Synthesis of 2,9β-Dimethyl-6,7-benzomorphan[1]

Tokuro Oh-ishi,[2] Arthur E. Jacobson, Raymond S. Wilson, Herman J. C. Yeh, and Everette L. May*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20034

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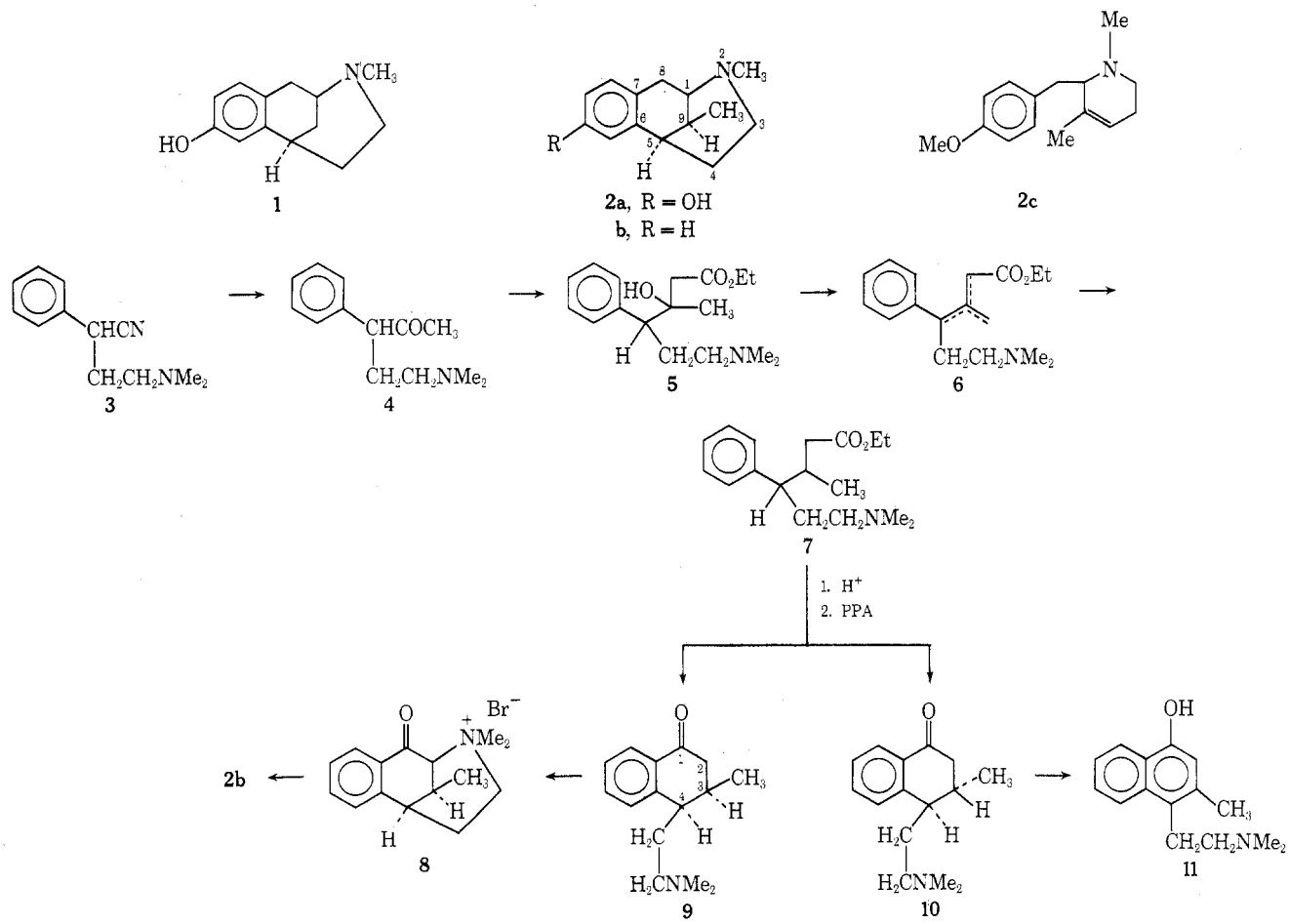
2,9β-Dimethyl-6,7-benzomorphan (**2b**) has been synthesized in 12 steps from phenylacetonitrile. The structure and configuration of **2b** and α-tetralone precursors **8** and **9** were deduced mainly from nmr data. Quaternization-rate studies with **2b** also indicated the 9β-methyl[1b] configuration. A diastereomeric (to **9**) α-tetralone, **10**, gave, instead of the expected 2,9α-dimethyl-6,7-benzomorphan, 4-(2-dimethylaminoethyl)-3-methyl-1-naphthol (**11**), obtained also as a by-product in the preparation of **8**. Compound **2b** has appreciable analgesic activity.

2′-Hydroxy-2-methyl-6,7-benzomorphan (**1**, without a quaternary carbon)[3] and its optical isomers are analgesics of moderate activity which possess, as well, properties of antagonism to narcotics.[4] Because of the demonstrated enhancing effect of a 9-methyl substituent on the analgesic activity of 2,5-dimethyl-2′-hydroxy-6,7-benzomorphan[5] we wished to examine the 9-methyl homolog (**2a**) of **1**. Attempts to synthesize **2a** by cyclization[6] of the appropriate tetrahydropyridine [in this case 1,3-dimethyl-2-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridine (**2c**)],[7] the usual route to 6,7-benzomorphans, failed. A 12-step sequence for the deoxy congener, **2b**, of **2a** has been developed and is described below.



Reformatsky product, **5**, was obtained in 50% overall yield by dimethylaminoethylation of phenylacetonitrile ($NaNH_2$), Grignard reaction (MeMgI) on the resultant **3**, and reaction of **4** with $BrZnCH_2CO_2Et$. Dehydration of **5** (*p*-TsOH–H_2O, refluxing C_6H_6, 1 week) afforded a mixture of olefins (90%) whose nmr spectrum did not rule out any of the structures indicated by **6** and which was reduced quantitatively to a mixture of diastereoisomers (**7**) with Pd. Hydrolysis of **7** with 6 *N* HCl and cyclization of the acid with polyphosphoric acid (PPA) at 100–110° gave a mixture of tetralones in 71% yield, separated as their HBr salts into **9** and **10** (4:1 ratio).

Bromination of **9** in acetic acid and neutralization of the resultant HBr salt with NH_4OH gave benzomorphan methobromide (**8**, 58%) and a low yield of the 1-naphthol **11**. Similar treatment of **10** gave no benzomorphan, simply aromatization to **11** (61%). Benzomorphan **2b** resulted (in 90% yield) from extrusion of MeBr from **8** (triethylene glycol, 195–200°) and subsequent Wolff-Kishner reduction.

The C-9 methyl protons of **2b** displayed their chemical shift at δ 1.32 (d, J = 7 Hz), typical of the 9β-methyl[1b] protons of 6,7-benzomorphans; the 9α-methyl signals are

known to appear about 0.8 ppm.[8] Further, the rate of formation of the methiodide **2b** approximated that of the 9β series. Thus, less than 15% of the base had reacted with methyl iodide during 24 hr (the 9α series generally shows 90–100% reaction in 24 hr).[8] The nmr spectrum of **8** indicated a definite downfield shift of the methyl group (δ 1.56) from that in **2b**, as might be expected from the deshielding effect of the ammonium cation, owing to its proximity to this methyl.

As **9** (not **10**) gave **8**, **9** must be the cis compound; only the cis isomer can cyclize to a 9β-methyl benzomorphan. The nmr data for **9** did not prove its cis stereochemistry. The spectrum of **9** shows a methyl group at δ 1.08 (d, J = 7 Hz). Decoupling of this C-3 methyl group from the C-3 proton clearly showed the C-3 proton as a doublet at δ 2.40. The coupling constant observed due to the coupling of the C-3 and C-4 protons (J = 4 Hz) is indicative of the axial–equatorial arrangement of these protons. It is noteworthy that the C-2 protons in **9** (and **10**) did not appear in the original spectra. These protons were found to rapidly exchange with deuterium (from the D_2O solvent used). The internal standard used, sodium 3-trimethylsilylpropionate-2,2,3,3-d_4 (TSP), was found to catalyze the exchange reaction. With sodium 3-trimethylsilylpropanesulfonate as the internal standard, or a fast spectral recording of **9** containing TSP, the C-2 protons centered at δ 2.64 (m) were clearly evident.[9]

Compound **2b** appears to be as active as codeine in preliminary animal testing.

Experimental Section

Melting points (Hershberg) are corrected. Infrared data are from a Perkin-Elmer 257, mass spectra from an Hitachi RMU;6E double-focusing spectrometer at 80 eV. Nmr spectra, at 60 MHz, were obtained on a Varian A-60 (TMS or TSP at δ 0.0 ppm as internal standard, D_2O as solvent unless otherwise specified); 100-MHz nmr spectra and decoupling experiments were done on a Varian HA-100. Spin decoupling was obtained in the conventional manner. A second radiofrequency field was obtained by side-band modulation using a Hewlett-Packard oscillator.

Ethyl 6-Dimethylamino-3-methyl-4-phenylhexanoate (Diastereoisomers, 7). To phenylacetonitrile (75 g, 0.64 mol), 50 g (0.47 mol) of $Me_2NCH_2CH_2Cl$, and 200 ml of C_6H_6 was added portionwide (stirring, below 40°) 20 g (0.54 mol) of $NaNH_2$. The mixture was refluxed for 1 hr and cooled. After addition of ice-H_2O the C_6H_6 layer was extracted with 10% HCl. The acid extracts were washed with C_6H_6, made alkaline with NH_4OH, and extracted with C_6H_6. Washing (H_2O), drying,[10] and evaporating the C_6H_6 gave 80.5 g (92%) of **3**, bp 100–107° (0.2 mm),[11] ir (neat) 2240 cm^{-1} (CN).

To the Grignard reagent (1.3 mol) prepared from 180 g of MeI, 31.2 g of Mg, and 350 ml of ether was added 80.5 g (0.43 mol) of **3** in 350 ml of toluene. Ether was distilled until vapor temperature was 100°; refluxing was continued for 7 hr. After cooling, NH_4Cl and H_2O were added. The organic layer was washed with H_2O, then refluxed for 30 min with 20% HCl. The acid layer was separated, made alkaline with NH_4OH, and extracted with ether. The ether was washed with H_2O, dried,[10] and evaporated to give 86.3 g (79.5%) of **4**, bp 89–90° (0.3 mm),[12] ir (neat) 1715 cm^{-1} (C=O).

To 67 g (1.0 mol) of Zn dust was added a small amount of $BrCH_2CO_2Et$ in methylal. Addition of a few iodine crystals initiated a vigorous reaction. Additional (total 114 g, 0.7 mol) $BrCH_2CO_2Et$ in 350 ml of methylal was added dropwise so as to maintain gentle refluxing. The mixture was refluxed for an additional 30 min. To this $BrZnCH_2CO_2Et$ solution was added 23.3 g of **4** in 50 ml of methylal while keeping the temperature below 30°. The mixture was stirred at room temperature for 1 hr, then refluxed for 3 hr and poured into 10% H_2SO_4. The acid layer was washed with C_6H_6, made basic with NH_4OH, and extracted with C_6H_6. The extract was washed with H_2O, dried,[10] and distilled to give 24.3 g (73%) of **ethyl 6-dimethylamino-3-hydroxy-3-methyl-4-phenylhexanoate (5):** bp 153–155° (0.8 mm); M^+ m/e 293; ir (neat) 3500 (OH), 1730, 1715 cm^{-1} (sh, C=O).

Ester **5** (24.3 g, 0.08 mol), 31.6 g (0.17 mol) of p-TsOH·H_2O, and 300 ml of C_6H_6 were refluxed (H_2O separator) for 1 week, made alkaline with dilute NH_4OH, washed with H_2O, dried,[10] and evaporated to dryness, giving 20.7 g (91%) of **6**: bp 120–128° (0.3 mm); M^+ m/e 275; ir (neat) 1740, 1715, 1450 cm^{-1} (m).

6 (21.2 g), 100 ml of CH_3OH, and 5 g of Pd/C absorbed 1 molar equiv of H_2 during 3.5 hr to give a 95% yield of **7** (two diastereoisomers as shown by tlc): bp 127–133° (0.3 mm); M^+ m/e 277; ir (neat) 1735 cm^{-1}.

Cyclization (PPA) of 7. The **7** mixture (20.2 g) and 200 ml of 6 N HCl were refluxed for 4 hr and evaporated to dryness *in vacuo*. The residue and 200 g of PPA were kept at 100–110° for 3 hr. Ice-H_2O was added to the cooled mixture, which was then made alkaline with 40% KOH (or KOH pellets). The resultant oil was dissolved in ether, washed with H_2O, and dried.[10] Evaporation of the ether gave a fluorescent oil (13.8 g) which was distilled, yield 11.9 g (71%), bp 115–127° (0.2 mm). Treatment (in acetone) with 33% HBr–acetic acid gave crystals which were filtered and recrystallized from ethanol, giving 9.7 g (42%) of prisms of ***cis*-4-(2-dimethylaminoethyl)-3-methyl-3,4-dihydro-1(2*H*)-naphthalenone (9 HBr):** mp 197–199°; M^+ m/e 231; ir (Nujol) 2650–2400, 1665 cm^{-1}; nmr (D_2O) δ 2.90 [s, $^+N(CH_3)_2$], 7.35–7.98 (m, aromatic, 4 H).

Anal. Calcd for $C_{15}H_{22}BrNO$: C, 57.7; H, 7.1; Br, 25.6; N, 4.5. Found: C, 57.5; H, 7.1; Br, 26.2; N, 4.2.

The filtrate from the 9.7 g of **9** HBr was evaporated to dryness. The residue crystallized from acetone, giving 2.3 g (10%) of thin plates of **10** HBr (trans isomer): mp 149–152°; M^+ m/e 231; ir (Nujol) 2700–2450, 1685 (sh), 1675 cm^{-1}; nmr δ 1.02 (d, J = 7 Hz, C-3 CH_3), 2.48 (m, C-2, 2 H), 3.0 [s, $^+N(CH_3)_2$], 7.3–8.04 (m, aromatic, 4 H), decoupled from C-3 CH_3 2.52 (d, J = 3 Hz, C-3 H).

Anal. Calcd for $C_{15}H_{22}BrNO$: C, 57.7; H, 7.1; Br, 25.6; N, 4.5. Found: C, 57.8; H, 7.2; Br, 26.2; N, 4.4.

2,9β-Dimethyl-8-oxo-6,7-benzomorphan Methobromide (8).[1b] The hydrobromide (9.7 g, 0.03 mol) of **9** in 50 ml of refluxing acetic acid was treated during 20 min with 5 g (0.03 mol) of bromine in 20 ml of acetic acid. After refluxing for an additional 10 min, the solution was evaporated to dryness *in vacuo* to give a syrup which was dissolved in 100 ml of ice-H_2O and neutralized by slow addition of 12 M NH_4OH (*ca.* 4 ml) under cooling. Extraction with ether, washing (H_2O), drying,[10] and evaporation of the ether gave an oil which was dissolved in CH_3OH. Brief refluxing and evaporation to dryness gave crystals which were recrystallized from absolute C_2H_5OH to give **8** (5.6 g, 58%) as prisms: mp 221–222° dec (with frothing); ir (Nujol) 1680 cm^{-1}; nmr δ 1.56 (d, J = 7.5 Hz, C-9 CH_3), 3.05 and 3.44 [s, $N(CH_3)_2$], 4.08 (m, C-1 H), 7.45–8.10 (m, aromatic, 4 H).

Anal. Calcd for $C_{15}H_{20}BrNO$: C, 58.1; H, 6.5; Br, 25.8; N, 4.5. Found: C, 58.3; H, 6.5; Br, 25.8; N, 4.3.

The filtrate contained a mixture of **8** and **11** HBr (see below).

4-(2-Dimethylaminoethyl)-3-methyl-1-naphthol (11) Hydrobromide. As described in the preparation of **8**, 1.0 g of **10** HBr gave (after heating the base of the bromo ketone in acetone) 630 mg (61%) of the HBr salt of **11**, mp 262° dec, ir (Nujol) 3280 cm^{-1} (OH). The nmr spectrum was consistent with structure **11**.

Anal. Calcd for $C_{15}H_{20}BrNO$: C, 58.1; H, 6.5; N, 4.5. Found: C, 58.1; H, 6.2; N, 4.3.

2,9β-Dimethyl-8-oxo-6,7-benzomorphan Hydrochloride.[1b] Triethylene glycol (36 ml) and 3.6 g of **8** were kept at 195–200° for 20 min, treated with H_2O, and made basic with 12 M NH_4OH, giving an oil which was dissolved in ether. The ether was washed with water, dried,[10] and evaporated. The resultant oil was distilled (bp *ca.* 115°, bath temperature 150°), yield 2.2 g (89%), mp 74–77° (yellow rods from hexane). The HCl salt (from *i*-PrOH–HCl) melted at 225–229° dec, ir (Nujol) 1680 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}ClNO$: C, 66.8; H, 7.2; Cl, 14.1; N, 5.6. Found: C, 66.6; H, 7.1; Cl, 14.1; N, 5.5.

2,9β-Dimethyl-6,7-benzomorphan (2b) Hydrochloride. Hydrazine–H_2O (2.5 ml), 2.2 g of the 8-oxo base above, 2.5 g of KOH, and 50 ml of triethylene glycol were heated at 170–180° as low-boiling substances were distilled. Then the mixture was kept at 195–205° for 4 hr, diluted with H_2O, and extracted with ether. The ether was washed with H_2O, dried, and evaporated, giving an oil, **2b**, which was distilled evaporatively at 0.2 mm (bath temperature 140°). The 1.8 g of colorless oil was converted to the hydrochloride with MeOH–HCl. Evaporation of solvent and crystallization of the residue from *i*-PrOH gave needles (1.6 g, 66%): mp 251–255° dec; M^+ m/e 201; nmr (base, $CDCl_3$) δ 2.34 (s, NCH_3), 7.0–7.3 (m, aromatic, 4 H).

Anal. Calcd for $C_{14}H_{20}ClN$: C, 70.7; H, 8.5; Cl, 14.9; N, 5.9. Found: C, 70.7; H, 8.5; Cl, 14.7; N, 5.7.

This compound underwent quaternization with methyl iodide at a very slow rate, less than 15% of base having reacted at room temperature after 24 hr.[8]

Registry No.—**2b** HCl, 50599-89-8; **3**, 50599-78-5; **4**, 50599-79-6; **5**, 50599-80-9; **6**, 50679-04-4; **7** isomer A, 50599-87-6; **7** isomer B, 50599-88-7; **8**, 50599-86-5; **9**, 50599-84-3; **9** HBr, 50599-85-4; **10** HBr, 50599-83-2; **11** HBr, 50599-81-0; phenylacetonitrile, 140-29-4; 2-dimethylaminoethyl chloride, 107-99-3; 2,9β-dimethyl-8-oxo-6,7-benzomorphan, 51096-41-4; 2,9β-dimethyl-8-oxo-6,7-benzomorphan hydrochloride, 50599-82-1.

References and Notes

(1) (a) Chemical Abstracts name: 3,11β-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine. (b) The β designation relates to the hydroaromatic ring.
(2) Visiting Associate of Tanabe Laboratories, Tokyo, Japan.
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(8) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).
(9) R. S. Wilson, H. J. C. Yeh, T. Oh-ishi, and A. E. Jacobson, unpublished results.
(10) Over Na_2SO_4.
(11) E. Tagman, E. Sury, and K. Hoffmann, *Helv. Chim. Acta*, **35**, 1235 (1952).
(12) W. Wilson, *J. Chem. Soc.*, 6 (1952), prepared **4** in 57% yield from $PhCH_2COMe$, $NaNH_2$, and $Me_2NCH_2CH_2Cl$.

Structure and Chemistry of the Aldehyde Ammonias. II. Phenylacetaldimines, Styrylamines, and 2,4,6-Tribenzyl-1,3,5-hexahydrotriazines

Arnold T. Nielsen,* Ronald L. Atkins,[1] John DiPol, and Donald W. Moore

Organic Chemistry Branch, Chemistry Division, Code 6056, Michelson Laboratory, Naval Weapons Center, China Lake, California 93555

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Reaction of phenylacetaldehyde, hydratropaldehyde, and diphenylacetaldehyde with ammonia in methanol or ether at −15° leads to 2,4,6-tribenzyl-1,3,5-hexahydrotriazines **2a–c**. Two of these products had been described by others as hydratropaldimine and diphenylacetaldimine. The platinum-catalyzed hydrogenation of 2,2-diphenyl-1-nitroethene gave 2,2-diphenylethenamine, not diphenylacetaldimine as previously reported. Oxidation of triazines **2a** and **2b** with *tert*-butyl hypochlorite gave 2,4,6-tribenzyl-1,3,5-triazabicyclo[3.1.0]hexanes **3a** and **3b**. The stereochemistry of triazines **2a–c** and oxidation products **3a** and **3b** was established from ^1H and ^{13}C nmr spectra. Thermolysis of triazines **2a–c** in aprotic solvents was followed by nmr spectroscopy; the principal initial products are ammonia and *N,N'*-distyryl-1,1-diamino-2-phenylethanes (**5a–c**). Prolonged heating of triazine **2c** or 2,2-diphenylethenamine gave bis(2,2-diphenylethen)amine (**6c**). 5,5-Diphenyl-2-(diphenylmethyl)-3-oxazoline (**14**) was isolated as a minor product of the reaction of diphenylacetaldehyde with methanolic ammonia.

Accounts of the synthesis of unsubstituted aldimines, RCH=NH, from aldehydes and ammonia are found in the literature.[2-13] However, recent reexamination of some of these reports has established that unsubstituted aldimines of this type cannot be isolated as stable free bases.[14-16] Rather, their self-reaction occurs extremely rapidly, leading to other products such as 2,4,6-trisubstituted 1,3,5-hexahydrotriazines and diimines, $(RCH{=}N)_2CHR$.[7,14-19] Unsubstituted aldimines often are described as reaction intermediates, *e.g.*, in photolysis of azides and primary aliphatic amines, and in reduction of oximes.[20-23]

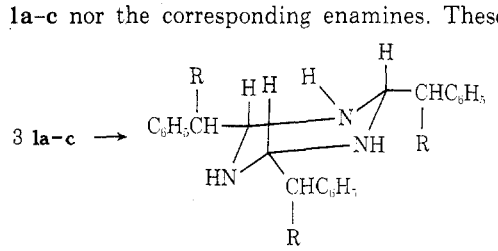
Reactions of hydratropaldehyde and diphenylacetaldehyde with ammonia have been reported by several workers to produce white crystalline solids described as monomeric aldimines **1b** and **1c**, respectively.[6,10,12,13]

$$C_6H_5CH(R)CHO + NH_3 \longrightarrow C_6H_5CH(R)CH{=}NH + H_2O$$

1a, R = H
b, R = CH_3
c, R = C_6H_5

Aldimine **1c** has erroneously been described as a product of hydrogenation of 2,2-diphenyl-1-nitroethene.[9] An unstable solid ammonia derivative of phenylacetaldehyde has been reported, but it could not be purified and its molecular formula was not established.[24] Enamine 2-phenyl-2-methylethenamine has been described as the product of reaction of hydratropaldehyde with ammonia in ethyl acetate solvent;[25] Witkop describes it as imine **1b**.[12]

In the present work the reactions of phenylacetaldehyde, hydratropaldehyde, and diphenylacetaldehyde with ammonia at low temperature were found to produce 2,4,6-tribenzyl-1,3,5-hexahydrotriazines **2a–c**, not aldimines **1a–c** nor the corresponding enamines. These reactions were usually conducted in methanol or ether solvent with a slight excess of ammonia at *ca.* −15° for a few days. Isolated products are white, crystalline solids obtained in variable yields (Table I). Only **2a**, derived from phenylacetaldehyde, forms a stable hydrate ($3H_2O$). Anhydrous **2a** was prepared and its trihydrate formation is reversible. These results agree with previous findings that 2,4,6-tris(*n*-alkyl)-1,3,5-hexahydrotriazines derived from *n*-alkanals form stable trihydrates whereas a 2,4,6-triisopropyl derivative obtained from the α-substituted isobutyraldehyde does not.[14] Repetition of earlier work said to produce **1b** and **1c** or the corresponding enamines gave



2a, R = H
b, R = CH_3
c, R = C_6H_5