An Approach to Simple Aminal Synthesis: Preparation of *N*-(6-Aminohexyl)-*N*-benzyl-*N'*-methylmethylenediamine

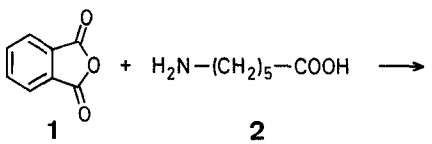
R. GRANADOS, M. ALVAREZ, F. LOPEZ-CALAHORRA, M. SALAS

Departamento de Química Orgánica y Farmaceútica, Facultad de Farmacia, Universidad de Barcelona, Barcelona, Spain

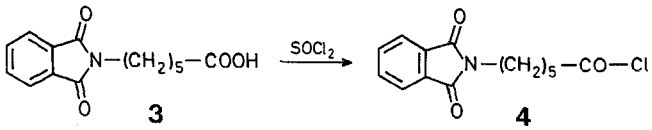
In connection with our research on α-adrenoceptor topography by means of pharmacological evaluation of potential α-blockers, we needed the aminal *N*-(6-aminohexyl)-*N*-benzyl-*N'*-methylmethylenediamine **(10)**. The synthetic routes available for the generally labile aminals[1] are applicable to (a) symmetrically substituted aminals[2,3], (b) cyclic aminals[4], and (c) the more stable systems with both nitrogen atoms completely substituted.

We describe here a new synthetic method for aminals with none of the above three characteristics and with general validity. The synthetic strategy is illustrated for the preparation of the title compound **10**. The amide-carbamate **9** is considered as a suitable precursor for the aminal **10**. The carbamate **9** is prepared by the Hofmann rearrangement of the amido-acetamide **8**.

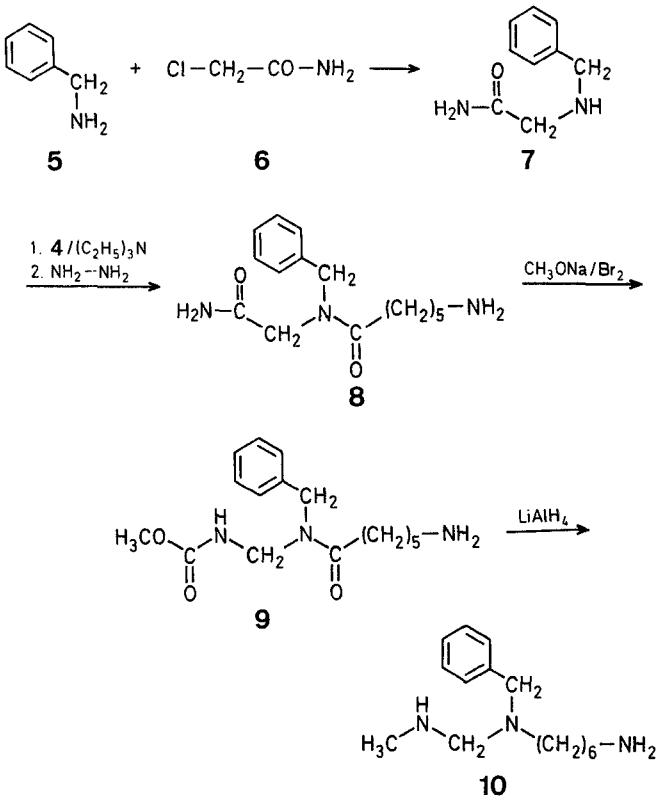
The starting material for the key synthetic sequence is the benzylaminoacetamide **(7)**, which is obtained in 50% yield by the simple method of reacting benzylamine **(5)** with chloroacetamide **(6)**. Our method for the preparation of **7** is a considerable improvement to the reported[6] complicated procedure



1 **2**



3 **4**



5 **6** **7** **8** **9** **10**

with a lower yield (18%). This product **7** decomposes under the Hofmann rearrangement conditions yielding benzylamine as the only isolable product.

The aminohexanoyl group is introduced to benzylaminoacetamide **(7)** as the phthalimido derivative in the second step of the synthesis by means of the corresponding acyl chloride **4** obtained by reacting 6-aminohexanoic acid **(2)** with phthalic anhydride **(1)**. The phthalimido group is removed by treatment with hydrazine hydrate to give the amido-acetamide **8**. Hofmann rearrangement of **8** in methanolic media at low temperature[5] gives the required amide-carbamate **9**. In this way, the aminal group is preformed and only in the last step is it transformed to the required structure. This is achieved in a convenient way by the lithium aluminium hydride reduction of the amide-carbamate **9** to give the aminal **10**.

The purification and characterization of the aminal **10** is very difficult because of its intrinsic structural instability. However, the product **10** was characterized by its spectral data, including the mass spectra, and the microanalysis of its dioxalate, which is the only sufficiently stable derivate that could be prepared.

6-Phthalimidohexanoic Acid (3):

An intimate mixture of 6-aminohexanoic acid (**2**; 63 g, 0.48 mol) and phthalic anhydride (**1**; 70.2 g, 0.48 mol) is heated with stirring at 145–150 °C for 30 min. After cooling, the resulting mixture is dissolved in hot methanol (300 ml) and diluted with cold water (300 ml). The white precipitate formed is filtered, washed with more cold water, and dried over phosphorus pentoxide; yield: 106.4 g (85%); m.p. 104–105 °C.

I.R. ($CHCl_3$): $\nu = 2900, 1780, 1710\ cm^{-1}$.

^1H-N.M.R. ($CDCl_3$)[7]: $\delta = 1.55$ (m, 6H, CH_2); 2.35 (t, $J = 6$ Hz, 2H, CH_2COOH); 3.6 (t, $J = 6$ Hz, 2H, N—CH_2); 7.73 ppm (s, $4H_{arom}$).

***N*-Benzylaminoacetamide (7):**

In a round-bottom flask are placed chloroacetamide (**6**; 5 g, 53.4 mmol), benzylamine (**5**; 11.4 g, 106.8 mmol) and water (50 ml). The resulting solution is heated at 90 °C for 20 min, cooled, and extracted with ether (3 × 20 ml). The aqueous layer is basified with 10% ammonium

hydroxide and extracted with ethyl acetate (3 × 20 ml). The organic layer is dried with anhydrous magnesium sulfate, the solvent removed under reduced pressure, and the residue digested with ether (100 ml) and filtered. Product **7** is obtained as a white solid; yield: 4.5 g (50%); m.p. 78–80 °C.

I.R. (KBr): $\nu = 3370, 3160, 1625\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$)[7]: $\delta = 1.93$ (s, 1H, NH); 3.23 (s, 2H, N—CH_2—CO); 3.76 (s, 2H, C_6H_5—CH_2—N); 7.26 ppm (s, 5H, C_6H_5).

***N*-Benzyl-*N*-aminocarbonylmethyl-6-aminohexanamide (8):**

A solution of 6-phthalimidohexanoic acid (**3**; 6.5 g, 24.8 mmol) in thionyl chloride (40 ml) is boiled for 1 h and the excess of the reagent is removed under reduced pressure. The dark oily residue of **4** is dissolved in dry chloroform (50 ml) and the solution added slowly to a mixture of *N*-benzylamidoacetamide (**7**; 4 g, 24.6 mmol), triethylamine (5 g, 49.2 mmol), and dry chloroform (40 ml). After the addition is finished the resulting reaction mixture is stirred for 2 h at room temperature. When the mixture is cooled a solid precipitates, which is filtered, and the organic solution is washed with 10% hydrochloric acid (40 ml) 10% sodium hydroxide (50 ml), and dried with anhydrous magnesium sulfate. The solvent is removed under reduced pressure and the resulting solid residue combined with the former to give the phthalimido derivative of **8**; yield: 9.4 g (95%); m.p. 165–166 °C (from methanol).

$C_{23}H_{25}N_3O_4$	calc.	C 67.78	H 6.18	N 10.31
(387.3)	found	68.03	6.27	10.42

I.R. (KBr): $\nu = 3345, 3200, 1770, 1710, 1675, 1630\ cm^{-1}$.

A mixture of the phthalimido derivative of **8** (5.1 g, 13.06 mmol), 80% hydrazine hydrate (1.86 g, 37.35 mmol), and ethanol (20 ml) is refluxed for 3 h, after which the solvent is removed under reduced pressure and the solid residue dissolved in 1 normal sodium hydroxide (100 ml). The alkaline solution is extracted with chloroform, the organic layer dried with anhydrous magnesium sulfate, and the solvent removed. The product **8** is obtained as a white solid; yield: 2.4 g (70%); m.p. 76–80 °C.

I.R. (KBr): $\nu = 3360, 3200, 1680, 1630\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$)[7]: $\delta = 1.9$–2.1 (m, 6H); 2.0–3.0 (m, 6H, NH_2, CH_2—CO, CH_2—NH_2); 3.86 (s, 2H, N—CH_2—CO); 4.60 (s, 2H, C_6H_5—CH_2—N); 6.1–6.9 (br. s, 2H, CO—NH_2); 7.15 ppm (s, 5H, C_6H_5).

Methyl *N*-(6-Aminohexanoyl)-*N*-benzylaminomethylcarbamate (9):

To a solution of sodium methoxide in methanol prepared from sodium (2.2 g, 0.094 mol) and methanol (48 ml) cooled to −45 °C, bromine (5 g, 31.5 mmol) is added slowly with stirring under a nitrogen atmosphere. When the solution turns colourless, compound **8** (8.72 g, 31.48 mmol) dissolved in methanol (100 ml) is added dropwise. The mixture is allowed to warm to room temperature and then refluxed for 20 min. After cooling, water (200 ml) is added and the solvent removed. The residue is suspended in water (100 ml) and extracted with chloroform (4 × 25 ml). The organic layer is washed with water (40 ml), dried with anhydrous magnesium sulfate, and the solvent removed. The oily residue (7.9 g) is chromatographed on silica gel eluting with mixtures of chloroform/methanol. The product **9** elutes from chloroform/methanol (96 : 4) to more methanol-enriched mixtures; yield: 6 g (60%).

I.R. ($CHCl_3$): $\nu = 3445, 1720, 1640\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$)[7]: $\nu = 1.9$–2.1 (m, 6H, CH_2); 2.1–2.9 (m, 6H, NH_2, CH_2—CO, CH_2—NH_2); 3.58 (s, 3H, OCH_3); 4.65 (s, 4H, C_6H_5—CH_2—N—CH_2—N); 5.66–6.23 (br. s, 1H, NH—CO); 7.13 ppm (s, 5H, C_6H_5).

Attempts to prepare an analytical sample of the hydrochloride of **9** by crystallization from ethyl acetate/methanol give the hydrolysis product, *N*-benzyl-6-aminohexanamide hydrochloride. The hydrolysis of **9** is probably the consequence of the acidic character of the hydrochloride, the presence of adventitious moisture in the crystallization solvents, and the high reactivity of the carbamate group.

N-Benzyl-6-aminohexanamide Hydrochloride; Hydrolysis product of **9**:

$C_{13}H_{21}ClN_2O$	calc.	C 60.80	H 8.24	N 10.91	Cl 13.8
(256.8)	found	60.82	8.26	10.89	13.9

I.R. (KBr): $\nu = 3300, 1635\ cm^{-1}$.

^{1}H-N.M.R. (DMSO-d_6)[7]: $\delta = 1.0$–1.9 (m, 6H, CH_2); 2.15 (t, $J = 6$ Hz, 2H, CH_2—CO); 2.7 (m, 2H, CH_2—$\overset{\oplus}{N}H_3$); 4.21 (d, $J = 6$ Hz, 2H, C_6H_5—CH_2—NH—CO); 7.2 (s, 5H, C_6H_5); 7.7–8.6 ppm (m, 4H, —$\overset{\oplus}{N}H_3$, NH—CO).

***N*-(6-Aminohexyl)-*N*-benzyl-*N'*-methylmethylenediamine (10):**

A solution of compound **9** (1.88 g, 6.12 mmol) in dioxan (30 ml) is added dropwise to a stirring suspension of lithium aluminium hydride (0.69 g, 18.3 mmol) in anhydrous dioxan (100 ml). The reaction mixture is refluxed for 7 h, cooled, and hydrolyzed with water (7.5 ml) and 2 normal sodium hydroxide solution (15 ml). The suspension formed is filtered, the solid residue washed with ether, the organic layer is dried with magnesium sulfate, and the solvent removed under reduced pressure; yield: 1.17 g (77%).

I.R. ($CHCl_3$): absence of carbonyl absorption.

^{1}H-N.M.R. ($CDCl_3$)[7]: $\delta = 1.3$ (m, 8H, CH_2); 2.12 (s, 3H, NCH_3); 2.2–2.8 (m, 4H, N—CH_2, CH_2—NH_2); 2.81 (s, 3H, NH, NH_2); 3.40 (s, 2H, N—CH_2—N); 3.75 (s, 2H, C_6H_5—CH_2—N); 7.15 ppm (s, 5H, C_6H_5).

M.S.: $m/e = 249$ (M^+), 219, 143 (8%), 134 (25%), 120 (28%), 91 (65%), 58 (14%), 44 (100%).

Compound **10** is converted to its dioxalate derivative by the method of Ref.[8], but working at the lowest possible temperature; m.p. 178–180 °C (from anhydrous methanol).

$C_{19}H_{31}N_3O_8$	calc.	C 53.13	H 7.27
(429.5)	found	53.25	7.10

Received: October 19, 1982

[1] W. C. Hunt, E. C. Wagner, *J. Org. Chem.* **16**, 1792 (1951).
[2] L. W. Jones, H. F. Whalen, *J. Am. Chem. Soc.* **47**, 1343 (1925).
[3] G. Bianchetti, D. Pocar, R. Stradi, *Gazz. Chim. Ital.* **100**, 726 (1970).
[4] H. W. Wanzlick, W. Löcher, *Chem. Ber.* **99**, 868 (1966).
[5] P. Radlick, L. R. Brown, *Synthesis* **1974**, 290.
[6] C. K. Bradsher, F. C. Brown, E. F. Sinclair, *J. Am. Chem. Soc.* **78**, 6192 (1956).
[7] All the given ^{1}H-N.M.R. data were recorded with a 60 MHz Hitachi Perkin Elmer R 24 B spectrometer.
[8] E. Hardegger, *Einführng in das Organisch-Chemische Praktikum*, Eidg. Technische Hochschule, Zürich; (Using anhydrous methanol for solutions).