conditions in DMF, which led to the formation of only I. By the action on it of thionyl chloride in absolute benzene at 20°C, we obtained 1-methyl-2-chloromethylperimidine (II) in 80% yield. If the reaction is carried out with heating, a mixture of products of chlorination in the naphthalene ring is formed (perimidines are very readily chlorinated by various reagents [5]).

The chlorine atom in II has high lability. Thus sulfide IIIa is formed in quantitative yield after 5 min in the reaction of II with n-butanethiol in alcohol in the presence of sodium ethoxide at 20°C. Compound II reacts more slowly with sodium phenoxide at 20°C, but 1-methyl-2-phenoxymethylperimidine (IIIb) is formed in 98% yield in the case of heating. Exchange of chlorine for diethylamino and piperidino groups occurs just as readily in the reaction of II with diethylamine and piperidine (2 moles of the amine were used to tie up the HCl). Compounds IIIa-d have IR spectra that are characteristic for 1,2-disubstituted perimidines: solutions of these substances in chloroform give two intense peaks at 1590 and 1630 cm^{-1}, which belong to the stretching vibrations of ring C=C and C=N bonds, respectively (the latter band is always somewhat less intense). In the PMR spectra of IIIa-d the methylene group shows up in the form of a singlet with an intensity of two proton units at 3.2-4.7 ppm (the position of the peak is determined by the electronegativity of the X group).

1-Methyl-2-cyanomethylperimidine (IIIe), which is formed in a few minutes by the action of sodium cyanide in DMSO on perimidine II, differs from I, II, and IIIa-d in color. Whereas the latter have the bright-yellow or orange color that is characteristic for perimidines, cyano derivative IIIe has the pale-yellow color that is typical for 2,3-dihydroperimidine structures [2]. We assumed that IIIe exists in the form of methylidene tautomer IVa. This assumption was confirmed by IR and PMR spectroscopic data. In the IR spectrum of a crystalline sample of IIIe the $\nu_{C\equiv N}$ band appears in the form of a very intense peak at 2190 cm^{-1}. The signal of the cyano group in the model compound of the benzimidazole series V appears in the same region ($\nu_{C\equiv N}$ 2170 cm^{-1}) [6], while 1-methyl-2-cyanomethylbenzimidazole, which exists in methylene form VI, absorbs at 2270 cm^{-1} [6]. In the PMR spectrum of IVa in solution

*See [1] for Communication 59.

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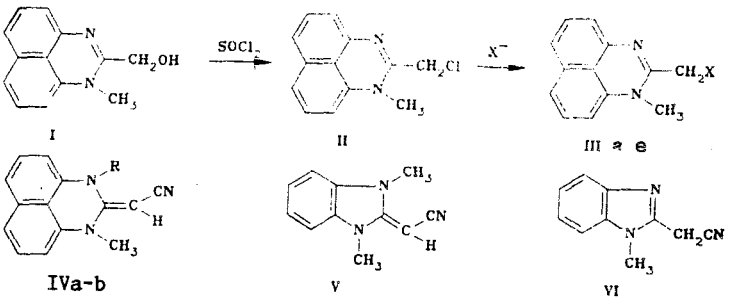
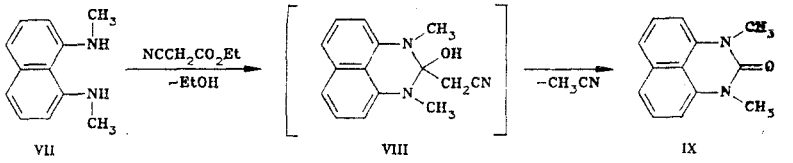
in d_6-DMSO the signals of the =CHCN proton and the NH proton appear in the form of singlets at 3.40 and 4.46 ppm, respectively. They both vanish upon deuteration.



III a X=n-C_4H_9S; b X=C_6H_5O; c X=$(C_2H_5)_2N$, d X=piperidyl; e X=CN; IV a R=H; b R=CH_3

One of the methods for obtaining V is the reaction of N,N'-dimethyl-o-phenylenediamine with cyanoacetic ester [7]. We attempted to synthesize 1,3-dimethyl-2-cyanomethylene-2,3-dihydroperimidine (IVb) via a similar method. However, 1,3-dimethylperimidone (IX) was obtained in 81% yield in the reaction of N,N'-dimethyl-1,8-diaminonaphthalene with cyanoacetic ester. Thus intermediate adduct VIII in this case is stabilized not by splitting out of a molecule of water as in the case of V but as a result of the elimination of a molecule of acetonitrile. We were also unable to obtain IVb by methylation of 1-methyl-2-cyanomethylperimidine in an alkaline medium; a complex mixture of unstable and difficult-to-separate substances is formed in this case.



Compound IVa, which is extremely difficult to obtain in chromatographically pure form, is also distinguished by significant lability. The synthesis of 2-cyanomethylperimidine by the reaction of 1,8-naphthalenediamine with isobutyl cyanoacetate has been described [8]. In attempts to reproduce this synthesis or to replace isobutyl cyanoacetate by ethyl cyanoacetate we invariably obtained an unstable and markedly contaminated product that could not be purified.

The reduced aromatic character of the heteroring in perimidine [2], as a consequence of which the conversion of the molecule to conjugated cyano enamine structure IVa compensates the loss in resonance energy on passing from the perimidine structure to the dihydroperimidine structure, can be considered to be the chief reason for the existence of 1-methyl-2-cyanomethylperimidine in methylidene form IVa. A tendency for conversion to the imino form was previously observed for 2-amino- and particularly 2-acylaminoperimidines [9]. A methylidene structure is also characteristic for 2-acetonylperimidine and ethyl 2-perimidinylacetate [4]. Proceeding from these data and the data that we obtained for IIIe it may be concluded that a necessary condition for conversion of 2-CH_2X-perimidines to the methylidene form is the ability of substituent X to manifest a negative electromeric effect. The latter assists effective involvement of the electron pair of the nitrogen atom of the dihydroperimidine ring in the conjugation chain with participation of the substituent in the 2 position.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Tesla BS-487 C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. Chromatography was carried out on Brockmann activity II Al_2O_3 (elution with chloroform) and on Silufol UV-254 with elution with chloroform–ethanol (12:1).

1-Methyl-2-hydroxymethylperimidine (I). A mixture of 19.8 g (0.1 mole) of 2-hydroxymethylperimidine [3], 12 ml (0.20 mole) of methyl iodide, and 80 ml of DMF was heated on a

boiling-water bath for 1.5 h, after which it was cooled, and the resulting precipitate was removed by filtration and dissolved in 700 ml of water. The undissolved starting substance was removed by filtration, and lemon-yellow crystals of I were precipitated from the mother liquor by means of 22% ammonium hydroxide. The crystals were removed by filtration, washed with water, and air dried. For purification the substance was dissolved in the minimum amount of chloroform, and the solution was passed through a column packed with aluminum oxide with collection of the first yellow fraction. After this, the product was recrystallized from ethyl acetate to give 12.6 g (59%) of crude product; recrystallization gave 7.0 g (33%) of product. The yellow-green crystals had mp 173-174°C (mp 165-167°C [4]). IR spectrum ($CHCl_3$): 1595 (C...C, 1630 (C=N), 3300-3400 cm^{-1} (associated OH). PMR spectrum (d_6-DMSO) 3.40 (s, 2H, CH_2), 3.60 (s, 3H, CH_3), 4.55 (s, OH), 6.59 (q, 1H, 9-H), 6.94 (q, 1H, 4-H), 7.42 ppm (m, 4H, 5-8-H). R_f 0.12 (Al_2O_3), 0.44 (Silufol). Found: C 72.7; H 5.7; N 13.2%. $C_{13}H_{12}N_2O$. Calculated: C 72.7; H 5.7; N 13.3%.

1-Methyl-2-chloromethylperimidine (II). A solution of 2.5 ml (42 mmole) of thionyl chloride in 12.5 ml of absolute benzene was added with stirring in the course of 20 min to a suspension of 5.6 g (25 mmole) of 1-methyl-2-hydroxymethylperimidine in 75 ml of absolute benzene, after which the mixture was stirred at 20°C for 3 h. The resulting dark-yellow precipitate of 1-methyl-2-chloromethylperimidine hydrochloride was removed by filtration and dispersed in 125 ml of water, and the base was precipitated by the addition of potassium carbonate until the mixture was strongly alkaline. The precipitated crystals of II were separated, washed with water, and dried successively in air and in a desiccator over $CaCl_2$. A saturated solution of the substance in chloroform was purified by column chromatography on aluminum oxide with collection of the first yellow fraction. The yield of the crude product was 4.6 g (80%), while the yield of the purified product was 2.7 g (46%). 1-Methyl-2-chloromethylperimidine has an irritating effect on the skin. The bright-yellow crystals had mp 164-165°C and R_f 0.69 (Al_2O_3) and 0.65 (Silufol). IR spectrum ($CHCl_3$) 1590 (C=C), 1630 (C=N). PMR spectrum ($CDCl_3$): 3.00 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 6.03 (q, 1H, 4-H), 7.10 ppm (m, 4-H, 5-8-H). Found: C 68.0; H 5.0; Cl 15.1%. $C_{13}H_{11}ClN_2$. Calculated: C 67.7; H 4.8; Cl 15.4%.

1-Methyl-2-n-butylthiomethylperimidine (IIIa). A 0.46-g (4.32 mmole) sample of n-butanethiol and 0.5 g (2.16 mmole) of 1-methyl-2-chloromethylperimidine were added with stirring in an inert gas atmosphere (nitrogen, argon) to a solution of sodium ethoxide obtained from 0.15 g (6.48 mmole) of sodium and 10 ml of alcohol. The color of the mixture changed almost instantaneously from yellow to bright yellow. The mixture was stirred for another 5 min at 20°C while the passage of the inert gas into it was continued. The precipitated sodium chloride was then removed by filtration, and the mother liquor was evaporated to dryness at reduced pressure. The substance was purified with a column packed with aluminum oxide (elution with chloroform) and recrystallized from petroleum ether. The yield of the crude product was 0.6 g (98%), while the yield of the purified product was 0.4 g (65%). The yellow-green crystals had mp 61-62°C. Solutions of the substance darkened on standing. R_f 0.70 (Al_2O_3) and 0.82 (Silufol). IR spectrum ($CHCl_3$) 1585 (C=C), 1625 cm^{-1} (C=N). PMR spectrum (CCl_4) 0.88 (t, 3H, CH_3), 1.43 (m, 4H, $CH_2\mathbf{CH_2}\mathbf{CH_2}CH_3$), 2.59 (t, 2H, $\mathbf{CH_2}CH_2CH_2CH_3$), 3.26 (s, 2H, CH_2), 5.93 (q, 1H, 9-H), 6.65 (q, 1H, 4-H), 7.00 ppm (m, 4H, 5-8-H). Found: C 71.5; H 7.2; S 10.8%. $C_{17}H_{20}N_2S$. Calculated: C 71.8; H 7.1; S 11.2%.

1-Methyl-2-phenoxymethylperimidine (IIIb). A 0.3-g (3.24 mmole) sample of phenol and 0.5 g (2.16 mmole) of 1-methyl-2-chloromethylperimidine were added to a solution of 0.18 g (4.5 mmole) of sodium hydride in 12 ml of ethanol, and the mixture was refluxed for 50 min. It was then cooled, and the precipitated crystals were removed by filtration and washed with cold alcohol. The yield was 0.6 g (98%). The light-yellow needles had mp 167-168°C (from ethyl acetate) and R_f 0.75 (Al_2O_3) and 0.88 (Silufol). IR spectrum ($CHCl_3$) 1590 (C=C), 1625 cm^{-1} (C=N). PMR spectrum ($CDCl_3$) 3.06 (s, 3H, CH_3), 4.71 (s, 2H, CH_2), 6.06 (q, 1H, 9-H), 7.00 ppm (m, 10H, 4 to 8-H, C_6H_5). Found: C 78.8; H 5.7; N 9.5%. $C_{19}H_{16}N_2O$. Calculated: C 79.1; H 5.6; N 9.7%.

1-Methyl-2-diethylaminomethylperimidine (IIIc). A mixture of 0.5 g (2.16 mmole) of 1-methyl-2-chloromethylperimidine and 0.66 ml (6.48 mmole) of diethylamine in 12 ml of ethanol was refluxed for 2 h, after which the solution was concentrated to 2 ml, and the precipitated crystals were separated and washed with a small amount of cold methanol. The light-yellow needles had mp 112-113°C (from methanol). The yield of the crude product was 0.59 g (100%), while the yield of the purified product was 0.35 g (59%). R_f 0.61 (Al_2O_3) and 0.62 (Silufol). IR spectrum ($CHCl_3$): 1580 (C=C), 1625 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 0.96 (t, 6H, $\mathbf{CH_3}$-CH_2), 2.53 (q, 4H, $CH_3\mathbf{CH_2}$), 3.15 (s, 3H, CH_3), 3.28 (s, 2H, CH_2), 6.06 (q, 1H, 9-H), 6.25

(q, 1H, 4-H), 7.09 ppm (m, 4H, 5 to 8-H). Found: C 76.0; H 7.9; N 15.4%. $C_{17}H_{21}N_3$. Calculated: C 76.4; H 7.9; N 15.7%.

1-Methyl-2-(N-piperidino)methylperimidine (IIId). This compound was obtained from 0.5 g of II and 0.44 ml of piperidine by a method similar to that used to prepare IIIc. The light-yellow needles had mp 130-132°C (from methanol). The yield of the crude product was 0.55 g (92%), while the yield of the purified product was 0.36 g (60%). R_f 0.64 (Al_2O_3) and 0.66 (Silufol). IR spectrum ($CHCl_3$) 1585 (C=C), 1625 cm^{-1} (C=N). PMR spectrum ($CDCl_3$) 1.39 (m, 6H, β- and γ-CH_2), 2.43 (m, 4H, α-CH_2), 3.21 (s, 5H, CH_3, CH_2), 6.13 (q, 1H, 9-H), 6.75 (q, 1H, 4-H), 7.08 (m, 4H, 5 to 8-H). Found: C 76.8; H 7.6; N 14.7%. $C_{18}H_{22}N_3$. Calculated: C 77.1; H 7.9; N 15.0%.

1-Methyl-2-cyanomethylperimidine (IIIe). A solution of 0.12 g (2.49 mmole) of sodium cyanide in 2 ml of DMSO was added dropwise to a solution of 0.5 g of II in 3 ml of DMSO. The color of the solution changed from orange to yellow almost immediately. The mixture was stirred for 20 min at 20°C, after which it was poured into 100 ml of water. The precipitated light-yellow flakes were removed by filtration, washed with water, and air dried. The yield of the crude product was 0.48 g (100%). It was dissolved in the minimum amount of acetone, and the solution was passed through a column packed with aluminum oxide (elution with acetone) with collection of the first yellow fraction. The substance was purified by preparative TLC on aluminum oxide (elution with chloroform) with collection of the second pale-yellow fraction. The pale-yellow crystals, which gradually darkened on heating above 160°C, melted with decomposition at 192-193°C and had R_f 0.51 (Al_2O_3, chloroform), 0.60 (Al_2O_3, acetone), and 0.74 (Silufol). IR spectrum (mineral oil): 1610, 1640 cm^{-1} (C=C), 2190 cm^{-1} (C≡N). PMR spectrum (d_6-DMSO): 3.35 (s, 3H, CH_3), 3.40 (s, 1H =CHCN), 4.46 (s, 1H, NH), 6.40 (q, 1H, 9-H), 6.95 (q, 1H, 4-H), 7.43 ppm (m, 4H, 5 to 8-H). The singlets at 3.40 and 4.46 ppm vanished after deuteration. Found: C 76.0; H 5.4; N 19.8%. $C_{14}H_{11}N_3$. Calculated: C 76.0; H 5.0; N 19.0%.

Reaction of N,N'-Dimethyl-1,8-diaminonaphthalene with Cyanoacetic Ester. A mixture of 0.5 g (2.69 mmole) of N,N'-dimethyl-1,8-diaminonaphthalene and 0.4 g (3.5 mmole) of cyanoacetic ester was heated at 150°C for 20 min, after which the resulting melt was cooled and treated with 3 ml of diethyl ether. The crystals were removed by filtration, washed on the filter with a mixture of 2 ml of diethyl ether and 1 ml of hexane, and air dried. The yield of chromatographically pure 1,3-dimethyl-2-perimidone was 81%. The colorless needles had mp 208-209°C (mp 209°C [10]). The only aliphatic signal in the PMR spectrum (d_6-DMSO) was found at 2.98 ppm (s, 6H, N-CH_3).

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