HETEROCYCLIC ANALOGS OF PLEIADIENE.

48.* PYROSULFITE AS A MILD DEHYDROGENATING AGENT IN THE 2,3-DIHYDROPERIMIDINE SERIES. SYNTHESIS OF 2-POLYHYDROXYALKYLPERIMIDINES

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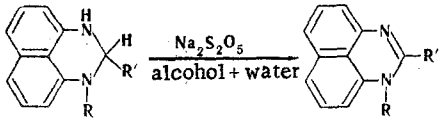
2,3-Dihydroperimidines are dehydrogenated smoothly by sodium pyrosulfite in refluxing aqueous alcohol, as a result of which the corresponding perimidines are formed in high yields. The reaction of 1,8-naphthalenediamine with the aldehydic forms of sugars gives 2-polyhydroxyalkyl-2,3-dihydroperimidines, which are also aromatized by sodium pyrosulfite to give the corresponding 2-polyhydroxyalkylperimidines in high yields.

In 1965 Ridley and co-workers [2] found that the corresponding 2-substituted benzimidazoles and perimidines rather than the expected 2,3-dihydro derivatives are formed in high yields when o-phenylenediamine or 1.8-naphthalenediamine is heated briefly with the bisulfite adducts of aldehydes. It was assumed [2] that the intermediately formed benzimidazolines and 2,3-dihydroperimidines are oxidized during the reaction by the bisulfite ion to give the aromatized structures. Bisulfites are also of interest to biochemists [3], since they oxidize coenzyme NAD–H to NAD^+. However, the dehydrogenating properties of the bisulfite ion have not yet been studied. We do not know of any studies in which bisulfites have been used for the preparative oxidation of genuine dihydro derivatives of heterocycles. With respect to the mechanism of the reaction, there are contradictory data on the conversion of bisulfite in the case of reduction by organic compounds to thiosulfate and dithionate ions [4] or dithionite ion [5]. It has also been assumed [3] that the reaction is a free-radical process that takes place with the participation of air oxygen and a superoxide anion radical, during which the bisulfite ion is actually a catalyst (an electron carrier).

The aim of the present research was to study the dehydrogenating capacity of bisulfites in the 2,3-dihydroperimidine (I) series, since most of the methods for dehydrogenation of them (with sulfur [6], palladium on carbon [7, 8], and chloranil or manganese dioxide [9]) require relatively severe conditions and do not always proceed sufficiently smoothly. This makes it impossible to use them for the dehydrogenation of compounds that contain labile and easily oxidized substituents. In addition, the synthesis of only one perimidine derivative (2-phenylperimidine) [2] has been described, and the dehydrogenation of genuine 2,3-dehydroperimidines has not been studied at all.

Instead of bisulfite we used sodium pyrosulfite ($Na_2S_2O_5$, SPS), which is easier to use. The reaction was carried out by refluxing an aqueous alcohol solution of equimolar amounts of I and SPS. The results of experiments involving the dehydrogenation of various 2,3-dehydroperimidines with SPS are presented in Table 1.

Both 2,3-dihydroperimidine itself and its 2-substituted derivatives with alkyl, phenyl, or π-surplus heteroaromatic (2-furyl, 2-thienyl, 1-methyl-2-benzimidazolyl, etc.) groups as substituents undergo quantitative dehydrogenation in ∿2 h under the indicated conditions.



I II

*See [1] for Communication 47.

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TABLE 1. Dehydrogenation of 2,3-Dihydroperimidines with Sodium Pyrosulfite

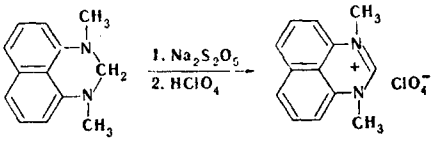
Type of compound, I or II[a]	R′	Reaction time, h	Compounds II	
			yield, %	mp, °C
a	H	2	95	225—226 [10]
b	CH_3	2	90	215—216 (dec.) [11]
c	C_6H_5	2	98	187—188 [12]
d	4-$CH_3OC_6H_4$	0,5	98	212—213 [13]
e	2-Furyl	2	97	178—179 [7]
f	2-Thienyl	2	98	165—166 [14]
g	1-Methyl-2-benzimidazolyl	2	95	202—203 [14]
h	2-$NO_2C_6H_4$	10	0	177—178 [15]
i	3-$NO_2C_6H_4$	10	0	184 (dec.) [15]
j	4-$NO_2C_6H_4$	10	0	180 (dec.) [15]
k	5-Nitro-2-furyl	10	0	330 (dec.) [14]
l	D-Glucopentahydroxypentyl	1	94	192—193
m	D-Glactopentahydroxypentyl	1	98	202 (dec.)
n	L-Arabinotetrahydroxybutyl	1	98	198—199
o	D-Mannopentahydroxypentyl	10	0[b]	—
p	H	1,5	80	120—121 [10]
q	H	10	95	110 [16]
r	C_6H_5	15	78	174—175 [17]
s	2-Furyl	30	80	146—147 [8]
t	4-$(CH_3)_2NC_6H_4$	30	90	242—243 [18]
u	C_6H_5	10	0	232—234 [18]
v	2-Furyl	10	0	166—167 [18]
w	2-Thienyl	10	0	—
x	4-$NO_2C_6H_4$	10	0	—

[a]For I and IIa-o, R = H; p, r, s, and x, R = CH_3; q, t, u, v, and w, R = C_6H_5. [b]Dihydroperimidine Io could not be aromatized, since it is insoluble in aqueous alcohol.

When electron-donor groups (for example, p-methoxy) are introduced in the phenyl substituent, the reaction is accelerated and is complete in 30 min. It was shown in the case of isomeric 2-(o-, m-, and p-nitrophenyl)-2,3-dihydroperimidines and 2-(5-nitro-2-furyl)-2,3-dihydroperimidine that the introduction of a nitro group in the substituent in the 2 position inhibits oxidation completely.

N-Substituted 2,3-dihydroperimidines are also dehydrogenated by SPS. Thus 1-methyl-2,3-dihydroperimidine (Ip) reacts with SPS just as readily as 2-phenyl-2,3-dihydroperimidine (Ic). 1-Phenyl-2,3-dihydroperimidine (Iq) is dehydrogenated completely in 10 h. The reduced hydride lability of this compound is explained by the electron-acceptor effect of the N-phenyl group in the perimidine system [19]. Dehydrogenation is hindered markedly when substituents are present simultaneously in the 1 and 2 positions of the dihydroperimidines. Thus 1-methyl-2-phenyl- (Ir) and 1-methyl-2-(2-furyl)-2,3-dihydroperimidine (Is) are oxidized by SPS, and the products are obtained in 80% yields in 15 and 30 h, respectively, whereas the 1-phenyl derivatives of 2-phenyl- (Iu), 2-(2-furyl)- (Iv), and 2-(2-thienyl)-2,3-dihydroperimidine (Iw), as well as 1,3-dimethyl-2-phenyl-2,3-dihydroperimidine, are not dehydrogenated by SPS at an appreciable rate. Both steric and electronic factors probably constitute the reason for this passivation. In fact, 1-phenyl-2-(p-dimethylaminophenyl)-2,3-dihydroperimidine (It), as a consequence of the electron-donor effect of the dimethylamino group, is capable of dehydrogenation, although the reaction proceeds slowly (the degree of reaction is 90% after 30 h). Compounds Ir, s, x were obtained by reaction of N-methyl-1,8-naphthalenediamine with the corresponding aldehydes in alcohol; we have previously reported our failure to realize these reactions with N-methyl-1,8-naphthalenediamine under somewhat different conditions [18].

The dehydrogenation of 1,3-dimethyl-2,3-dihydroperimidine (III) goes to completion only when excess SPS is used. This is evidently explained by the fact that the resulting cation (IV) itself is readily reduced to III (the transformation products of SPS may be reducing agents), and it is necessary to use excess SPS to shift the equilibrium to the right.



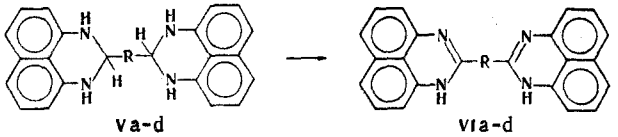
III IV

A great advantage of SPS is the exceptional ease with which the reaction takes place: as a rule, the reaction is not complicated by side processes, and the resulting perimidines do not require additional purification for most purposes. The reason for this is evidently the constant presence in the reaction mixture of mild reducing agents (SPS, bisulfite, dithionite ions, etc.), which inhibit the more profound oxidation processes that are characteristic for perimidines. This fact makes SPS an indispensable reagent for the synthesis of perimidines that contain readily oxidized groups, particularly polyhydroxyalkyl groups. Thus for the first time we have accomplished the synthesis of 2-polyhydroxyalkylperimidines (IIℓ-n) by oxidation with SPS of 2-polyhydroxyalkyl-2,3-dihydroperimidines (Iℓ-n), which also were previously unknown. Their preparation is accomplished by reaction of 1,8-naphthalenediamine with monosaccharides (D-glucose, D-galactose, D-mannose, and L-arabinose) in the presence of a small amount of acetic acid. The reaction does not take place at an appreciable rate without the addition of the acid, since monosaccharides exist in the unreactive cyclic form under these conditions. 1,8-Naphthalenediamine reacts unambiguously with saccharides, while ortho-substituted diamines such as o-phenylenediamine under the same conditions give a mixture of three types of substances: Schiff bases, polyhydroxyalkylquinoxalines, and 2-polyhydroxyalkylbenzimidazoles [20].

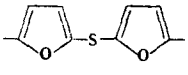
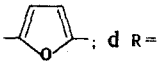
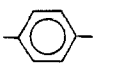
A weak positive Cotton effect at 330-340 nm is observed in the circular dichroism spectra of 2,3-dihydroperimidines (Iℓ-n). The small amplitude of the effect is explained by free rotation of the heteroring. The configuration of the $C_{(1)}$ atom in the polyhydroxyalkyl group of the compounds is the same.

The use of SPS also proved to be convenient in a number of other cases, as, for example, in the preparation of 2,2'-diperimidinyl (VIa) from the previously described [21] 2,3,2',3'-tetrahydro-2,2'-diperimidinyl (Va). Although the oxidation of Va proceeds relatively slowly (VIa is obtained in 75% yield after 10 h), the purity of the reaction product is of a degree that is unattainable when other methods are used to synthesize VIa. In view of the low solubility of VIa, this is an extremely important fact, since it is difficult to free it from impurities by crystallization. Compound Vb is dehydrogenated by SPS with approximately the same ease; however, we were unable to aromatize 2,5-bis(2,3-dihydro-2-perimidinyl)furan (Vc) and 1,4-bis(2,3-dihydro-2-perimidinyl)benzene (Vd) under these conditions. Their dehydrogenation to VIc,d was accomplished by means of sulfur.

The difference in the behavior of Vb and Vc with respect to SPS is evidently due to the fact that the hydride lability in the former is increased by the donor effect of the sulfur atom.



Va-d VIa-d

V-VIa R = a single bond; b R =  ; c R =  ; d R = 

Thus, this research has shown that SPS is a mild and effective agent for the oxidation of many 2,3-dihydroperimidines. Its use in conjunction with other dehydrogenating agents makes the reaction of 1,8-naphthalenediamines with aldehydes a virtually universal method for the synthesis of various 2-substituted perimidines.

EXPERIMENTAL

The UV spectra of solutions of the compounds in methanol were recorded with an SF-16 spectrophotometer. The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer.

Compounds Ia-k, p-r, t-w were described in [9, 14, 21, 22]; the constants for the new substances are presented in Table 2.

1,4-Bis(2,3-dihydro-2-perimidinyl)benzene (Vd). A saturated alcohol solution of 0.7 g (5 mmole) of 1,4-diformylbenzene was added to a solution of 1.6 g (10 mmole) of 1,8-naphthalenediamine in 20 ml of alcohol, and the resulting solution was maintained at room temperature for 3 h. The precipitated crystals of Vd were removed by filtration, washed with a small amount of alcohol, and crystallized. Compound Vc (Table 2) was similarly obtained.

TABLE 2. New 2,3-Dihydroperimidines I and V and Perimidines II and VI

Compound	mp, °C*	ν_{N-H}, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
Il	150—151	3430, 3380	60,0	6,2	8,9	$C_{16}H_{20}N_2O_5$	60,0	6,3	8,7	94
Im	171—172	3450—2400	60,0	6,4	9,0	$C_{16}H_{20}N_2O_5$	60,0	6,3	8,7	95
In	160—161	3430, 3380	62,1	6,4	10,0	$C_{15}H_{18}N_2O_4$	62,1	6,2	9,6	95
Io	201—202	3490, 3420, 3300	60,2	6,3	9,1	$C_{16}H_{20}N_2O_5$	60,0	6,3	8,7	95
Ix	173—174	3390	70,9	4,8	14,0	$C_{18}H_{15}N_3O_2$	70,8	4,9	13,8	77
Vc	221—222	3380	77,1	4,8	14,0	$C_{26}H_{20}N_4O$	77,2	5,0	13,8	95
Vd	222—224	3360, 3340	81,5	5,5	13,6	$C_{28}H_{22}N_4$	81,1	5,3	13,5	75
III	192—193	3360	60,5	5,6	8,8	$C_{16}H_{18}N_2O_5$	60,4	5,7	8,8	94
IIm	202—203	3400—2400	60,6	5,7	9,0	$C_{16}H_{18}N_2O_5$	60,4	5,7	8,8	98
IIn	198—199	3400, 3260	62,6	5,4	9,5	$C_{15}H_{16}N_2O_4$	62,5	5,5	9,7	98
VIc	350	3300—2100	77,7	4,0	14,1	$C_{26}H_{16}N_4O$	78,0	4,0	14,0	95
VId	265 (dec.)	3300—2100	81,8	4,4	13,7	$C_{28}H_{18}N_4$	81,9	4,4	13,7	92

*The compounds were crystallized: II*l* from aqueous alcohol, Ix, IIm,n, and Vc, d from alcohol, I*l*-n from water, Io from acetic acid, VIc from aqueous acetone, and VId from ethyl acetate.

1-Methyl-2-(p-nitrophenyl)-2,3-dihydroperimidine (Ix). This compound was similarly obtained from N-methyl-1,8-naphthalenediamine and p-nitrobenzaldehyde. Compounds Ir, s were similarly obtained, but the reaction products were not isolated from the reaction mixtures.

2-Polyhydroxyalkyl-2,3-dihydroperimidines (I*l*-o). A mixture of 15.8 g (0.1 mole) of 1,8-naphthalenediamine, 0.1 mole of the monosaccharide, 200 ml of alcohol, 100 ml of water, and 1 ml of acetic acid was refluxed for 2 h, after which the solution was evaporated under reduced pressure. The crystals of I*l*-o that precipitated on cooling were removed by filtration, washed with alcohol, and dried in vacuo at 110°C.

Dehydrogenation of 2,3-Dihydroperimidines with Sodium Pyrosulfite. A mixture of 0.01 mole of the corresponding 2,3-dihydroperimidine, 1.9 g (0.01 mole) of sodium pyrosulfite, 75 ml of alcohol, and 25 ml of water was refluxed until the reaction was complete [according to monitoring by thin-layer chromatography (TLC)]. The hot solution was filtered, and the filtrate was cooled and diluted with water. The precipitated crystals were removed by filtration, washed with water, and crystallized.

Yellow-green crystals precipitated gradually in the aromatization of I*l*-n by refluxing. At the end of the heating period the crystals were removed by filtration, washed with hot water, and crystallized.

2,2'-Diperimidinyl (VIa). A mixture of 3.4 g (0.01 mole) of Va, 3.8 g (0.02 mole) of SPS, 150 ml of alcohol, and 50 ml of water was refluxed for 10 h, during which red crystals of VIa precipitated gradually. At the end of the heating period the crystals were removed by filtration and washed with hot acetone and hot water. The yield was 2.5 g (75%). IR spectrum: 3365 (N—H), 1630 (C=N), and 1600 cm^{-1} (C—C_{arom}). The bright-red crystals had mp 330°C (dec.), in agreement with the data in [12].

Bis[2-(2-perimidinyl)-5-furyl] Sulfide (VIb). A mixture of 3.2 g (0.02 mole) of 1,8-naphthalenediamine, 2.2 g (0.01 mole) of bis(2-formyl-5-furyl) sulfide [23], 3.8 g (0.02 mole) of SPS, and 150 ml of alcohol in 50 ml of water was refluxed for 10 h, during which red crystals gradually precipitated. The solution was cooled, and perimidine VIb was removed by filtration and washed with hot acetone and hot water to give 4.9 g (95%) of red crystals with mp 350°C (dec.), in agreement with the data in [6]. IR spectrum: 2100-3300 (N—H), 1640 (C=N), and 1600 cm^{-1} (C—C_{arom}).

1,3-Dimethylperimidinium Perchlorate (IV). A mixture of 2 g (0.01 mole) of 1,3-dimethyl-2,3-dihydroperimidine (III), 5.7 g (0.03 mole) of SPS, 75 ml of alcohol, and 25 ml of water was refluxed for 6 h, after which the alcohol was removed by distillation, and the residue was diluted with water to twice its original volume. Perchloric acid (5 ml) was added to the resulting solution, and the precipitated crystals of salt IV were removed by filtration, washed with water, and dried. The melting point (222°C) and IR spectrum were identical to those of an authentic sample [24].

2,5-Di(2-perimidinyl)furan (VIc). A mixture of 4 g (0.01 mole) of 2,5-bis(2,3-dihydro-2-perimidinyl)furan (Vc), 30 ml of xylene, and 0.32 g (0.01 g-atom) of sulfur was refluxed for 3 h, during which dark-red crystals of VIc precipitated gradually. At the end of the heating period the crystals were removed by filtration, washed with acetone, and crystallized. IR spectrum: 2100-3300 (N–H), 1640 (C=N), and 1600 cm^{-1} (C–C_{arom}). UV spectrum, λ_{max} (log ε): 210 (4.60); 238 (4.78); 340 (4.59); 490 nm (3.38).

1,4-Di(2-perimidinyl)benzene (VId). This compound was obtained by a method similar to that used to prepare VIc. IR spectrum: 2100-3300 (N–H), 1640 (C=N), and 1600 cm^{-1} (C–C_{arom}). UV spectrum, λ_{max} (log ε): 210 (4.71); 238 (4.77); 335 (4.55); 360 (4.35); 430 nm (5.38).

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