at reflux for 20 hr with benzalacetone (1.0 g, 0.0069 mole) in 50 ml of methanol. At this time, TLC (cyclohexane–ether, 1:1) indicated that all of the starting material had been converted to cyclocoumarol (III). The solvent was removed under reduced pressure and the residue was dissolved in 50 ml of acetone. An equal volume of 5 *N* HCl was added, and the solution was agitated in a 37° water bath for 4 hr or until TLC indicated complete hydrolysis to warfarin. Saturated aqueous NaCl (10 ml) was added and the mixture was extracted three times with 50 ml of ether. The combined ether extracts were back-extracted three times with 20 ml of 10% NaOH; the aqueous layer was filtered and reacidified to pH 2 with 5 *N* HCl. The resulting precipitate was collected by filtration, triturated with ether, and dried. Recrystallization from acetone–water (13) gave 1.98 g (93% yield) of I, mp 159–161° [lit. (12) 161°]. The NMR (dimethyl sulfoxide-d_6) was identical to that of authentic warfarin.

6-Hydroxywarfarin [4,6-Dihydroxy-3-(1-phenyl-3-oxobutyl)-2*H*-1-benzopyran-2-one] (VI)—6-Hydroxywarfarin was synthesized following the aforementioned procedure using 4,6-dihydroxycoumarin (0.5 g, 0.0028 mole) and benzalacetone (0.5 g, 0.0034 mole) in 30 ml of methanol. The product was recovered as described above and recrystallized from acetone–chloroform (12) to give 0.83 g (91% yield) of VI, mp 217–220° [lit. (12) 219–220°].

7-Hydroxywarfarin [4,7-Dihydroxy-3-(1-phenyl-3-oxobutyl)-2*H*-1-benzopyran-2-one] (VII)—7-Hydroxywarfarin was synthesized following the aforementioned procedure using 4,7-dihydroxycoumarin (0.2 g, 0.0011 mole) and benzalacetone (0.2 g, 0.0014 mole) in 20 ml of methanol. The product was recovered as described above and recrystallized from acetone–chloroform (12) to give 0.27 g (77% yield) of VII, mp 206–209° [lit. (12) 208–210°].

REFERENCES

(1) R. A. O'Reilly and P. M. Aggeler, *Pharmacol. Rev.*, **22**, 35 (1970).

(2) W. B. Jackson, P. J. Spear, and C. G. Wright, *Pest Control*, **39**, 13 (1971).

(3) W. R. Porter, C. Wheeler, and W. F. Trager, *Biochem. Pharmacol.*, **30**, 3099 (1981).

(4) M. J. Fasco, K. P. Vatsis, L. S. Kaminsky, and M. J. Coon, *J. Biol. Chem.*, **253**, 7813 (1978).

(5) L. S. Kaminsky, M. J. Fasco, and F. P. Guengerich, *J. Biol. Chem.*, **254**, 9657 (1979).

(6) M. J. Fasco, L. J. Piper, and L. S. Kaminsky, *Biochem. Pharmacol.*, **28**, 97 (1978).

(7) L. R. Pohl, S. D. Nelson, W. R. Porter, W. F. Trager, M. J. Fasco, F. D. Baker, and J. W. Fenton II, *Biochem. Pharmacol.*, **25**, 2153 (1976).

(8) W. N. Howald, E. D. Bush, W. F. Trager, R. A. O'Reilly, and C. H. Motley, *Biomed. Mass Spectrom.*, **7**, 35 (1980).

(9) M. J. Fasco, M. J. Cashin, and L. S. Kaminsky, *J. Liq. Chromatogr.*, **2**, 565 (1979).

(10) A. M. Duffield, P. H. Duffield, D. J. Birkett, M. Kennedy, and D. N. Wade, *Biomed Mass Spectrom.*, **6**, 209 (1979).

(11) C. E. Cook, N. H. Ballentine, T. B. Seltzman, and C. R. Tallent, *J. Pharmacol. Exp. Ther.*, **210**, 391 (1979).

(12) M. A. Hermodson, W. M. Barker, and L. P. Link, *J. Med. Chem.*, **14**, 167 (1971).

(13) C. Schroeder, Ph.D. Thesis, University of Wisconsin, Madison, Wis. (1955).

(14) M. J. Fasco, L. J. Piper, and L. S. Kaminsky, *J. Chromatogr.*, **131**, 365 (1977).

(15) C. E. Cook, R. Tallent, N. H. Ballentine, G. F. Taylor, and J. A. Kepler, *J. Label. Comp. Radiopharm.*, **16**, 623 (1979).

ACKNOWLEDGMENTS

This investigation was supported by the National Institutes of Health Grant IR01GM25136 (W.F.T.).

Synthesis of 4-Substituted *N*-[(Dimethylamino)methyl]benzamides: New Compounds

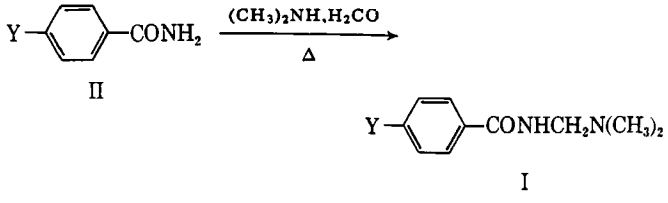
NILO ZANATTA and ROBERTO RITTNER *x

Received November 23, 1981 from the Instituto de Química, Universidade de São Paulo, C.P. 20.780, São Paulo, Brazil. Accepted for publication June 16, 1982. *Present address: Instituto de Química—UNICAMP, Caixa Postal 6154, 13.100—Campinas—São Paulo, Brazil.

Abstract □ Nine 4-substituted-*N*-[(dimethylamino)methyl]benzamides were obtained in high yield from the corresponding 4-substituted benzoic acids *via* the corresponding benzamides.

Keyphrases □ *N*-[(Dimethylamino)methyl]benzamides—4-substituted synthesis *via* Mannich–Einhorn reaction □ Amidomethylation reaction—synthesis of 4-substituted *N*-[(dimethylamino)methyl]benzamides

To investigate the possible relationship between electronic structure and local anesthetic properties, simple model compounds were required. The 4-substituted *N*-[(dimethylamino)methyl]benzamides[1] (I) were chosen as models since they are closely related to the procainamides, which are widely used as local anesthetics (1). These compounds have the advantage of being readily available from the 4-substituted benzamides (II) in a single step, using the Mannich–Einhorn reaction (2, 3). The 4-substituted benzamides (II) are either commercially available (4), or are readily prepared by conventional methods (5–9).



Y = H,F,Cl,Br,I,OCH$_3$,CH$_3$,N(CH$_3$)$_2$.

Scheme I

This study reports the application of the Mannich–Einhorn reaction (Scheme I) to the synthesis of I, and discusses the preparation of the starting materials (II), which were not commercially available.

EXPERIMENTAL[2]

4-Substituted *N*-[(dimethylamino)methyl]benzamide (I) was prepared by refluxing a mixture of a 4-substituted benzamide (II) (0.071 mole), 40% aqueous dimethylamine (17.4 ml; 0.142 mole), 35% aqueous formaldehyde (12.2 ml; 0.142 mole), and water (15 ml) with stirring for 4 hr.

[1] The key to the labeling of the 4-substituted amides (I) is in Table I.

[2] Melting points were determined in a Kofler apparatus and are uncorrected. IR spectra were determined in a Perkin-Elmer 457A spectrophotometer. NMR spectra were obtained with a Varian T-60 spectrometer using tetramethylsilane as the internal standard. Elemental analyses were performed at the Microanalysis Laboratories of the Instituto de Química—USP, São Paulo.

0022-3549/83/0700-0831$01.00/0

Table I—Physical Data of 4-Substituted *N*-[(Dimethylamino)methyl]benzamides

Compound	Y	Melting Point	Yield[a], %	Molecular Formula	Analysis, %	Calc.	Found
Ia	H	59–60°	48	$C_{10}H_{14}N_2O$	C	67.39	67.10
					H	7.92	8.06
					N	15.72	16.04
Ib	F[b]	—	86	$C_{10}H_{13}FN_2O$	C	61.21	55.22
					H	6.68	6.33
					N	14.28	12.27
Ic	Cl	82–83°	82	$C_{10}H_{13}ClN_2O$	C	56.47	56.16
					H	6.16	6.10
					N	13.17	13.51
Id	Br	107–108°	83	$C_{10}H_{13}BrN_2O$	C	46.71	47.37
					H	5.10	5.04
					N	10.89	11.19
Ie	I	123–125°	90	$C_{10}H_{13}IN_2O$	C	39.49	39.34
					H	4.31	5.15
					N	9.21	9.38
If	OCH_3	68–70°	82	$C_{11}H_{16}N_2O_2$	C	63.44	63.09
					H	7.74	7.93
					N	13.45	13.72
Ig	CH_3	56–58°	88	$C_{11}H_{16}N_2O$	C	68.72	68.43
					H	8.39	8.38
					N	14.57	14.51
Ih	$N(CH_3)_2$	95–97°	81	$C_{12}H_{19}N_3O$	C	65.13	64.83
					H	8.65	8.53
					N	18.99	19.01
Ii	NO_2	78–80°	41	$C_{10}H_{13}N_3O_3$	C	53.80	53.98
					H	5.87	5.89
					N	18.82	18.87

[a] Yields were based on the benzamides (II), recrystallized from benzene–*n*-hexane. [b] The oil did not crystallize. More accurate analytical data could not be obtained.

Table II—Spectral Data of 4-Substituted *N*-[(Dimethylamino)methyl]benzamides

Compound	Y	IR, (nujol), ν cm^{-1}	^{1}H-NMR ($CDCl_3$), δ H-2,6	H-3,5	N—H	CH_2	CH_3	Others
Ia	H	3340, 1640, 1600, 795, 685	7.84	7.46	6.88	4.26	2.40	
Ib	F	3300, 1650, 1605, 842	7.83	7.07	7.43	4.20	2.31	
Ic	Cl	3318, 1640, 1598, 840	7.75	7.35	7.05	4.18	2.31	
Id	Br	3310, 1640, 1590, 840	7.78	7.56	6.82	4.31	2.44	
Ie	I	3300, 1640, 1590, 827	7.90	7.58	6.86	4.32	2.46	
If	OCH_3	3372, 1635, 1605, 1250, 1020, 831	7.81	6.92	6.76	4.21	2.33	3.84
Ig	CH_3	3300, 1630, 830	7.73	7.23	6.76	4.21	2.33	2.38
Ih	$N(CH_3)_2$	3340, 1628, 1605, 817	7.79	6.73	6.73	4.25	2.35	3.05
Ii	NO_2	3145, 1670, 1600, 1512, 1343, 851	7.95	8.30	6.81	4.25	2.35	

The cooled solution was poured into a saturated aqueous sodium carbonate solution (50 ml), extracted with diethyl ether (3 × 30 ml), and dried over magnesium sulfate. The solvent was evaporated *in vacuo*, and the residue was recrystallized from benzene–petroleum ether to give a 40–90% yield of product.

DISCUSSION

The syntheses of the starting materials (II) for the Mannich–Einhorn reaction, were carried out as described previously (5–9). Oxidation of 4-anisaldehyde, 4-tolualdehyde, and 4-*N*-dimethylaminobenzaldehyde with an aqueous solution of silver nitrate–sodium hydroxide (10) gave the corresponding benzoic acids in yields of 40, 53, and 81%, respectively. The alternative procedure using silver oxide–ammonium hydroxide (5) failed and led to an explosive mixture. The 4-fluoro-, 4-bromo-, and 4-iodobenzoic acids were prepared as described previously (6–8) in yields of 86, 52, and 50%, respectively, following the diazotization of 4-aminobenzoic acid. Benzoic, 4-chlorobenzoic, and 4-nitrobenzoic acids were commercial products. All 4-substituted benzoic acids were converted to the corresponding benzoyl chlorides using thionyl chloride and catalytic amounts of dimethylformamide (11). The crude products were poured onto an excess of concentrated ammonium hydroxide (9) which led to the formation of the corresponding benzamides in yields of 70–80%. These 4-substituted benzamides, when treated with 35% aqueous formaldehyde and 40% aqueous dimethylamine gave the corresponding Mannich bases (I) (12), which were characterized by physical and spectral data (Tables I and II, respectively).

REFERENCES

(1) J. Büchi and X. Perlia, in "Drug Design," vol. 3, E. J. Ariëns, Ed., Academic, New York, N.Y., 1972, p. 243.

(2) H. Hellmann, *Angew. Chem.*, **69**, 463 (1957).

(3) M. Tramontini, *Synthesis*, **1973**, 703.

(4) "1981–1982 Aldrich Catalog Handbook of Fine Chemicals," Aldrich Chemical Co., Milwaukee, Wis., 1980.

(5) B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, and A. R. Tatchell, "Vogel's Textbook of Practical Organic Chemistry," 4th ed., Longman, London, 1978, p. 1072.

(6) B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, and A. R. Tatchell, *ibid.*, p. 705.

(7) B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, and A. R. Tatchell, *ibid.*, p. 700.

(8) B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, and A. R. Tatchell, *ibid.*, p. 695.

(9) B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, and A. R. Tatchell, *ibid.*, p. 517.

(10) E. Campaigne and W. M. Le Suer, in "Organic Syntheses," vol. IV, N. Rabjohn, Ed., Wiley, New York, N.Y., 1963, p. 919.

(11) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

(12) H. Hellmann and G. Haas, *Chem. Ber.*, **90**, 50 (1957).

ACKNOWLEDGMENTS

The authors thank the Conselho Nacional de Pesquisas for a grant to Roberto Rittner and a scholarship to Nilo Zanatta.