Preparation and Stereochemistry of Some Substituted 2,6-Diphenyl-4-aminotetrahydropyrans

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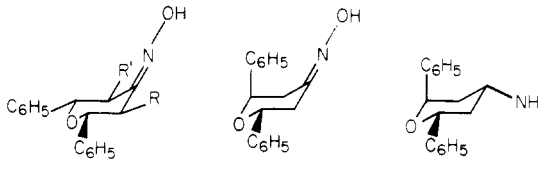
Four epimeric pairs of 2,6-diphenyl-4-aminooxanes (tetrahydropyrans) have been prepared by the reduction of oximes of 2,6-diphenyl-4-oxanones. Lithium aluminum hydride reduction of oximes affords a mixture of epimeric amines rich in the equatorially substituted isomer. The configuration and conformation of these amines are discussed in terms of ^1H NMR and ^{13}C NMR spectral analysis as well as the kinetics of the reaction of substituted 2,6-diphenyl-4-aminooxanes with 2,4-dinitrochlorobenzene. The configurations assigned to these amines are also confirmed by synthesis of the amines by a stereospecific method with pure epimeric 4-oxanols as the starting material. A tentative assignment of a possible twist arrangement was made for the oxime of *r*-2,*cis*-6-diphenyl-*trans*-3,5-dimethyl-4-oxanone on the basis of the NMR analysis.

Although the stereochemical aspects of six-membered heterocycles is an area of active interest,[2] a search of the literature did not reveal good procedures for or any stereochemical analysis of substituted oxanes (tetrahydropyrans) and particularly for 4-aminooxanes. Cornubert and Robinet[3] isolated two isomers of 2,6-diphenyl-4-oxanone but of unspecified stereochemistry. Earlier Petrenko-Kritschenko and Plotnikoff[4] had only been able to obtain the higher melting isomer. Baxter and Whiting[5] isolated *cis*- and *trans*-2,6-diphenyloxane and tentatively identified each via ^1H NMR techniques.

Vorlauder and Hobohm[6] as well as Japp and Maitland[7] reported very early that they had prepared 2,6-diphenyl-3,5-dimethyl-4-oxanone, but no stereochemistry was provided. Baxter and Whiting[5] suggested the stereochemistry to be such that all groups were attached in equatorial portions via ^1H NMR analysis. Finally, in 1972 Ziriakus and Haller[8] recorded the synthesis of isomeric 2,6-diphenylaminooxanes, but the pure compounds could not be separated. The *N*-acetyl derivatives were obtained, however.

Thus, the stereochemistry of substituted aminooxanes and the precursor thereof are virtually unknown. The present work describes our synthetic efforts for and stereochemical analysis of 4-amino-substituted derivatives of 3-alkyl- and 3,5-dialkyl-2,6-diphenyoxanes which are the first recorded in this family of heterocycles.

Synthesis of 4-Aminooxanes. Oximes can be reduced to primary amines by reduction with sodium and alcohol,[9] by catalytic reduction,[10-12] and by reduction with lithium aluminum hydride.[9-13] In the present investigation, oximes of 2,6-diphenyl-4-oxanones have been reduced by lithium aluminum hydride (LAH), and the epimeric amines obtained were separated by column chromatography over neutral alumina. The less strongly adsorbed amines (axial C–NH_2) were eluted in petroleum ether–benzene fractions, and the more strongly adsorbed amines (equatorial C–NH_2) were eluted in benzene–ether fractions. Reduction of oximes **1a,b,d** afforded a mixture of amines



1a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = C_2H_5; R′ = H
d, R = CH_3; R′ = CH_3

2 **3**

rich in the equatorial isomer. Oxime **1c** gave a mixture with a slight excess of the isomer with an axial C–NH_2 bond. Apparently, a steric factor involving the ethyl group at C(3) and LAH is in operation and promotes formation of this isomer. Reduction of the oxime **2** from *trans*-2,6-diphenyl-4-oxanone afforded single amine **3**, but since the isomer of **3** (with axial C–NH_2) can undergo ring reversal at room temperature, the result is not unexpected. *r*-2,*cis*-6-Diphenyl-*trans*-3,5-dimethyl-4-oxanone gave only one oxime, **1d**, which, on deoximation with 20% oxalic acid, yielded the starting ketone exclusively. Chromatography of **1d** over neutral alumina indicated a single compound. Consequently, epimerization of the ketone in this case at the 3,5-positions appears not to proceed under oximation conditions. The ^1H NMR spectrum of **1d** deserves comment and does suggest that the oxime may have a twist-boat conformation as shown in **4**. The oxime has two different methyl signals [δ 1.25 (d, J = 4 Hz, $CH_3C(3)$), 1.32 (d, J = 4 Hz, $CH_3C(5)$] and two different vicinal H–H couplings ($^3J_{H(2)H(3)}$ = 9 Hz and $^3J_{H(5)H(6)}$ = 6. Hz) which also differ from the normal values for J_{a-a} or J_{a-e}. The oxime **1d** may assume a twist-boat conformation to minimize the A^{1-3} strain[14-16] due to the hydroximino group. Hydrogen bonding between the OH and pyran oxygen may also stabilize such a twist-boat conformation. A similar 2,5 twist-boat conformation has been suggested for analogously constituted 1-methyl-*cis*-2,6-diphenyl-3,5-di-

(1) Taken in part from the Ph.D. Thesis of N. Chandrasekara to be submitted to the University of Madras, India.
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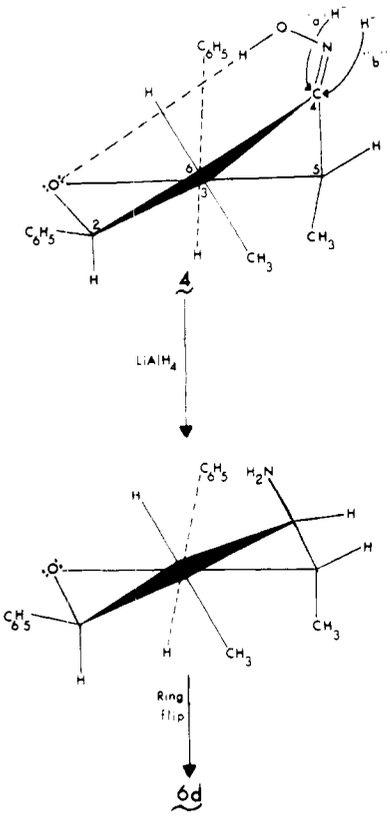

methylpiperidine-4-oxime.[17] An examination of Dreiding stereochemical models of **1d** indicates that in the twist conformation of **1d** one of the phenyl is in a pseudoaxial arrangement. This may hinder the approach of the hydride ion from the axial-like phenyl side, "a". Preferential approach of the hydride from the less hindered methyl side, "b", followed by a ring flip should lead to more (52%) of the more stable equatorial amine **6d**.

It has been reported that sodium–ethanol reduction of oximes of stereoidal ketones yields a mixture rich in the isomer with axial amino groups. In the reduction of oximes of 2,6-diphenyl-4-oxanones, transition state **4** can be envisoned and is probably predominant, giving more of the amino compound with an equatorial C–NH_2 bond. The amines synthesized, along with their physical constants, are given in Table I. The substituted 4-aminooxanes were converted into their corresponding 4-(acetylamino)oxanes by treatment with acetic anhydride in pyridine. The relevant information is also given in Table I. The compositions of the products formed from the reduction of 4-oxanone oximes with LAH are given in Table II.

Stereochemistry of 4-Aminooxanes. The two bulky phenyl groups in **5** and **6** anchor the pyran ring to a single chair conformation with the two phenyl groups bonded by equatorial C–C_6H_5 bonds. The configurations assigned to these amines were confirmed by synthesis of the amines via the stereospecific method of Bose and co-workers[18] with pure epimeric 4-oxanols as the starting materials. The amines with axial C–NH_2 bonds have been prepared from alcohols with equatorial C–OH bonds. The latter were converted into tosylates which were changed into azides (with inversion of configuration). Reduction of the azides into the corresponding amines proceeded smoothly only in ether. The amine **5a** (Scheme I), obtained from *cis*-2,*cis*-6-diphenyloxan-*r*-4$_e$-ol (equatorial OH), was found to

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Table I. Substituted 2,6-Diphenyl-4-aminooxanes and the Corresponding *N*-Acetyl Derivatives

compd	yield,[a] %	mp, °C	formula[g]
3	49	102-104[b]	$C_{17}H_{19}NO$
5a	59	101-103[b]	$C_{17}H_{19}NO$
5b	62	99-100[b]	$C_{18}H_{21}NO$
5c	60	95-97[b]	$C_{19}H_{23}NO$
5d	7	121-122[b]	$C_{19}H_{23}NO$
5e	70	181-183[c]	$C_{19}H_{21}NO_2$
5f	70	200-202[d]	$C_{20}H_{23}NO_2$
5g	68	218-220[d]	$C_{21}H_{25}NO_2$
5h	70	256-258[f]	$C_{21}H_{25}NO_2$
6a	54	54-55[b]	$C_{17}H_{19}NO$
6b	58	102-103[b]	$C_{18}H_{21}NO$
6c	40	91-93[b]	$C_{19}H_{23}NO$
6d	23	149-150[b]	$C_{19}H_{23}NO$
6e[s]	59	226-228[e]	$C_{19}H_{21}NO_2$
6f	61	116-163[d]	$C_{20}H_{23}NO_2$
6g	63	133-135[d]	$C_{21}H_{25}NO_2$
6h	43	168-170[e]	$C_{21}H_{25}NO_2$

[a] Yield based on the oxan-*r*-4-ol as starting material. [b] Recrystallized from petroleum ether (bp 60–80 °C). [c] Recrystallized from ethanol/water. [d] Recrystallized from benzene/petroleum ether (bp 60–80 °C). [e] Recrystallized from 60% ethanol. [f] Recrystallized from benzene (lit.[7] mp 219 °C). [g] Satisfactory analyses for C, H, and N were reported.

Table II. Composition of the Products from the $LiAlH_4$ Reduction of Substituted 2,6-Diphenyl-4-oxanone Oximes

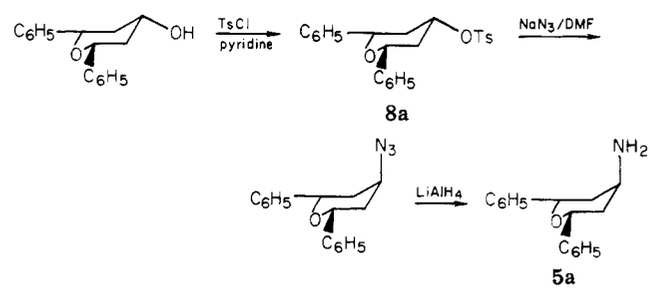
oxime reduced	% total recovery	% yield of epimeric 4-aminooxanes		
		axial	equatorial	mixture
1a	59	15	37	7
1b	72	17	39	16
1c	80	38	31	11
1d	93	30	52	11
2	49		49	

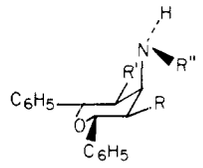
Table III. Substituted 2,6-Diphenyloxan-*r*-4-ol Tosylates

no.	oxan-*r*-ol tosylate	% yield	mp, °C	formula[c]
7a	*trans*-2,6-diphenyl	90	174-176[a] dec	$C_{24}H_{24}SO_4$
7b	*trans*-2,6-diphenyl-*cis*-3-methyl	90	133-135[a]	$C_{25}H_{26}SO_4$
7c	*trans*-2,6-diphenyl-*cis*-3-ethyl	80	140-142[a]	$C_{26}H_{28}SO_4$
7d	*trans*-2,6-diphenyl-*cis*-3,5-dimethyl	70	112-112.5[b]	$C_{26}H_{28}SO_4$
8a	*cis*-2,6-diphenyl	92	98-100[b]	$C_{24}H_{24}SO_4$
8b	*cis*-2,6-diphenyl-*trans*-3-methyl	90	139-140[a]	$C_{25}H_{26}SO_4$
8c	*cis*-2,6-diphenyl-*trans*-3-ethyl	85	109-111[a] dec	$C_{26}H_{28}SO_4$
8d	*cis*-2,6-diphenyl-*trans*-3,5-dimethyl	70	112-113.5[b]	$C_{26}H_{28}SO_4$

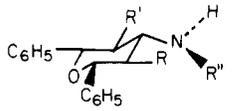
[a] Crystallized from ethanol. [b] Crystallized from ethanol/H_2O. [c] Satisfactory analyses for C, H, and S were reported.

Scheme I



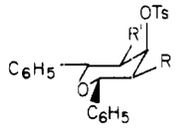


5a, R = H; R′ = H; R″ = H
b, R = CH_3; R′ = H; R″ = H
c, R = C_2H_5; R′ = H; R″ = H
d, R = CH_3; R′ = CH_3; R″ = H
e, R = H; R′ = H; R″ = $COCH_3$
f, R = CH_3; R′ = H; R″ = $COCH_3$
g, R = C_2H_5; R′ = H; R″ = $COCH_3$
h, R = CH_3; R′ = CH_3; R″ = $COCH_3$

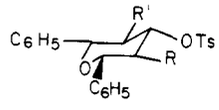


6a, R = H; R′ = H; R″ = H
b, R = CH_3; R′ = H; R″ = H
c, R = C_2H_5; R′ = H; R″ = H
d, R = CH_3; R′ = CH_3; R″ = H
e, R = H; R′ = H; R″ = $COCH_3$
f, R = CH_3; R′ = H; R″ = $COCH_3$
g, R = C_2H_5; R′ = H; R″ = $COCH_3$
h, R = CH_3; R′ = CH_3; R″ = $COCH_3$

be identical with the axial amine (obtained from petroleum ether–benzene fractions upon chromatography of the reduction ($LiAlH_4$) product of the oxime **1a**). Likewise, the amine **6a** with an equatorial C–NH_2 was obtained from *trans*-2,*trans*-6-diphenyloxan-*r*-4$_a$-ol (axial OH). The physical constants and other information on the tosylates (**7** and **8**) are given in Table III. Interestingly, when this



7a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = C_2H_5; R′ = H
d, R = CH_3; R′ = CH_3



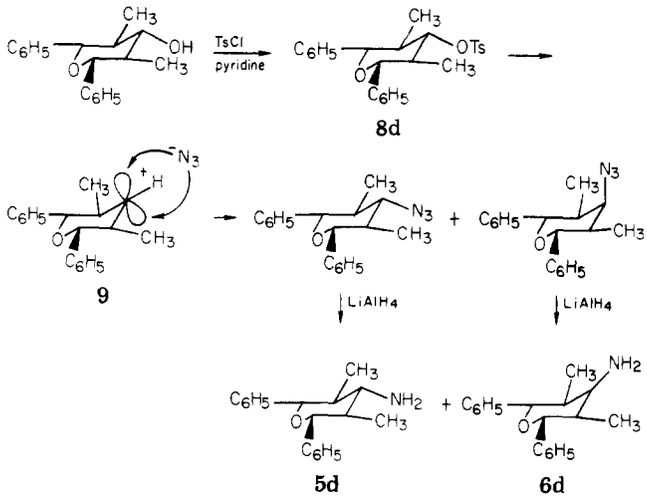
8a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = C_2H_5; R′ = H
d, R = CH_3; R′ = CH_3

reaction sequence was applied to *cis*-2,6-diphenyl-*trans*-3,5-dimethyloxan-*r*-4$_e$-ol, it afforded a mixture of amines **5d** (6.6%) and **6d** (35.47%). Possibly, the formation of carbonium ion **9** (Scheme II) occurred, and the latter was attacked by azide ion, mostly from the equatorial side. Consequently, an S_N1-type mechanism rather than an S_N2-type may operate, possibly because of increased front strain in the tosylate (between the two methyl groups and TsO) which may promote ionization. Yields of **5d** and **6d** are low, however, and the reaction mixture appears complex.

The ^1H NMR spectra of 2,6-diphenyl-4-aminooxanes **5a–d** and **6a–d** proved useful for the conformational and configurational assignments. The signals at δ 4.00 (d, J = 10 Hz) and 4.51 (dd, J = 12 Hz and 3 Hz) for **6b** correspond to the H(2) and H(6) protons, repectively. The observed large coupling constants $^3J_{H(2)H(3)}$ for **6b** suggest that the phenyl and methyl groups are in equatorial positions. The coupling constants of 12 and 3 Hz for $^3J_{H(6)_aH(5)_a}$ and $^3J_{H(6)_aH(5)_e}$, respectively, are typical of vicinal coupling constants in the rigid chair conformation and suggest that the H(6) proton is in an axial position. The ^1H NMR spectral signals of protons H(2) and H(6) in **5b,c** and **6c** are quite similar to those of **6b**, suggesting that 3-alkyl-substituted 4-aminooxanes have similar chair conformations.

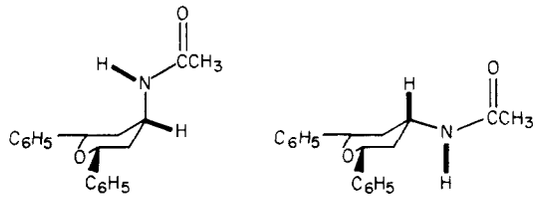
The ^1H NMR data of the epimeric 4-aminooxanes are given in Table IV. The assignment of the configuration of the amino group may be obtained from the chemical shift data of the H(4) proton. The H(4) proton of the system with an equatorial C–NH_2 bond is shielded to a

Scheme II



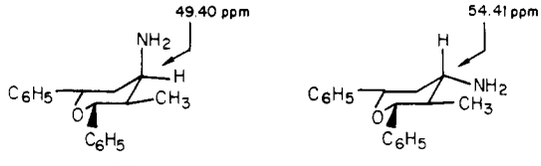
greater extent than the H(4) proton of the axial amine. It is also interesting to note from Table IV that the half-widths[19] of the H(4) proton signal in the axial amines **5a–d** are 8, 6, 6, and 5 Hz, respectively, as compared with 24, 25, 25, and 20 Hz, respectively, for the corresponding equatorial epimers (with axial protons).

The NH proton signals of the 4-(acetylamino)oxanes appear as a doublet (J = 7–10 Hz) in each case and may suggest a trans arrangement[8] for H(4) and N(H)C(O)CH_3 as shown (**5e** and **6e**). Although ^{13}C chemical shift data



5e 6e

of substituted heterocyclic alcohols are reported,[20] there is no literature available on the ^{13}C chemical shift of heterocyclic primary amines. The ^{13}C chemical shifts of the epimeric 4-aminooxanes studied in the present investigation are given in Table V. To the best of our knowledge these data are the first on epimeric 4-aminooxanes. An inspection of Table V reveals that the shielding of C(4) in epimeric 4-aminooxanes depends largely upon the configuration of the amino group. An axial amino group shields the carbon bearing the amino group by about 4–5 ppm. Hence ^{13}C chemical shift differences can be employed for the successful assignment of the configuration of the amino function (see **5b** and **6b**).



5b 6b

The effect of methyl substitution on the methyl bearing carbon resonance has been noted in methylcyclohexanes,[21]

(19) For a general review of the significance in assigning proton signals from an axial or equatorial C–H bond, see L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Oxford, 1969, Chapter 4-2.
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Table IV. ^{1}H NMR Data (δ) for Substituted 2,6-Diphenyl-4-aminooxanes and Corresponding 4-(Acetylamino)oxanes

compd	H(2)	H(3)	H(4)	H(5)	H(6)	others
3	5.33 (d, J = 5 Hz)	1.24–2.76 (m, 6 H, H(3), H(5), NH_2)	2.93–3.28 (m, $w_{1/2}$ = 28 Hz)		4.46 (dd, J = 3, 12 Hz)	7.18–7.56 (m, 10 H, ArH)
5a	4.98 (dd, J = 4, 11 Hz, 2 H, H(2), H(6))	1.53–2.00 (m, 4 H, H(3), H(5))	3.38–3.57 (m, $w_{1/2}$ = 8 Hz)			1.27 (s, 2 H, NH_2), 7.08–7.50 (m, 10 H, ArH)
5b	4.59 (d, J = 10 Hz)	1.68–2.14 (m, 3 H, H(3), H(5))	3.18–3.35 (m, $w_{1/2}$ = 6 Hz)		4.97 (dd, J = 3, 11 Hz)	0.64 (d, 3 H, CH_3, J = 7 Hz), 1.24 (s, 2 H, NH_2), 7.06–7.48 (m, 10 H, ArH)
5c	4.59 (d, J = 10 Hz)	1.46–2.12 (m, 3 H, H(3), H(5))	3.33–3.50 (m, $w_{1/2}$ = 6 Hz)		4.96 (dd, J = 4, 10 Hz)	0.67 (t, 3 H, CH_3, J = 6 Hz), 0.81–1.08 (m, 2 H, $CHCH_3$), 1.12 (s, 2 H, NH_2), 6.96–7.58 (m, 10 H, ArH)
5d	4.59 (d, J = 11 Hz, 2 H, H(2), H(6))	1.80–2.22 (m, 2 H, H(3), H(5))	2.96–3.20 (m, $w_{1/2}$ = 8 Hz)			0.66 (d, 6 H, CH_3, J = 7 Hz), 1.07 (s, 2 H, NH_2), 7.01–7.52 (m, 10 H, ArH)
5e	4.80 (dd, J = 3, 11 Hz, 2 H, H(2), H(6))	1.62–2.24 (m, 4 H, H(3), H(5))	4.24–4.59 (m, $w_{1/2}$ = 14 Hz)			1.94 (s, 3 H, $COCH_3$), 6.80 (d, 1 H, NH, J = 9 Hz), 7.02–7.46 (m, 10 H, ArH)
5f	4.42 (d, J = 10 Hz)	1.72–2.22 (m, 3 H, H(3), H(5))	4.25–4.64 (m, overlapped with H(2))		4.77 (dd, J = 4, 10 Hz)	0.66 (d, 3 H, CH_3, J = 7 Hz), 2.15 (s, 3 H, $COCH_3$), 6.99 (d, 1 H, NH, J = 8 Hz), 7.09–7.56 (m, 10 H, ArH)
5g	4.44 (d, J = 10 Hz)	1.64–2.30 (m, 3 H, H(3), H(5))	4.36–4.86 (m, overlapped with H(2))		4.76 (dd, J = 3, 11 Hz)	0.7 (t, 3 H, CH_3, J = 6 Hz), 0.84–1.18 (m, 2 H, CH_2CH_3), 6.73 (d, 1 H, NH, J = 10 Hz), 7.01–7.44 (m, 10 H, ArH)
5h	4.25 (d, J = 10 Hz, 2 H, H(2), H(6))	1.80–2.44 (m, 2 H, H(3), H(5))	4.40–4.72 (m, $w_{1/2}$ = 12 Hz)			0.68 (d, 6 H, CH_3, J = 8 Hz), 2.18 (s, 3 H, $C(O)CH_3$), 6.06 (d, 1 H, NH, J = 12 Hz), 7.14–7.46 (m, 10 H, ArH)
6a	4.57 (dd, J = 3, 11 Hz, 2 H, H(2), H(6))	1.18–2.26 (m, 4 H, H(3), H(5))	3.01–3.36 (m, $w_{1/2}$ = 24 Hz)			1.34 (s, 2 H, NH_2), 7.20–7.50 (m, 10 H, ArH)
6b	4.00 (d, J = 10 Hz)	1.90–2.16 (m)	2.48–2.78 (m, $w_{1/2}$ = 25 Hz)	1.23–1.69 (m)	4.51 (dd, J = 3, 12 Hz)	0.70 (d, 3 H, CH_3, J = 7 Hz), 1.13 (s, 2 H, NH_2), 7.05–7.43 (m, 10 H, ArH)
6c	4.23 (d, J = 10 Hz)	1.86–2.16 (m)	2.74–3.08 (m, $w_{1/2}$ = 25 Hz)	1.47–1.69 (m)	4.50 (dd, J = 2, 11 Hz)	0.67 (t, 3 H, CH_3, J = 8 Hz), 1.11 (s, 2 H, NH_2), 1.20–1.46 (m, 2 H, CH_2CH_3), 7.06–7.48 (m, 10 H, ArH)
6d	4.06 (d, J = 11 Hz, 2 H, H(2), H(6))	1.34–1.78 (m, 2 H, H(3), H(5))	2.23 (t, J = 10 Hz, $w_{1/2}$ = 20 Hz)			0.73 (d, 6 H, CH_3, J = 7 Hz), 1.10 (s, 2 H, NH_2), 7.04–7.44 (m, 10 H, ArH)
6e	4.64 (dd, J = 2, 11 Hz, 2 H, H(2), H(6))	2.10–2.40 (m, 2 H, $H(3)_e$, $H(5)_e$)	4.12–4.52 (m, $w_{1/2}$ = 36 Hz)	1.20–1.64 (m, 2 H, $H(3)_a$, $H(5)_a$)		1.94 (s, 3 H, $COCH_3$), 5.50 (d, 1 H, NH, J = 9 Hz), 7.02–7.46 (m, 10 H, ArH)
6f	4.14 (d, J = 9 Hz)	2.02–2.30 (m)	3.86–4.24 (overlapped with H(2))	1.34–1.86 (m)	4.6 (dd, J = 2, 11 Hz)	0.69 (d, 3 H, CH_3, J = 6 Hz), 1.94 (s, 3 H, $COCH_3$), 6.05 (d, 1 H, NH, J = 9 Hz), 7.10–7.63 (m, 10 H, ArH)
6g	4.34 (d, J = 10 Hz)	2.09–2.42 (m)	4.02–4.44 (overlapped with H(2))	1.40–1.79 (m)	4.56 (dd, J = 2, 11 Hz)	0.69 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.00–1.40 (m, 2 H, CH_2CH_3), 2.93 (s, 3 H, $COCH_3$), 5.96 (d, 1 H, NH, J = 9 Hz), 7.04–7.62 (m, 10 H, ArH)
6h	4.19 (d, J = 10 Hz, 2 H, H(2), H(6))	1.44–2.21 (m, 2 H, H(3), H(5))	3.60–3.94 (m, $w_{1/2}$ = 15 Hz)			0.70 (d, 6 H, CH_3, J = 7 Hz), 2.00 (s, 3 H, $COCH_3$), 5.80 (d, 1 H, NH, J = 10 Hz), 7.06–7.44 (m, 10 H, ArH)

Table V. ^{13}C Chemical Shifts (δ) for Substituted 2,6-Diphenyl-4-aminooxanes and Corresponding 4-(Acetylamine)oxanes

compd	C(2)	C(3)	C(4)	C(5)	C(6)	others
3	73.66	36.63	44.18		71.60	Ar, 142.19, 140.10, 128.40, 128.16, 127.23, 126.73, 126.39, 125.80
5a	73.39	40.62	44.30			Ar, 143.10, 127.90, 126.81, 125.54
5b	79.60	42.62	49.40	40.55	73.24	CH_3, 14.24; Ar, 127.93, 127.86, 127.29, 127.08, 126.85, 125.64
5c	79.26	44.28	46.84	42.54	73.13	CH_2CH_3, 10.68; CH_2CH_3, 19.88; Ar, 143.08, 141.67, 127.85, 127.26, 126.79, 125.60
5d	79.34	42.54	54.77			CH_3, 14.50; Ar, 141.53, 127.95, 127.34, 127.17
5e	74.58	37.41	43.92			$COCH_3$, 23.40; C=O, 169.92; Ar, 142.09, 128.11, 127.23, 125.51
5f	80.92	39.62	47.83	39.17	74.29	CH_3, 13.83; $COCH_3$, 23.43; C=O, 170.07; Ar, 141.82, 140.40, 127.96, 127.61, 127.06, 126.83, 125.39
5g	80.54	44.18	45.40	39.53	74.33	CH_2CH_3, 10.83; CH_2CH_3, 20.16; $COCH_3$, 23.47; C=O, 169.80; Ar, 141.85, 140.56, 127.99, 127.67, 127.03, 125.42
5h	81.14	41.05	52.14			CH_3, 13.68; $C(O)CH_3$, 23.31; C=O, 170.33; Ar, 140.12, 127.98, 127.63, 126.84
6a	78.51	44.21	48.97			Ar, 142.36, 128.09, 127.15, 125.64
6b	85.17	45.52	54.41	43.89	78.35	CH_3, 13.40; Ar, 127.92, 127.87, 127.38, 127.26, 126.98, 125.51
6c	82.73	50.44	50.58	44.25	78.34	CH_2CH_3, 9.56; CH_2CH_3, 19.13; Ar, 142.33, 140,82, 127.96, 127.49, 127.30, 126.99, 125.55
6d	85.28	45.11	60.63			CH_3, 14.03; Ar, 141.00, 127.88, 127.39, 127.24
6e	78.26	40.45	46.75			$COCH_3$, 23.44; C=O, 169.10; Ar, 141.91, 128.19, 127.35, 125.57
6f	85.38	42.74	51.80	41.13	78.22	CH_3, 13.65; $COCH_3$, 23.25; C=O, 169.48; Ar, 141.64, 140.24, 128.01, 127.71, 127.11, 125.36
6g	83.04	47.59	48.64	41.58	78.17	CH_2CH_3, 9.90; CH_2CH_3, 19.70; $COCH_3$, 23.40; C=O, 169.39; Ar, 141.79, 140.36, 128.19, 128.10, 127.87, 127.26, 125.47
6h	85.53	43.80	57.66			CH_3, 13.92; $COCH_3$, 23.11; C=O, 169.88; Ar, 140.47, 128.02, 127.66, 127.14

in certain 1-hetera-2,6-diaryl-4-cyclohexanones[20] and in 1-hetera-2,6-diaryl-4-cyclohexanols.[20] A downfield shift of 1–2 ppm (Table V) is observed for C(3) in **5b**, **6b**, **5d**, and **6d** compared with the corresponding signals in the 3-substituted compounds **5a** and **6a**. The presence of a methyl group causes a large β effect of 6–7 ppm (compared with 3-unsubstituted ones) in all methyl-substituted 4-aminooxans. For example, a downfield shift of 6.66 ppm is observed for C(2) in **6b** compared to the corresponding carbon signal for C(2) in **6a**. Similarly C(2) of **5b** is shielded by 6.21 ppm. The C(4) resonance in **6b** is also shifted downfield by 5 ppm compared to the C(4) signal in **6a**. Interestingly, this effect of a methyl group on the C(4) resonance positions seems to be roughly additive. For example, on comparison of **6a** with **6b** and **6d**, differences of 5.44 and 11.46 ppm, respectively, are noted for the C(4) resonances. It is noteworthy that the additivity of the methyl group effect was detected in certain 1-hetera-4-cyclohexanols.[20] Similarly, differences of 5.10 and 10.47 ppm are observed when **5a** is compared with **5b** and **5d**, respectively.

Conversion of the 4-aminooxanes into the corresponding *N*-acetyl derivatives causes an upfield shift of the C(4), C(3), and C(5) carbon resonances. This is presumably due to increased steric crowding around the C(4), C(3), and C(5) carbons.

In the present investigation the configuration of the 4-aminooxanes was also corroborated by the kinetics of the reaction of 2,4-dinitrochlorobenzene with substituted 2,6-diphenyl-4-aminooxanes. The reaction follows second-order kinetics, as shown by the constancy of the second-order rate constants within the individual runs and the near constancy of rate constants determined at different concentrations of the 4-aminooxanes. The rate constants at 50 °C for four epimeric pairs of 2,6-diphenyl-4-aminooxanes are given in Table VI. The reaction of a primary amine with 2,4-dinitrochlorobenzene is known to proceed by a nucleophilic bimolecular substitution process.[23] Any steric crowding of groups around nitrogen would increase the energy of the activated state and lower the rate constants. Comparison of second-order rate constants of a series of 4-aminooxanes should reveal the effect of 3-alkyl substituents. Inspection of Table VI indicates that for a given epimeric series the rate follows the order unsubstituted > methyl > ethyl > 3,5-dimethyl.

Table VI. Second-Order Rate Constants for the Reaction of Substituted 2,6-Diphenyl-4-Aminooxanes with 2,4-Dinitrochlorobenzene in 80% Dioxane at 50 °C

compd	$10^4 k_2$, L mol^{-1} s^{-1}	compd	$10^4 k_2$, L mol^{-1} s^{-1}
5a	7.78 ± 0.03	6a	5.65 ± 0.01
5b	2.52 ± 0.01	6b	2.35 ± 0.01
5c	1.56 ± 0.01	6c	1.64 ± 0.02
5d	0.39 ± 0.01	6d	0.42 ± 0.01

Amines **5a** and **5b** with axial C–NH_2 bonds react at a slightly faster rate than the corresponding equatorial epimers **6a** and **6b**. Eliel and co-workers reported a similar order of reactivity for the reaction of 2,4-dinitrochlorobenzene with epimeric *cis*- and *trans*-4-*tert*-butylcyclohexylamines.[23] The lower rate of the equatorial epimer compared with the axial epimer may be attributed to a greater solvation of the nitrogen lone pair in the equatorial epimer. In the axial epimer the nitrogen lone pair is relatively unsolvated and may be available for substitution reactions.

The almost identical rate constants for *trans*-2,*trans*-6-diphenyl-*cis*-3-ethyl-*r*-4-aminooxane (**5c**; $k_2 = 1.56 \times 10^{-4}$ L mol^{-1} s^{-1}) and *cis*-2,*cis*-6-diphenyl-*trans*-3-ethyl-*r*-4-

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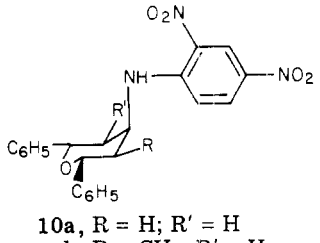
Table VII. Substituted 2,6-Diphenyl-*N*-(2,4-dinitrophenyl)-4-aminooxanes

no.	*N*-(2,4-dinitrophenyl)-*r*-4-aminooxan	% yield	mp, °C	formula[b]
10a	*trans*-2,6-diphenyl	33.3	212–214[a]	$C_{23}H_{21}N_3O_5$
10b	*trans*-2,6-diphenyl-*cis*-3-methyl	41.6	186–188[a]	$C_{24}H_{23}N_3O_5$
10c	*trans*-2,6-diphenyl-*cis*-3-ethyl	38.9	194–196[a]	$C_{25}H_{25}N_3O_5$
10d	*trans*-2,6-diphenyl-*cis*-3,5-dimethyl	39.4	258–260[a]	$C_{25}H_{25}N_3O_5$
11a	*cis*-2,6-diphenyl	33.6	205–207[a]	$C_{23}H_{21}N_3O_5$
11b	*cis*-2,6-diphenyl-*trans*-3-methyl	41.1	196–197[a]	$C_{24}H_{23}N_3O_5$
11c	*cis*-2,6-diphenyl-*trans*-3-ethyl	39.5	196–198[a]	$C_{25}H_{25}N_3O_5$
11d	*cis*-2,6-diphenyl-*trans*-3,5-dimethyl	33.4	264–266[a]	$C_{25}H_{25}N_3O_5$

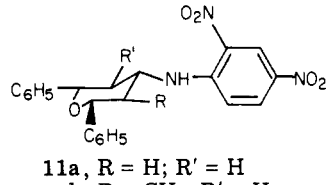
[a] Recrystallized from absolute ethanol. [b] Satisfactory analyses for C, H and N were reported.

aminooxane (**6c**; $k_2 = 1.64 \times 10^{-4}$ L mol^{-1} s^{-1}) hint that a steric effect in the axial isomer **5c** is more important than solvation. A similar trend is also observed for *trans*-2,-*trans*-6-diphenyl-*cis*-3,*cis*-5-dimethyl-*r*-4-aminooxane (**5d**) and its equatorial epimer **6d**.

The primary amines were also characterized by their *N*-(2,4-dinitrophenyl) derivatives **10** and **11**. The pertinent information on these compounds is given in Table VII.



10a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = C_2H_5; R′ = H
d, R = CH_3; R′ = CH_3



11a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = C_2H_5; R′ = H
d, R = CH_3; R′ = CH_3

Experimental Section

General Data. Melting points were determined with a BOETIUS micro heating table and were uncorrected. Proton magnetic resonance spectra were obtained on a Varian XL-100(15) high-resolution NMR spectrometer (with a time-averaging computer accessory, C-1024) operating at 100.0 MHz and have been expressed in δ values relative to internal standard Me_4Si. Proton-noise-decoupled ^{13}C NMR spectra were recorded at 25.2 MHz on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 Fourier transform accessory. Chemical shift data encompassing a 5000-Hz spectral region were collected into 8K data points. Single-frequency, off-resonance ^{13}C spectra were obtained by irradiation with a continuous-wave frequency at about δ −5 compared to Me_4Si in the proton spectrum. The analyses were performed on 0.3 and 1.0 M solutions as an internal reference at 37 °C. Assignments for ^{13}C signals have been made on the basis of signal multiplicity found in the off-resonance decoupled spectra which also revealed the magnitude of $^1J_{^{13}CH}$ couplings (which were largest for carbon attached directly to oxygen).

Preparation of Oximes of 4-Oxanones. A mixture of 1 g of the 4-oxanone, 1.5 g of hydroxylamine hydrochloride, 3.3 g of sodium acetate trihydrate, and ethanol (50 mL) was boiled for 2.5 h. The reaction mixture was then poured into water (300 mL). The precipitated oxime was filtered, washed with water, and dried.

***r*-2,*cis*-6-Diphenyl-4-oxanone Oxime (1a).** Oximation of *r*-2,*cis*-6-diphenyl-4-oxanone[5] under the usual conditions gave **1a** after recrystallization from aqueous ethanol: mp 150–151.5 °C (lit.[15] mp 144–145 °C); yield 98%.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.32; H, 6.19; N, 5.42.

***r*-2,*cis*-6-Diphenyl-*trans*-3-methyl-4-oxanone Oxime (1b).** This compound was obtained from *r*-2,*cis*-6-diphenyl-*trans*-3-methyl-4-oxanone[24] and was recrystallized from absolute ethanol: mp 204–206 °C; yield 99%.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.90; H, 7.02; N, 5.01.

***r*-2,*cis*-6-Diphenyl-*trans*-3-ethyl-4-oxanone Oxime (1c).** *r*-2,*cis*-6-Diphenyl-*trans*-3-ethyl-4-oxanone[24] gave **1c**, which was recrystallized from absolute ethanol: mp 187–189 °C; yield 98%.

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.20; H, 7.30; N, 4.92.

***r*-2,*cis*-6-Diphenyl-*trans*-3,5-dimethyl-4-oxanone Oxime (1d).** Oximation, under the standard conditions, of *r*-2-*cis*-6-diphenyl-*trans*-3,5-dimethyl-4-oxanone[24] gave an oil which solidified to **1d** upon being allowed to stand: yield 96% (recrystallized from aqueous ethanol); mp 42–42 °C; ^1H NMR ($DCCl_3$) δ 1.25 (d, 3 H, $CH_3C(5)$, J = 4.0 Hz), 1.32 (d, 3 H, $CH_3C(3)$, J = 4.0 Hz), 2.87 (t, J = 7.0 Hz, 1 H, H(5)), 3.37 (t, J = 8.0 Hz, 1 H, H(3)), 4.45 (dd overlapped to a t, J = 9.0 Hz, 1 H, H(2)), 4.53 (dd overlapped to a t, J = 6.0 Hz, 1 H, H(6)), 7.05–7.06 (m, 10 H, Ar H). In pyridine-d_5, the signals are at essentially the same positions except the pseudotriplet at δ 4.6–4.8 is separated into two doublets with J = 4.0 and 6.0 Hz. Thus, the conformation may change slightly in pyridine-d_5, but the coupling values are, nevertheless, abnormal compared with those expected for a nearly perfect chair form.

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.42; H, 7.31; N, 4.82.

***r*-2,*trans*-6-Diphenyl-4-oxanone Oxime (2).** *r*-2,*trans*-6-Diphenyl-4-oxanone[5] gave **2** (recrystallized from aqueous ethanol): mp 159–161 °C (lit.[3] mp 154 °C); yield 95%.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.44; H, 6.62; N, 5.31.

Reduction of 4-Oxanone Oximes with Lithium Aluminum Hydride. To a well-stirred slurry of LAH (0.05 mol) in dry tetrahydrofuran (30 mL) was added dropwise a solution of 4-oxanone oxime (0.01 mol) in dry tetrahydrofuran (45 mL). The mixture was stirred under relfux for 8 h. Excess hydride was carefully destroyed by the dropwise addition of ice-cold water. The resultant mixture was extracted with ether (4 × 30 mL), and the ethereal solution was dried (Na_2SO_4). Evaporation of the ether left a light yellow viscous oil. This crude product was subjected to chromatography.

Chromatographic Separation of the Mixture of Epimeric 4-Aminooxanes. For 1 g of the mixture of amines, 25 g of Brockman grade neutral alumina (BDH) was used. Elutions were carried out with petroleum ether (bp 60–80 °C), petroleum ether–benzene (1:1), benzene, benzene–ether (1:1), and ether in the order given. Six fractions of 25 mL were collected for each eluant, and the solvent was removed on a water bath. The contents of each flask was triturated with 1 mL of petroleum ether (bp 60–80 °C) and left overnight, whereupon solidification occurred. The yield and melting point of each solid from each fraction were determined. The fractions melting at the same temperature were collected and purified by crystallization from a suitable solvent. The amines with an axial C–NH_2 bond were obtained from petroleum ether–benzene and benzene eluates whereas the equatorially substituted isomers were obtained from benzene–ether and ether eluates. The details are given in Table II.

Preparation of *p*-Toluenesulfonates. *cis*-2,6-Diphenyloxan-*r*-4-ol, *cis*-2,6-diphenyl-*trans*-3-methyloxan-*r*-ol, *cis*-2,6-diphenyl-*trans*-3-ethyloxan-*r*-4-ol, *cis*-2,6-diphenyl-*trans*-3,5-dimethyloxan-*r*-4-ol, *trans*-2,6-diphenyloxan-*r*-4-ol, *trans*-2,6-diphenyl-*cis*-3-methyloxan-*r*-4-ol, *trans*-2,6-diphenyl-*cis*-3-ethyloxan-*r*-4-ol, and *trans*-2,6-diphenyl-*cis*-3,5-dimethyloxan-*r*-4-ol were synthesized by previously described methods.[24] A solution of the oxan-4-ol (0.04 mol) in dry pyridine (30 mL) was mixed with a solution of *p*-toluenesulfonyl chloride (0.08 mol) in 40 mL of pyridine at 0 °C. The solution was allowed to stand for 2 days at room temperature, was then poured over crushed ice, and was left overnight. The precipitated tosylate was filtered, washed with

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water, dried, and crystallized from a suitable solvent. The details are furnished in Table III.

Conversion of Tosylates into Amines. A solution of the tosylate (0.03 mol) and sodium azide (22.3 g, 0.34 mol) in dimethylformamide (120 mL) and water (20 mL) was heated to 75–85 °C with stirring for 10 h. The mixture was diluted with water and extracted with ether (4 × 50 mL). The ethereal layer was washed with a saturated solution of sodium chloride (3 × 50 mL) and water and dried (Na_2SO_4). The solvent was then removed under vacuum, and the residue was taken up in dry ether (50 mL) and added, in the course of 20 min, to a slurry of lithium aluminum hydride (3 g, 0.08 mol) in ether (60 mL) with stirring. The mixture was stirred under reflux for 6 h. Excess hydride was carefully destroyed with wet ether, and the resultant mixture was extracted with ether (4 × 30 mL). The combined ethereal extracts were extracted with 1:2 H_2O–HCl (4 × 25 mL). When the aqueous layer was basified with 1:1 H_2O–ammonia, a solid separated and was filtered, washed with water, dried, and recrystallized from a suitable solvent. The details are given in Table I.

***N*-Acetyl Derivatives of the 4-Aminooxanes.** To a solution of the 4-aminooxane (0.004 mol) in pyridine (3 mL) was added acetic anhydride (1 mL, 0.009 mol), and the solution was heated on a water bath for 4 h and poured onto crushed ice. The *N*-acetyl derivative was recrystallized from a suitable solvent. The details are given in Table I. This general procedure was used for the preparation of other related compounds.

Preparation of Substituted 2,6-Diphenyl-*N*-(2,4-dinitrophenyl)-4-aminooxanes. To a solution of the 4-aminooxane (0.004 mol) in 90% ethanol (5 mL) was added 2,4-dinitrochlorobenzene (0.97 g, 0.005 mol), and the solution was boiled on a water bath for 6 h. When the mixture cooled the derivative of the amine crystallized, was filtered and washed with cold ethanol (10 mL), and was then recrystallized from a suitable solvent. Relevant details are given in Table VII.

Kinetic Procedure. The pure 4-aminooxanes were dried in vacuo before use. The 2,4-dinitrochlorobenzene was also dried before use. Dioxane was purified as mentioned in the literature,[25] and 80% dioxane was used as the solvent.

The rate was followed conductometrically.[26] The concentration of the amine was maintained at twice the concentration of 2,4-dinitrochlorobenzene in order to trap the HCl formed during the reaction. Solutions of the selected amine (0.4 mol) and 2,4-dinitrochlorobenzene (0.2 mol) were prepared and thermostated at 50 °C. Equal volumes (2 mL) of the solutions were mixed in the conductance cell. Immediately after mixing, the conductance was recorded as was also done at appropriate time intervals. The infinity readings were measured after the reaction mixture had been kept in the conductance cell at 75 °C for 72 h. The rate constant k_2 is given by eq 1, where b = the concentration of

$$k_2 = \left(\frac{1}{2tb}\right)\left(\frac{C_t - C_0F}{C_\infty - C_tF}\right) \quad (1)$$

2,4-dinitrochlorobenzene in moles/liter, C_0 = the initial conductance, C_t = the conductance at the time t, and C_∞ = the conductance at infinite time.

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Registry No. **1a**, 28144-10-7; **1b**, 74854-67-4; **1c**, 74854-68-5; **1d**, 74854-69-6; **2**, 18458-73-6; **3**, 74854-70-9; **5a**, 74854-71-0; **5b**, 74854-72-1; **5c**, 74854-73-2; **5d**, 74854-74-3; **5e**, 74854-75-4; **5f**, 74854-76-5; **5g**, 74854-77-6; **5h**, 74854-78-7; **6a**, 74854-79-8; **6b**, 74854-80-1; **6c**, 74854-81-2; **6d**, 74854-82-3; **6e**, 38132-31-9; **6f**, 74854-83-4; **6g**, 74854-84-5; **6h**, 74854-85-6; **7a**, 74854-86-7; **7b**, 74854-87-8; **7c**, 74854-88-9; **7d**, 74854-89-0; **8a**, 74854-90-3; **8b**, 74854-91-4; **8c**, 74854-92-5; **8d**, 74854-93-6; **10a**, 74854-94-7; **10b**, 74854-95-8; **10c**, 74854-96-9; **10d**, 74854-97-0; **11a**, 74854-98-1; **11b**, 74892-12-9; **11c**, 74854-99-2; **11d**, 74855-00-8; *r*-2,*cis*-6-diphenyl-4-oxanone, 18458-71-4; *r*-2,*cis*-6-diphenyl-*trans*-3-methyl-4-oxanone, 68226-08-4; *r*-2-*cis*-6-diphenyl-*trans*-3-ethyl-4-oxanone, 68226-10-8; *r*-2-*cis*-6-diphenyl-*trans*-3,5-dimethyl-4-oxanone, 68226-09-5; *r*-2-*trans*-6-diphenyl-4-oxanone, 18458-72-5; *cis*-2,6-diphenyloxan-*r*-4-ol, 65042-30-0; *cis*-2,6-diphenyl-*trans*-3-methyloxan-*r*-4-ol, 69291-48-1; *cis*-2,6-diphenyl-*trans*-3-ethyloxan-*r*-4-ol, 69291-49-2; *cis*-2,6-diphenyl-*trans*-3,5-dimethyloxan-*r*-4-ol, 69291-50-5; *trans*-2,6-diphenyloxan-*r*-4-ol, 25830-15-3; *trans*-2,6-diphenyl-*cis*-3-methyloxan-*r*-4-ol, 69291-45-8; *trans*-2,6-diphenyl-*cis*-3-ethyloxan-*r*-4-ol, 69291-46-9; *trans*-2,6-diphenyl-*cis*-3,5-dimethyloxan-*r*-4-ol, 69291-47-0; 2,4-dinitrochlorobenzene, 97-00-7.

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