Notes

Analogs of Sparteine. I. A Reexamination of the Reaction of *N*-Methyl-4-piperidone with Formaldehyde and Methylamine. A Revised Synthesis of *N,N'*-Dimethylbispidinone

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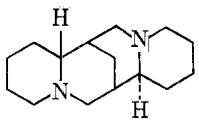
In a study of uterotropic agents related to sparteine (**1**) it was desired to prepare *N,N'*-dimethylbispidine (3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane) (**2a**). Bispidine (**2b**) had been prepared previously,[3,4] but all attempts to convert it into **2a** produced derivatives of diazadamantane.[5]



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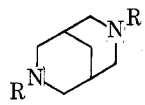
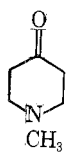


2a, R = CH_3
b, R = H

The synthesis of various *N,N'*-dialkylbispidines was reported in 1968.[6] Douglass and Ratliff utilized a double-Mannich condensation of *N*-methyl-4-piperidone (**3**) with methylamine and formaldehyde to give **4**. The amino ketone **4** was subjected to Wolff–Kishner reduction conditions to give **2a**. In this laboratory the published procedure[6] did not give the results described but a mixture of products.



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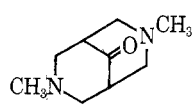

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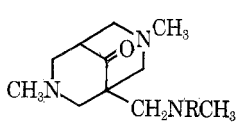
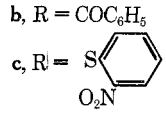
The mixture obtained consisted of 58% of **4** and 42% of a by-product which was shown to have the structure **5a**. The product composition was determined by gas–liquid chromatography—mass spectrometry (glc–ms). Distillation, *in vacuo*, of the mixture resulted in the enrichment of **5a** in the distillate (20% **4**, 80% **5a**). This enrichment was not due to conversion of **4** into **5a** during distillation. Complete spectroanalytic characterization of **5a** was made through its benzamide derivative **5b**.

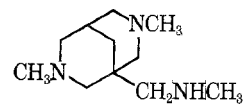


5a, R = H
b, R = COC_6H_5



c, R =

It was found that separation of **4** and **5a** could best be conducted by conversion of **5a** into **5c** by treatment of the mixture with *o*-nitrophenylsulfenyl chloride.[7] After separation, **5c** could be converted into **5a** by treatment with dry



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hydrogen chloride. From the Huang-Minlon modified Wolff–Kishner reduction of **5a, 6** was obtained in low yield.

The conditions of the double-Mannich condensation were altered (see Experimental Section) to give predominantly the desired product **4**, in the absence of **5a**. This amino ketone was readily reduced to **2a** *via* the published procedure.[6]

Experimental Section

General. Analytical glc was performed with a F&M 810 gas chromatograph using dual column flame ionization detection, and with a Varian Aerograph in glc–eims experiments. The carrier gas was helium (55 ml/min) and the detector gases were hydrogen (55 ml/min) and compressed air (250 ml/min). Columns: 6 ft × ⅛ in. stainless steel containing Dowfax 9N9/KOH supported on 80-100x A/W DMCS-treated HP Chrom G. Instrument temperatures: injection port, 210°; oven, 170° isothermal; detector, 225°. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were taken on Beckman IR 10 and IR 33 spectrophotometers. Nuclear magnetic resonance spectra were obtained using Varian A-60A and T-60 spectrometers using tetramethylsilane as the internal standard. Electron impact mass spectra (eims) were recorded at 70 eV using Finnegan 1015 and Varian CH 5 spectrometers. Chemical ionization mass spectra (cims) were obtained from the Finnegan instrument using isobutane as the ionizing gas. Elemental analysis were obtained using a F&M 185 CHN analyzer, and from Midwest Microlab, Inc., Indianapolis, Ind.

Synthesis of *N,N'*-Dimethylbispidinone (4) and 1-(*N*-Methylamino)methyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (5a). The initial procedure utilized was that of Douglass and Ratliff.[6] A modification was developed in which the two products were separated by treating 1.0 g of a 1:4 mixture of **4** and **5a** (3.9 mmol of **5a**) with 1.0 g (5.3 mmol) of *o*-nitrophenylsulfenyl chloride in 10 ml of chloroform. After standing at 25° for 18 hr, the solution was poured into 10 ml of water, and the mixture was shaken. The aqueous phase was separated and adjusted to pH 9 with 1.5 ml of 10% aqueous sodium hydroxide and extracted with three successive 20-ml portions of chloroform. The combined dried (sodium sulfate) extracts were filtered and concentrated to give 0.9 g of a red oil, **5c**: nmr ($CDCl_3$) δ 2.30 (s, 6, NCH_3), 3.10 (s, 3, $NHCH_3$), 2.30–3.50 (m, 10, NCH_2 and bridgehead CH), 7.20–8.50 (m, 4, C_6H_5). This was dissolved in 15 ml of chloroform and treated with excess ethereal hydrogen chloride. After stirring for 24 hr at room temperature, the suspension was filtered and washed with ether. The gummy yellow solid was partitioned between 10 ml of cold chloroform and 10 ml of 10% aqueous sodium hydroxide. Concentration of the dried (sodium sulfate) layer gave **5a** as a clear colorless liquid, 0.5 g (60%): bp (bath) 76–78° (0.1 mm); glc >98% purity, retention time 10.25 min; ir (neat) 3.41, 3.62, 5.83 μ (C=O); nmr ($CDCl_3$) δ 2.25 (s, 6, NCH_3), 2.40 (s, 3, $NHCH_3$), 2.50–3.0 (m, 12, remaining protons); eims *m/e* 212 (QM), 210 (M − 1), 193 (B, M − 18).

Anal. Calcd for $C_{11}H_{21}N_3O$: C, 62.52; H, 10.02; N, 19.89. Found: C, 62.48; H, 9.74; N, 19.94.

The pH 9 aqueous phase, after removal of **5c** by chloroform extraction was made strongly basic by addition of 10% aqueous sodium hydroxide and extracted with four 10-ml portions of cold chloroform. The combined extracts were dried (sodium sulfate), filtered, and concentrated to give 0.1 g (59%) of **4** as a colorless oil which solidified on cooling: bp (bath) 130–135° (0.25 mm); mp 51–52°; glc >98% purity, retention time 4.25 min; nmr ($CDCl_3$) δ 2.35 (s, 6, NCH_3), 2.10–3.20 (m, 10, remaining protons); eims *m/e* 168 (M), 58 (B). Treatment of an ethereal solution of **4** with an equivalent amount of aqueous ethanolic perchloric acid gave the

monoperchlorate salt as white needles from ethanol, mp 218–220° dec.

Anal. Calcd for $C_9H_{17}ClN_2O_5$: C, 40.23; H, 6.38; N, 10.42. Found: C, 39.92; H, 6.42; N, 10.08.

1-(*N*-Methylbenzamido)methyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (5b). To an enriched mixture of **5a** (1.33 g, 6.3 mmol) in 10 ml of chloroform was added 1.4 g (10 mmol) of benzoyl chloride. After stirring for 4 hr at room temperature, the solution was poured into 10 ml of water. The chloroform was separated and discarded. The aqueous phase was washed once with 10 ml of chloroform. The aqueous layer was adjusted to pH 12 with 10% aqueous sodium hydroxide and extracted with two 15-ml portions of chloroform. The combined, dried (sodium sulfate), and filtered extracts were concentrated *in vacuo* leaving a yellow oil. This was dissolved in ether and treated with excess aqueous ethanolic perchloric acid. The dried precipitate was triturated with 5 ml of water, filtered, and washed with water to give the monoperchlorate of **5b** as a white solid, 0.5 g (50%): mp 224–226° dec; ir (KBr) 3.18 (w, C_6H_5), 5.78 (s, C=O), 6.14 (s, N-C=O), 9.26 μ (s, ClO_4^-).

Anal. Calcd for $C_{18}H_{26}N_3O_6Cl$: C, 51.98; H, 6.30; N, 10.10. Found: C, 52.24; H, 6.30; N, 9.89.

The monoperchlorate salt (149 mg, 0.36 mmol) was partitioned between 5 ml of 10% aqueous sodium hydroxide and 6 ml of chloroform. The combined, dried extracts were filtered and concentrated *in vacuo* to give 110 mg of a colorless, semicrystalline oil: nmr (CCl_4) δ 2.30 (s, 6, amine NCH_3), 3.05 (s, 3, amide NCH_3), 3.60 (s, 2, amide NCH_2), 7.35 (s, 5, aromatic), 2.30–3.30 (m, 8, amine NCH_2 and bridgehead CH); eims *m/e* 315 (M), 58 (B).

1-(*N*-Methylamino)methyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane (6). Crude amino ketone **5a** (4 g) was reduced by the literature procedure.[6] The distillate that collected was saturated with sodium chloride and extracted with 25 ml of ether; the ether extracts contained 50 mg of **4**: nmr (identical with the published spectrum[6]); eims *m/e* 154 (M), 58 (B). Amino ketone **6** was recovered from the reaction solution by steam distillation as a white solid (0.85 g, 25%): mp 45–46°; ir (neat) 3.41 (s), 3.61 (s), 6.90, 6.99, 7.94 μ; nmr (C_6H_6) δ 1.30 (d, J = 3 Hz, 2, CH_2 bridge), 1.80 (m, 1, bridgehead CH), 2.20 (s, 6, NCH_3), 2.30 (s, 3, $NHCH_3$), 2.10–2.70 (m, 10, NCH_2); eims *m/e* 197 (M), 58 (B). The base was converted into the diperchlorate by treatment with excess perchloric acid. It crystallized from ethanol as white needles, mp 227–230° dec.

Anal. Calcd for $C_{11}H_{25}Cl_2N_3O_8$: C, 33.18; H, 6.33; Cl, 17.81; N, 10.55. Found: C, 33.32; H, 6.63; Cl, 18.00; N, 10.82.

Revised Synthesis of *N,N'*-Dimethylbispidinone (4). In a 2000-ml round-bottomed flask were placed 44.3 g of paraformaldehyde, 18.7 g (0.2 mol) of methylamine acetate, and 1000 ml of methanol. To this magnetically stirred suspension was added a solution of 36 g (0.2 mol) of *N*-methyl-4-piperidone acetate in 100 ml of methanol in increments over a period of 14 days. The paraformaldehyde slowly dissolved during this time. After completion of addition, the solution was stirred at room temperature for an additional 32 days. Then the solvent was removed *in vacuo*, and the residual oil, dissolved in 150 ml of water, was extracted twice with 75-ml portions of chloroform. These extracts were discarded. To the aqueous phase was cautiously added 20 g of anhydrous sodium carbonate. The resulting suspension was filtered and extracted with five successive 200-ml portions of chloroform. The pH of the aqueous phase was maintained at 8.5–9.0 with 10% aqueous sodium carbonate. The chloroform extracts, containing starting materials and polymeric products, were discarded. The aqueous phase was concentrated at an oil pump to a volume of 50 ml, filtered, and made strongly alkaline with 10% aqueous sodium hydroxide. This suspension was extracted with five successive 90-ml portions of chloroform. Work-up of the combined extracts left 24.7 g of an amber oil. Distillation of this crude product gave 6.82 g (10%) of **4** which crystallized upon cooling; analytical data were identical with those of the extraction-purified sample (see above).

Registry No.—**3** acetate, 53210-06-3; **4**, 14789-54-9; 4 $HClO_4$, 53210-07-4; **5a**, 53210-08-5; **5b**, 53210-09-6; **5b** $HClO_4$, 53210-10-9; **5c**, 53210-11-0; **6**, 53230-02-7; **6** $2HClO_4$, 53230-03-8; *o*-nitrophenylsulfinyl chloride, 7669-54-7; methylamine acetate, 6998-30-7.

References and Notes

(1) Deceased July 14, 1974.
(2) NIH predoctoral trainee, University of Kansas, 1971–1974. Correspondence should be addressed to School of Pharmacy, University of Georgia, Athens, Ga. 30602.
(3) (a) H. Stetter and H. Hennig, *Chem. Ber.*, **88**, 789 (1955); (b) H. Stetter and R. Merten, *ibid.*, **90**, 868 (1947).
(4) J. A. Weis, Ph.D. Thesis, University of Kansas, Lawrence, Kan., 1968.
(5) E. E. Smissman and J. A. Weis, *J. Heterocycl. Chem.*, **5**, 405 (1968).
(6) J. E. Douglass and T. B. Ratliff, *J. Org. Chem.*, **33**, 355 (1968).
(7) L. Zervas, D. Borovas, and E. Gazis, *J. Amer. Chem. Soc.*, **85**, 3660 (1963).

2-(2-Imidazolyl)acetophenones. Preparation and Some Reactions

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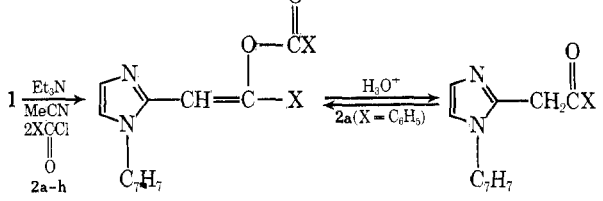
Imidazoles, in their behavior with acid chlorides, can be made to react in a number of ways. In the absence of N substituents, benzoylation[1] and acetylation[2] in inert solvents give rise to N-substituted derivatives. Imidazole with benzoyl chloride (BzCl) in aqueous alkali, instead, initially provides a 1,3-dibenzoyl cation which then suffers hydrolytic ring cleavage to give 1,2-dibenzoylaminoethylene.[3] N-Substituted imidazoles have also been shown to react with BzCl; on conducting the reaction in Et_3N-containing acetonitrile, 2-benzoyl derivatives are obtained.[4]

Interest in the electrophilic substitution pattern of 1,2-disubstituted imidazoles[5] prompted a study of the behavior of 1-benzyl-2-methylimidazole (**1**) with various benzoyl chlorides.[6] This showed that **1** with 2 equiv of various benzoyl chlorides in Et_3N-containing acetonitrile gave enol esters **3a–e** in essentially quantitative yield. Subsequent acid hydrolysis then provided 2-(2-imidazolyl)acetophenones **4a–e** (Scheme I). The present paper demonstrates the generality of the method.

Scheme I



X: **a**, C_6H_5; **b**, *p*-$CH_3OC_6H_4$; **c**, *p*-$CH_3C_6H_4$; **d**, *p*-ClC_6H_4; **e**, *p*-$O_2NC_6H_4$; **f**, $(CH_3)_3C$; **g**, Cl_3C; **h**, C_2H_5O

Formation of **3a–e** is surprising since, to our knowledge, a nonactivated 2-methyl group on a 1,2-disubstituted imidazole is reluctant to partake in electrophilic processes. 1,2-Dimethylimidazole, for example, undergoes hydroxymethylation at C-5 exclusively;[5] lithiation, previously reported to proceed solely at C-5,[7] has recently been shown to occur at both C-5 and at the C-2 methyl.[8] In the case at hand, formation of **3a–e** is to be ascribed to an irreversible O-aroylation of anionic intermediates serving to displace all prior equilibria in favor of a final conjugated system. O-Aroylation stems, *i.e.*, from minimal anion solvation in the polar, aprotic acetonitrile, a view consistent with the observation that **4a** with BzCl under the reaction conditions provides **3a**.

In the present work, the reactions of **1** with some acyl chlorides were examined. Acetyl chloride, under the reaction conditions, formed intractable product mixtures.