An Improved Synthesis of Gliamilide®, A High-Potency Sulfamylurea Hypoglycemic Agent (1)

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An efficient synthesis of the sulfamylurea, Gliamilide®, is described, which involves as a key feature the selective reduction of the more basic alkyl-substituted pyridine ring in the monohydrochloride salt of dipyridyl compound **11** to form **12** without affecting the 2-methoxynicotinamide moiety.

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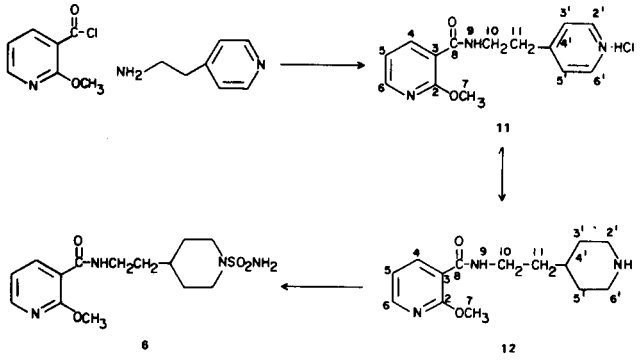
The preparation of a series of high-potency sulfamylurea hypoglycemic agents is described in a previous paper (2) from these laboratories. One compound from this series, Gliamilide® (**10**), showed positive clinical results (3), prompting development of an efficient process suitable for the large scale preparation of this drug candidate. Details of this improved process are presented below.

The original Gliamilide® synthesis (Scheme I), designed to facilitate preparation of a large number of analogs, was inefficient, requiring a blocking group for the preparation of key intermediate **6** and a tedious isomer separation in the preparation of **9**.

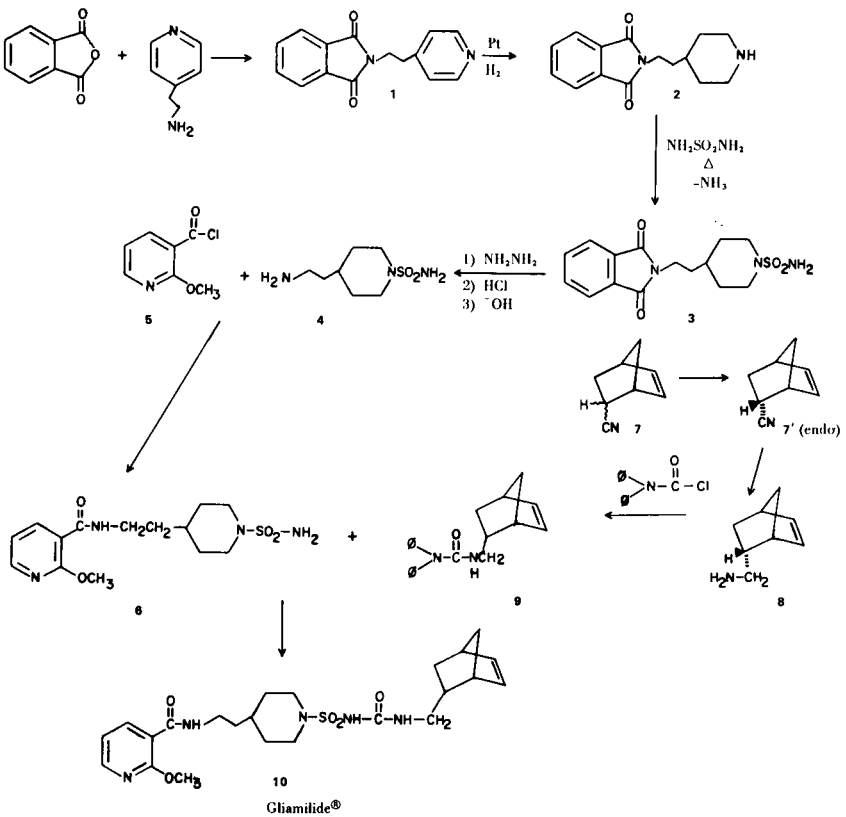
A retrosynthetic analysis suggested the following approach to intermediate **6** (Scheme II): introduction of the desired 2-methoxynicotinyl radical at the beginning of the synthetic sequence would obviate the need for the phthaloyl protecting group in the sulfamide preparation; success of this route would then depend on selective reduction of one of the pyridine rings in **11** to give **12**.

Precedent for selective hydrogenation of a dipyridyl

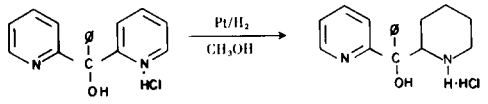
Scheme II



Scheme I – The Original Gliamilide® Synthesis



compound was found in a report by McCarty and co-workers (4) in which the monohydrochloride salt of α-phenyl-α-(2-pyridyl)-2-pyridinemethanol (**13**) was reduced to give α-phenyl-α-(2-pyridyl)-2-piperidine methanol (**14**) in 75% isolated yield. In this example the pyridyl rings in the starting material (13) are equivalent; consequently protonation (5) and reduction of either pyridine ring in



13 14

13 gave **14** as the initial reduction product. The more strongly basic piperidine ring in **14** then apparently sequesters effectively the single equivalent of hydrochloric acid present, preventing protonation and subsequent reduction of the other pyridine ring.

In the present study the two pyridine rings in **11** are non-equivalent, however literature p*K*a data on model compounds (6) suggested that the alkyl pyridine ring in **11** was at least a thousand-fold more basic than the 2-methoxynicotinamide ring. If selectivity in reduction were to parallel the expected selectivity in protonation, then reduction of **11** monohydrochloride would be expected to give **12** exclusively.

In actual practice, coupling of 2-methoxynicotinyl-chloride (2) with 4-(2-aminoethyl)pyridine (7) was staightforward giving **11** in 75% yield. Catalytic hydrogenation of a methanolic solution of **11**, containing one equivalent of hydrochloric acid, then gave **12** in greater than 95% yield. Examination of nmr spectra of crude reaction mixtures showed no starting material, or the other possible partially reduced compound, or over-reduced material. Heating **12** in pyridine with sulfamide gave **6** in 70% yield.

Attention was also directed toward optimizing the synthesis of *endo*-urea **9**. Originally its precursor (**8**) was prepared by fractionation of an isomeric (60 endo/40 exo) mixture of nitriles **7** (9) to give pure *endo*-nitrile **7′** followed by lithium aluminum hydride reduction as described by Wilder and Knight (8). Under these reduction conditions partial isomer equilibration occurred and **8** was obtained as a 91:9:endo/exo mixture.

An alternate synthesis of **8**, which avoided both the fractionation and the hydride reduction, was adapted from the literature. Using a modification of the procedures of Alder and Windemuth (10) and Hall (11), allylamine was condensed with cyclopentadiene dimer under cracking conditions (165-180° for 16-50 hours) affording a 30-40% yield of **8** as an 85/15:endo/exo mixture (12) after simple distillation. Treatment of this mixture with a limiting amount of diphenylcarbamyl chloride, followed by crystallization, gave a 74% yield of pure *endo*-**9**.

Condensation of **6** with **9** as previously described (2) gave Gliamilide® (**10**) in 65% yield.

EXPERIMENTAL

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were carried out by the Physical Measurements Laboratory of Pfizer Inc. Ir spectra were determined with a Perkin-Elmer Model 21 and Model 727B spectrophotometer. Nmr spectra were recorded on a Varian Associates Model A-60 spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), intergration, coupling constants, and interpretation. Gas chromatographic studies were carried out using a Varian 90P model instrument with a 10′ x 1/4′ Carbowax 20M (20% on alk. (KOH) fire brick) at 105°.

4-[2-(2-Methoxynicotinamido)-ethyl]pyridine (**11**).

A three liter, three neck, round bottom flask equipped with a mechanical stirrer, reflux condenser and dropping funnel was charged with 4-(2-aminoethyl)pyridine (7) (61.0 g., 0.5 mole) in 50 ml. of methylene chloride. Sodium carbonate monohydrate (124.0 g., 1.0 mole) in 500 ml. of water was added in one portion, and the stirred heterogeneous reaction mixture was cooled in an ice-bath. 2-Methoxynicotinyl chloride (2) (86 g., 0.5 mole) in methylene chloride (500 ml.) was added dropwise after which the mixture was allowed to warm to room temperature. Vigorous stirring was continued for 2 hours. The organic layer was removed and the aqueous layer extracted twice with 100 ml. portions of methylene chloride. The combined organic layers were then extracted three times with cold, dilute (0.5*N*) sodium hydroxide. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to a yellow oil, which solidified upon standing, affording 97 g. (75%) of product. Recrystallization from cyclohexane gave the analytical sample, a white crystalline solid, m.p. 84-87°; ir (potassium bromide): δ max 2.98 (N-H) 6.02 and 6.08 μm (C = O); nmr (deuteriochloroform): δ 2.95 (t, 2, J = 7.0 Hz, H-11), 3.78 (q, 2, J = 7.0 Hz, H-10, really a dt with fortuitous overlap, irradiation of the amide N-H signal simplifies this signal to a triplet), 3.96 (s, 3, O-*CH*$_3$), 7.03 (dd, 1, $J_{5,6}$ = 5.0 Hz, $J_{4,5}$ = 7.5 Hz, H-5), 7.12-7.28 (m, 2, H-3′ and H-5′), 7.80-8.12 (m, 1, -CON*H*-), 8.23 (dd, 1, $J_{5,6}$ = 5.0 Hz, $J_{4,6}$ = 2.0 Hz, H-6), 8.46 (dd, 1, H-4) and 8.40-8.60 (m, 2, H-2′ and H-6′).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.24; H, 5.90; N, 16.04.

4-[2-(2-Methoxynicotinamido)ethyl]piperidine (**12**).

4-[2-(2-Methoxynicotinamido)ethyl]pyridine (**11**) (25.7 g., 0.1 mole) in anhydrous methanol (150 ml.) was placed in a Parr hydrogenation bottle (500 ml. capacity). Exactly one equivalent of aqueous hydrochloric acid (17 ml. of 0.589 *N* acid) and 1.0 g. of platinum oxide were added and the mixture hydrogenated at 50 psi until hydrogen uptake was complete (about 2 hours). The catalyst was removed by filtration and the reaction mixture concentrated *in vacuo* to a yellow, viscous oil. This oil was dissolved in chloroform (500 ml.) and extracted with sodium hydroxide (4x with 200 ml. portions of 2*N* sodium hydroxide). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness to give 27 g. (*ca.* 100%) of product, a light yellow oil; nmr ($DMSO_{d-6}$): 0.96-2.18 (m, 7, H-3′, H-4′, H-5′ and H-11) 2.49-3.61 (m, 7, H-2′, H-6′, H-10 and piperidine N*H* proton) 3.97 (s, 3, O*Me*), 7.12 (dd, 1, $J_{5,6}$ = 5.0 Hz $J_{4,5}$ = 7.5 Hz, H-5) and 8.04-8.42 (m, 3, H-4, H-6 and CON*H*). This material was used directly in the next step of the reaction. An analytical sample of the picrate was prepared for reference.

Crude 4-[2-(2-methoxynicotinamido)ethyl]piperidine (270 mg., 1 mole) in methanol was treated with an excess of ethanolic picric acid solution. A yellow solid immediately precipitated. This solid was recrystallized twice from methanol to give the analytical sample, 4-[2-(2-methoxynicotinamido)ethyl]piperidine picrate, m.p. 204-206°.

Anal. Calcd. for $C_{20}H_{24}N_6O_9$: C, 48.78; H, 4.91; N, 17.08. Found: C, 48.49; H, 5.15; N, 17.13.

4-[2-(2-Methoxynicotinamido)ethyl]-piperidinesulfonamide (**6**).

Crude 4-[2-(2-methoxynicotinamido)ethyl]piperidine (**12**) (26.5 g., 0.1 mole) was dissolved in pyridine (40 ml.), sulfamide (9.6 g., 0.1 mole) added, and the mixture refluxed for 1 hour. The yellow solution was poured into ice water and the white solid which precipitated was removed by filtration to give 24.0 g. (70%) of product, m.p. 179-181°. Recrystallization from methanol afforded the analytical sample, m.p. 180-182°. This material was identical to an authentic sample of **6** prepared *via* the literature (2) method.

Bicyclo[2.2.1]hept-5-en-2-ylmethylamine (**8**).

A mixture of 66 g. (0.5 mole) of dicyclopentadiene (9) and of 57 g. (1 mole) of allylamine (9) was placed in a steel pressure vessel and kept at 175° for 24 hours. The vessel was cooled, opened, and the contents diluted with 250 ml. of ethyl acetate. This mixture was carefully treated with 500 ml. of 3*N* hydrochloric acid at low temperature. The layers were separated, the aqueous layer was washed once with 250 ml. of ethyl acetate, and then adjusted to *p*H 10 with a 50% sodium hydroxide at low temperature. The basic layer was extracted three times with 350 ml. of ethyl acetate; the organic extracts were combined, dried over magnesium sulfate, filtered, and evaporated. The residue (53 g.) was distilled under reduced pressure to give 43 g. (35%) of bicyclo[2.2.1]hept-5-en-2-ylmethylamine, b.p. 78-80°/30 mm, containing 85% of the endo isomer by VPC analysis.

1-Bicyclo[2.2.1]hept-5-en-2-yl-*endo*-methyl-3,3-diphenylurea (**9**) (2).

To a stirred, biphasic mixture of 2 g. (16.3 mmoles) of the amine mixture **8** prepared above in 30 ml. of methylene chloride and 1.73 g. (16.3 mmoles) of sodium carbonate in 30 ml. of water was added dropwise a solution of 3.4 g. (14.7 mmoles) of diphenylcarbamyl chloride over a period of 30 minutes. The reaction mixture was stirred vigorously for another 2 hours at room temperature. The layers were than separated, the organic layer washed successively with 1*N* hydrochloric acid and water, dried over magnesium sulfate and evaporated. The residue was crystallized from a chloroform-hexane mixture to give 3.5 g. (74%) of pure *endo* product, m.p. 129-130° (lit. (2) m.p. 129-130°).

REFERENCES AND NOTES

(1) Paper VII in a series from these laboratories dealing with sulfamylurea hypoglycemic agents. For paper VI see reference 2.

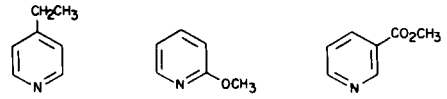
(2) R. Sarges, D. E. Kuhla, H. W. Wiedermann, and D. A. Mayhew, *J. Med. Chem.*, 19, 695 (1976).

(3) J. R. Ryan, F. G. McMahon and A. K. Jain, *Clin. Pharmacol. Ther.*, 17, 243 (1975).

(4) F. J. McCarty, C. H. Tilford, and M. G. Van Campen Jr., *J. A. Chem. Soc.*, 79, 472 (1957).

(5) It is well known that protonation activates a pyridine ring for catalytic hydrogenation. See for example: M. Freifelder, in "Advances in Catalysis", Vol. 14, D. D. Eley, H. Pines and P. B. Weisz, Ed., Academic Press, New York, N.Y., 1963, pp. 203-253.

(6) "Handbook of Organic Structural Analysis", Y. Yukawa, Ed., W. A. Benjamin Inc., New York, N.Y. (1965), p. 597 gives the following acidic dissociation constants for sbustituted pyridines.



(7) L. E. Brady, M. Freifelder, and G. R. Stone, *J. Org. Chem.*, 26, 4757 (1961).

(8) P. Wilder Jr. and D. B. Knight, *ibid.*, 30, 3078 (1965).

(9) Commercial sample obtained from Aldrich Chem. Co.

(10) K. Alder and E. Windermuth, *Ber.*, 71, 1939 (1938).

(11) H. K. Hall Jr., *J. Am. Chem. Soc.*, 82, 1209 (1960).

(12) Isomer ratios of this magnitude should be expected based on literature reports for closely related systems. For example, R. R. Sauers, R. A. Parent, and S. B. Damle, *J. Am. Chem. Soc.*, 88, 2257 (1966) reported that allyl bromide or chloride undergo Diels-Alder reaction with cyclopentadiene to give *endo*, *exo*-5-bromo(chloro)methylbicyclo[2.2.1]hept-2-ene as an 80/20 isomer mixture.