s, H). *S*-(*p*-Chlorobenzyl)thiouroium salt, mp 165–170 °C. (±)-Phenylglycine salt, mp 164–166 °C. Anal. Calcd for $C_{18}H_{27}NO_5S$: C, 58.51; H, 7.37; N, 3.79; S, 8.68. Found: C, 58.35; H, 7.51, N, 3.76; S, 8.44.

Resolution of (±)-Phenylglycine by Acid of 8b. The hydroxy sulfonate sodium salt **8b** (0.092 mol) in 90% ethanol was passed through an ion-exchange column in the acid form (ANGC-242). Evaporation of the solvent yielded the oily sulfonic acid, which was dissolved in water (90 mL), and to this was added (±)-phenylglycine (0.066 mol). The reaction mixture was heated and filtered and the filtrate was allowed to stand at room temperature overnight. Filtration gave 5.6 g of a crystalline adduct: mp 201–203 °C; $[\alpha]_D$ −48.2 ° (*c* 8.5, H_2O). Anal. Calcd for $C_{18}H_{29}NSO_6$: C, 55.79; H, 7.54; N, 3.62; S, 8.28. Found: C, 56.06; H, 7.49; N, 3.74; S, 8.03. To the adduct (2.0 g) in water (50 mL) was carefully added ammonium hydroxide to pH 8. Filtration of the resulting white plates gave (+)-phenylglycine (0.37 g): $[\alpha]_D$ +154° (1.0 N HCl) (lit.,[18] 158.6 ± 0.8°); sublimes 249–254 °C (lit.[18] 245–250 °C).

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Registry No.—**1,** 19902-08-0; **2,** 69239-17-4; **2** *S*-(*p*-chlorobenzyl)thiouronium salt, 69239-19-6; **3,** 6153-17-9; **4a,** 6909-30-4; **4b,** 4680-25-5; **5a,** 69239-20-9; **5b,** 69239-21-0; **5b** (+)-phenylglycine salt, 69239-23-2; **6,** 69239-24-3; **6** *S*-(*p*-chlorobenzyl)thiouronium salt, 69307-88-6; **6** (±)-phenylglycine salt, 69307-89-7; **7a,** 4680-24-4; **7b,** 4959-34-6; **8a,** 69239-25-4; **8b,** 69239-26-5; **8b** free acid, 69239-27-6; **8b** (+)-phenylglycine salt, 69239-28-7; (4*R*,8*S*)-**9**, 69239-29-8; (4*R*,8*R*)**9,** 69239-30-1; **10,** 69239-31-2; **11,** 4031-57-6; **12,** 38630-75-0; (+)-limonene, 5989-27-5; (4*R*,8*R*)-limonene 8,9-oxide 28098-68-2; (4*R*,8*S*)-limonene 8,9-oxide, 28098-67-1; (±)-phenylglycine, 2835-06-5.

Supplementary Material Available: Complete ^{13}C NMR data for compounds, **2, 5, 6, 8, 9, 10, 11,** and **12** (1 page). Ordering information is given on any current masthead page.

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Synthesis and Stereochemistry of 2,6-Diphenyl-3-alkyltetrahydro-4-pyranones and the Corresponding 4-Pyranols

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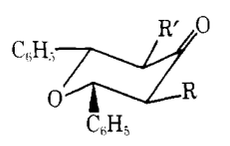
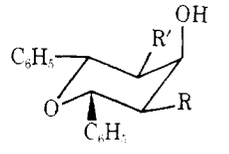
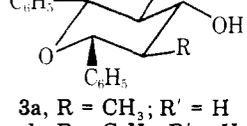
Japp and Maitland reported[1] the formation of a mixture of stereoisomeric diphenylmethyltetrahydro-4-pyranones during the condensation of benzaldehyde and 2-butanone in basic medium. However, in our hands such a condensation[2] afforded pure *r*-2,*cis*-6-diphenyl-*trans*-3-methyltetrahydro-4-pyranone (**1a**). Similarly, condensation of benzaldehyde with 2-pentanone yielded pure *r*-2,*cis*-6-diphenyl-*trans*-3-ethyltetrahydro-4-pyranone (**1b**). The structures of **1a** and **1b** were assigned primarily on the basis of ^1H NMR data. The relevant details are recorded in Table I. The ketones **1a–c** were



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



2a, R = CH_3; R′ = H
b, R = C_2H_5; R′ = H
c, R = R′ = CH_3



3a, R = CH_3; R′ = H
b, R = C_2H_5; R′ = H
c, R = R′ = CH_3

subjected to reduction with lithium aluminum hydride and with Meerwein–Ponndorf–Verley conditions. A mixture of epimeric alcohols resulted which was separated by column chromatography over alumina. The less strongly adsorbed axial alcohols were eluted in a petroleum ether–benzene mixture, and the more strongly adsorbed equatorial alcohols were eluted in benzene–ether fractions. The configuration and conformation of the pyranols were assigned on the basis of IR, ^1H NMR, and ^{13}C NMR spectral data, which are given in Tables II and III.

If a regular chair conformation is assumed for the heterocyclic ring, the two phenyl groups and the methyl group in **1a** or the ethyl group in **1b** may be expected to occupy the stable equatorial positions. Detailed information on the stereochemistry of 4-pyranones **1a** and **1b** can be gleaned from their ^1H NMR spectra. The signals at δ 4.33 (d, J = 11 Hz) and 4.81 (d, J = 10 and 5 Hz) for **1a** correspond to H(2) and H(6) protons, respectively. The observed large coupling constant

0022-3263/79/1944-1559$01.00/0

Table I. IR and ^{1}H NMR Data for Tetrahydro-4-pyranones[a,c]

compd	mp,[b] °C	yield, %	IR C=O stretch, cm^{-1}	δ, ppm H(2)	H(3)	H(5)	H(6)	other
1a	82–83	14	1697	4.33 (d, J = 11 Hz	2.60–2.82 (m)		4.81 (dd, J = 5, 10, Hz)	0.86 (d, 3 H, CH_3, J = 6 Hz), 7.20–7.50 (m, 10 H, Ar–H)
1b	104–105	12	1694	4.45 (d, J = 11 Hz)	2.54–2.83 (m)		4.79 (dd, J = 5, 10 Hz)	0.78 (t, 3 H, $-CH_2CH_3$, J = 7 Hz), 0.99–1.75 (m, 2 H, $-CH_2CH_3$), 7.20–7.52 (m, 10 H, Ar–H)

[a] ^{13}C Chemical shift data will be reported elsewhere.[7] [b] Solvent of crystallization: **1a** (methanol); **1b** (ethanol). [c] Abbreviations used: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet.

Table II. IR and ^{1}H NMR Data for Tetrahydro-4-pyranols

compd	mp,[a] °C	yield,[b] %	IR C-O stretch, cm^{-1}	δ, ppm H(2)	H(3)	H(4)	H(5)	H(6)	other
2a	88–89	44	1021	4.6 (d, J = 10 Hz	1.80–2.12 (m)	4.08 (b s, $W_{1/2}$ = 7 Hz)		5.00 (dd J = 5, 10 Hz)	0.74 (d, 3 H, CH_3, J = 7 Hz), 1.67 (b s, 1 H, OH), 7.18–7.52 (m, 10 H, Ar–H)
2b	123–125	42	1026	4.61 (d, J = 10 Hz)	1.50–1.70 (m)	4.18–4.24 (b m, $W_{1/2}$ = 10 Hz)	1.88–2.18 (m)	4.98 (dd, J = 3, 10 Hz)	0.72 (t, 3 H, $-CH_2CH_3$, J = 7 H), 0.9–1.4 (m, 2 H, $-CH_2CH_3$), 1.74 (b s, 1 H, OH), 7.18–7.48 (m, 10 H, Ar–H)
2c	129–130	59	1010	4.55 (d, J = 10 Hz)	1.80–2.12 (m)	3.68–3.82 (m, $W_{1/2}$ = 7 Hz)			0.78 (d, 6 H, C-2 CH_3, C-6 CH_3, J = 7 Hz), 1.78 (s, 1 H, OH), 7.15–7.44 (m, 10 H, Ar–H)
3a	100–101	67	1042	4.04 (d, J = 10 Hz	1.50–1.70 (m)	3.30–3.70 (m, $W_{1/2}$ = 26 Hz)	2.10–2.31 (m)	4.56 (dd, J = 3, 10 Hz)	0.77 (d, 3 H, CH_3, J = 6 Hz), 1.75 (s, 1 H, OH), 7.12–7.44 (m, 10 H, Ar–H)
3b	92–94	71	1040	4.2 (d, J = 10 Hz)	1.44–2.32 (m)	3.62–4.00 (b m, $W_{1/2}$ = 24 Hz)		4.49 (dd, J = 3, 12 Hz)	0.68 (t, 3 H, $-CH_2CH_3$, J = 7 Hz), 1.12–1.42 (m, 2 H, $-CH_2CH_3$), 1.98 (b s, 1 H, OH), 7.16–7.52 (m, 10 H, Ar–H)
3c	121–122	51	1040	4.09 (d, J = 10 Hz)	1.60–1.92 (m)	3.03–3.30 ($W_{1/2}$ = 20 Hz)			0.80 (d, 6 H, C-2 CH_3, C-6 CH_3, J = 6 Hz), 1.94 (s, 1 H, OH), 7.18–7.48 (m, 10 H, Ar–H)

[a] All pyranols were crystallized from petroleum ether (60–80 °C). [b] Yields for **2a, 2b,** and **2c** are based on MPV reduction; for **3a, 3b,** and **3c** the yields are based on $LiAlH_4$ reduction. Elemental analysis data were as follows. **1a** Found: C, 81.03; H, 6.79. Calcd: C, 81.19; H, 6.81. **1b** Found: C, 81.53; H, 7.17. Calcd: C, 81.37; H, 7.19. **1c** Found: C, 81.25, H, 7.21. Calcd: C, 81.37; H, 7.19. **2a** Found: C, 80.78; H, 7.55. Calcd: C, 80.60; H, 7.52. **2b** Found: C, 80.62; H, 7.82. Calcd: C, 80.81; H, 7.85. **2c** Found: C, 81.02; H, 7.89. Calcd: C, 80.81; H, 7.85. **3a** Found: C, 80.79; H, 7.55. Calcd: C, 80.60; H, 7.52. **3b** Found: C, 80.99; H, 7.84. Calcd: C, 80.81; H, 7.85. **3c** Found: C, 80.65; H, 7.87. Calcd: C, 80.81; H, 7.85.

Table III. ^{13}C Chemical Shifts (δ) for Tetrahydro-4-pyranols

compd	C(2)	C(3)	C(4)	C(5)	C(6)	other
2a[a]	80.18	42.20	69.40	41.14	73.66	CH_3, 13.82; Ar, 142.73, 141.18, 128.04, 127.49, 127.35, 127.20, 127.03, 125.74
2b[a]	79.87	47.37	65.16	42.17	73.60	$-CH_2CH_3$, 10.83; $-CH_2CH_3$, 19.64; Ar, 142.78, 141.24, 128.04, 127.73, 127.49, 127.41, 127.26, 127.02, 125.74
2c	79.83	42.77	73.91	42.77	79.83	CH_3, 14.01; Ar, 141.14, 127.95, 127.40, 127.19
3a[a]	84.85	45.20	73.91	43.33	77.88	CH_3, 13.13; Ar, 141.87, 140.30, 128.09, 127.69, 127.37, 127.28, 125.70
3b[a]	82.67	50.33	70.82	43.62	78.15	$-CH_2CH_3$, 10.16; $-CH_2CH_3$, 19.46; Ar, 141.87, 140.33, 128.11, 127.75, 127.46, 127.25, 125.68
3c	84.82	45.13	79.36	45.13	84.82	CH_3, 13.56; Ar, 140.38, 128.04, 127.63, 127.28

[a] The signals for the carbons other than those for the ethyl group assume four magnetically nonequivalent groups of aromatic carbons and five magnetically nonequivalent ring carbons for **2b.** The nonequivalency of some of these carbons is apparently lost in **3b**. A similar situation is apparently true in **2a** and **3a,** but neither show total nonequivalency of the carbons.

Table IV

fraction	bp, °C	compd
I	55–60	mainly unreacted benzaldehyde
II	95–111	monobenzylidene derivative
III	166–180	dibenzylidene derivative
IV	186–192	4-pyranone (**1a**)

Table V

fraction	bp, °C	compd
I	55–58	mainly unreacted benzaldehyde
II	120–126	monobenzylidene derivative
III	170–180	dibenzylidene derivative
IV	200–202	4-pyranone (**1b**)

$J_{H(2)-H(3)}$ = 11 Hz for **1a** suggests that H(2) and H(3) are diaxial and that the phenyl and methyl groups are in equatorial positions. The coupling constants of 10 and 5 Hz for $J_{H(6_a)H(5_a)}$ and $J_{H(6_a)H(5_e)}$, respectively (which are typical of vicinal coupling constants J_{anti} and J_{gauche} in the chair conformation), suggest that the proton at C(6) is in an axial position.[3] The ^1H NMR spectra of the protons at C(2) and C(6) in **1b** are quite similar to those in **1a**, suggesting that the two ketones have identical conformations.

The ^1H NMR data of the epimeric 4-pyranols are summarized in Table II. The assignment of the configuration of the hydroxyl group may be deduced from the chemical shift data of the H(4) proton. The H(4) proton of the equatorial alcohol is shielded to a greater extent than the H(4) hydrogen of the axial alcohol.[3] It can also be seen from Table II that the half-width signal for H(4) in the axial alcohols **2a, 2b,** and **2c** is 7, 10, and 7 Hz, respectively, as compared to that of 26, 24, and 20 Hz, respectively, for the corresponding equatorial epimers **3a, 3b,** and **3c.** The configuration of the 4-pyranols was also corroborated by the ^{13}C chemical shift data furnished in Table III.[4] In general, it was noted that the carbinyl carbon shielding depends largely upon the configuration of the hydroxyl group; an axial hydroxyl group shields the hydroxyl-bearing carbon by about 5 ppm. Such chemical shift differences for epimeric alicyclic alcohols have been clearly established.[5]

Experimental Section

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 are expressed in δ values, relative to internal Me_4Si. IR spectra were recorded on a Beckman-5A spectrophotometer as KBr pellets and are expressed in cm^{-1}. 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 6000-Hz spectral region were collected into 8K data points. Single-frequency, off-resonance spectra were obtained by irradiating with a continuous wave frequency at about δ −5 compared to Me_4Si in the proton spectrum. The samples were run as 0.3 and 1.5 M solutions in $DCCl_3$ containing tetramethylsilane as an internal reference. The spectra of all samples were recorded at 37 °C. Assignments have been made on the basis of signal multiplicity found in the off-resonance decoupled spectra and from the magnitude of the $^1J_{^{13}C-H}$ couplings (which were largest for carbon attached directly to oxygen).

Preparation of *r*-2,*cis*-6-Diphenyl-*trans*-3-methyltetrahydro-4-pyranone (1a). The procedure adopted was similar to that of Japp and Maitland[1] with modifications. A mixture of benzaldehyde (223 g, 2.1 mol), 2-butanone (72 g, 1 mol), ethanol (66%, 575 g, 12.5 mol), water (1080 g, 60 mol), and sodium hydroxide (10%, 80 mL, 2 mol) was vigorously stirred for 8 days. The thick yellow oily layer was washed with water and taken up in ether, and the ethereal solution was dried (Na_2SO_4). Evaporation of the solvent gave a residue which was fractionated under reduced pressure (2–3 mm), whereupon the fractions listed in Table IV were collected. The final fraction (bp 186–192 °C) solidified upon standing. Crystallization (methanol) gave shining crystals of **1a** (38 g, 14%), mp 82–83 °C.[1]

Preparation of *r*-2,*cis*-6-Diphenyl-*trans*-3-ethyltetrahydro-4-pyranone (1b). Condensation of benzaldehyde (2.2 mol) with 2-pentanone (1 mol) via the above procedure yielded a residue which on fractionation under reduced pressure (2–3 mm) gave the fractions listed in Table V. The final fraction (bp 200–202 °C) solidified upon standing. Crystallization (ethanol) gave shining crystals of **1b** (35 g, 12%), mp 104–105 °C.

The method of Japp and Maitland[1] was followed for the preparation of **1c,** mp 111–112 °C.

General Procedure for Reductions. Lithium Aluminum Hydride Reduction. To a well-stirred slurry of lithium aluminum hydride (0.6 g, 0.016 mol) in dry ether was added dropwise a solution of 0.03 mol of 4-pyranone in dry ether (150 mL). The mixture was heated under reflux for about 6–8 h and then allowed to stand overnight. Excess hydride was carefully destroyed by the dropwise addition of ethyl acetate. The resultant mixture was neutralized (1:3 HCl–H_2O, 15 mL) and extracted (ether). The ether extract was washed with a saturated solution of $NaHCO_3$ and dried (Na_2SO_4). The epimeric mixture of 4-pyranols, obtained after evaporation of the ether, was subjected to chromatography over alumina with benzene–petroleum ether (bp 60–80 °C) as the solvent system in the procedure described below.

Meerwein–Ponndorf–Verley Reduction. The procedure described in the literature[6] was followed, but with a slight modification. The 4-pyranone (0.03 mol) was placed in 175–200 mL of dry 2-propanol. A solution of 5.019 g of aluminum isopropoxide (0.02 mol) in 10 mL of dry 2-propanol was added to the solution of the ketone, and the mixture was boiled for 4–6 h. Most of the solvent was distilled off, and the residue was acidified with 1:1 HCl–H_2O (50 mL) and extracted (ether). The ethereal portion was washed with saturated $NaHCO_3$ solution and dried (Na_2SO_4). The epimeric mixture of 4-pyranols, obtained after removal of the ether, was subjected to chromatography as described below.

Chromatographic Separation of Mixture of Epimeric 4-Pyranols. For 1 g of the mixture of alcohols, 20 g of neutral alumina (BDH, active) was used. The mixture of alcohols was dissolved in a minimum amount of cold benzene and added to the prepared column of alumina. 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 25-mL fractions were collected for each eluant. The solvent was removed on a water bath. The contents of each flask were triturated with 1–2 mL of petroleum ether (60–80 °C) and left overnight, whereupon solidification occurred. The melting point of the solid from each flask was determined, and fractions melting at the same temperature were collected and purified by crystallization from a suitable solvent. The axial alcohols were obtained from petroleum ether–benzene eluates and the equatorial alcohols from the benzene–ether eluates. The yield, melting point, and solvent of crystallization of the 4-pyranols are recorded in Table II.

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Registry No.—**1a,** 68226-09-4; **1b,** 68226-10-8; **1c,** 68226-09-5; **2a,** 69291-45-8; **2b,** 69291-46-9; **2c,** 69291-47-0; **3a,** 69291-48-1; **3b,** 69291-49-2; **3c,** 69291-50-5; benzaldehyde, 100-52-7; 2-butanone, 78-93-3; 2-pentanone, 107-87-9.

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Cyanoimine Chemistry: New Routes to Pyrimidinones and (Carbonylamino)-iminopropanamides

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We have investigated the chemistry of 2,4-diamino-6-piperidinopyrimidine 3-oxide, a hypotensive compound.[1] We now report the synthesis of related *N*-alkylpyrimidinones and the preparation of substituted ureas. Pyrimidinones in which particular nitrogens are alkylated are often prepared with difficulty. The direct alkylation of 2-amino-4-hydroxypyrimidines is ambiguous because of multiple sites of possible alkylation.[2] Similarly, condensation route to *N*-alkyl-2-amino-4-hydroxypyrimidines which employ substituted guanidines can in principle give either of two possible products.[3] 3-(Cyanimino)propionic systems are useful precursors of various pyrimidines.[4] We now report their intermediacy in the preparation of *N*-alkylpyrimidinones and complex ureas of clearly defined structure.

N-Alkyl-3-imino-3-ethoxypropanamide hydrochlorides (**2**) are readily prepared from the corresponding *N*-alkyl-2-cyanoacetamides, ethanol, and hydrogen chloride (step 1, Scheme I). Amides of structure **2** react with cyanamide in toluene or methylene chloride (step 2) to yield *N*-alkyl-3-(cyanimino)-3-ethoxypropanamides (**3**). Secondary amines readily displace ethanol from compound **3** to produce *N*-alkyl-3-(cyanimino)-3-(alkylamino)propanamides of structure **4** (step 3).

Amides of structure **4** are versatile intermediates. These 3-(cyanimino)propanamides, when reacted with 2 or more equivalents of potassium *tert*-butoxide, yield 2-amino-3-alkyl-6-(alkylamino)-4-pyrimidinones of structure **5** (step 4). Similarly, *N*-*n*-butyl-3-(cyanimino)-3-ethoxypropanamide, when treated with 2 equiv of base, yields 2-amino-3-*n*-butyl-6-ethoxy-4-pyrimidinone (**6**) (step 5).

Base-mediated intramolecular cyclizations of amides on nitriles are reported in the art.[5] For example, *N*-phenyl-*N'*-(*o*-cyanophenyl)urea, when treated with sodium methoxide, affords 3-phenyl-4-(3*H*)-imino-2(1*H*)-quinazolone.[6]

N-Alkyl-3-[(aminocarbonyl)imino]-3-(alkylamino)propanamides of structure **7** can be prepared by hydrolysis of 3-(cyanimino)propanamide **4** with concentrated hydrochloric acid in acetic acid (Scheme I, step 6).

Scheme I

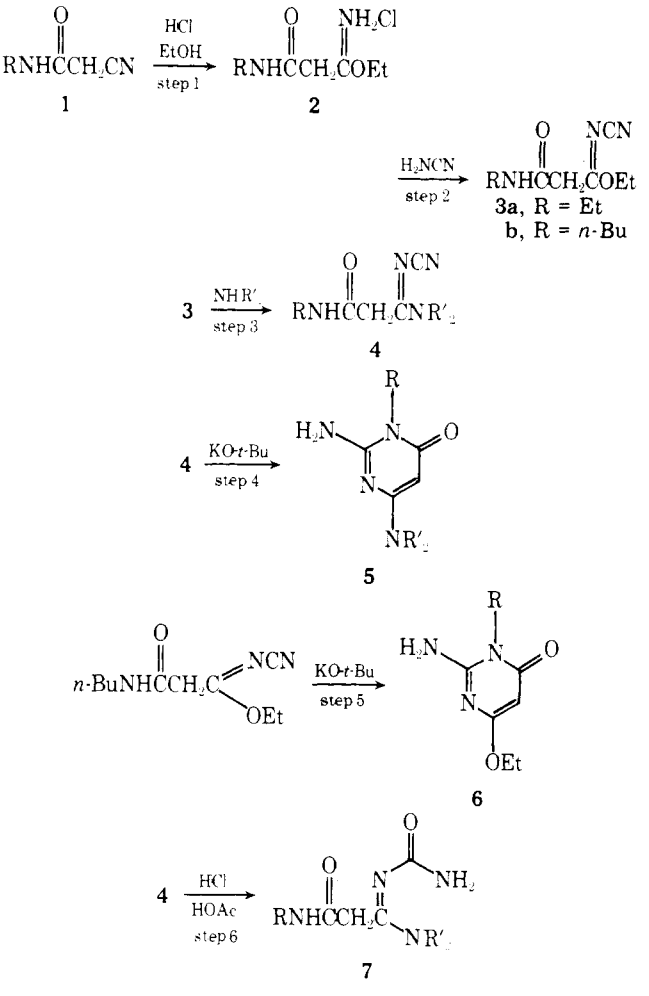

Table I

compd[a]	R	NR^1_2	yield of **4**, %	mp, °C	yield of **5**, %	mp, °C	yield of **7**, %	mp, °C
a	Et		87	117–118.5[d,i]	87	276–277[e]	89	126–127.5[e,j]
b	Et		84	188–189.5[d]	58	240–241[e]	52	115–115.5[f,g]
c	*n*-Bu		88.7	oil[b]	77	197–198[g]	52	133–141[h]
d	*n*-Bu		38	105–110[c,f]	47	195–196.5[g]	77	109–110[g]
e	*n*-Bu	NEt_2	44	oil[b]	77	120–120.5[g]	72	164–165.5[g]

[a] Unless otherwise noted, these compounds gave satisfactory elemental analyses (±0.4% C, N, N). [b] Not analyzed. [c] Sublimation point. [d] Crystallized from toluene. [e] Crystallized from ethyl acetate. [f] Crystallized from methylene chloride/cyclohexane. [g] Crystallized from ethyl acetate/cyclohexane. [h] From ethyl acetate. [i] C analysis is 0.78 off. [j] N analysis is 0.47 off.

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