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The Synthesis of Tertiary Pyridylmethylbenzylamines

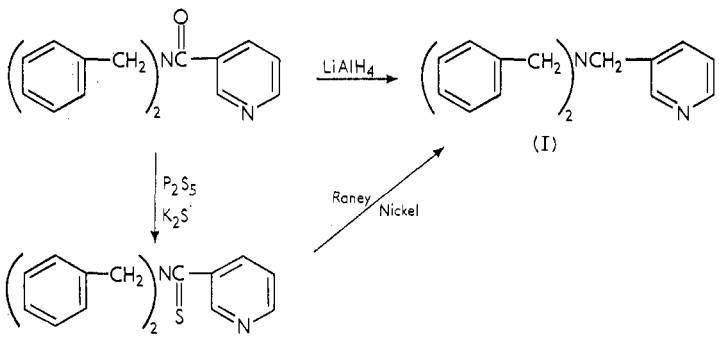
THOMAS S. GARDNER, E. WENIS and JOHN LEE, *Hoffmann-La Roche Inc., Nutley, N.J.*

The quinidine-like action of tribenzylamine has been reported,[1] and it was thought of interest to investigate how the replacement of one or more phenyl residues with pyridyl residues would affect the antifibrillatory action of the compound. These substitutions, it was found, had a completely dystherapeutic effect. In further screening of these compounds, it was found, however, that they had considerable antiulcer activity.[2] The number of compounds for investigation was therefore somewhat extended and forms the basis of this report.

The classical synthesis of tertiary amines is the reaction of the desired organic halides with ammonia[3] or a primary or secondary amine.[4] The success of such procedures is usually considered to be a function of the halide used, temperature, and time of reaction. In attempts to prepare mixed tertiary heterocyclic benzylamines in which the heterocyclic group was pyridylmethyl, it was found that classical procedures failed to give sufficient material to be identified by distillation or crystallization procedures; for example, 3-pyridylmethyl chloride or bromide with ammonia, 3-pyridylmethylamine, or dibenzylamine. Reversal of reactants using benzyl chloride or bromide on 3-pyridylmethylamine or 3-pyridylmethylbenzylamine also failed to yield tertiary amines, using various solvents such as alcohols, pyridine, dimethylformamide, or acetone alone or with potassium carbonate as a condensing agent. Sodium amide[5] or sodium hydride[6] as condensing agents on mixed secondary amines and halides also did not give the desired products.

In an indirect approach, it was found that the *N*,*N*-disubstituted amides in this series could be reduced by lithium aluminium

hydride, or alternatively could be converted to the thioamide and desulphurized with Raney nickel.[7] *N*-(3-Pyridylmethyl)-*N*-dibenzylamine (I) was also prepared by these methods.



This scheme was also successful with *N*-(3-pyridylmethyl)-*N*-benzylbenzamide. However, if two or more pyridyl groups were in the amide, lithium aluminium hydride failed and the starting compound was recovered in good yield.

The mixed secondary amines were conveniently prepared by the reductive condensation[8] of amine and aldehyde, using palladium on carbon as a catalyst. This procedure was also practicable if both rings were heterocyclic.

The heterocyclic primary amines were prepared by reduction of the corresponding nitriles in concentrated ammonium hydroxide solutions[9] using Raney nickel as a catalyst.

The condensation of hydroxynitriles with secondary amines to produce α-cyanobenzyl tertiary amines has been reported,[10] and α-cyanotribenzylamine and *N*-(α-cyanobenzyl)-*N*-(3-pyridylmethyl)-benzylamines were so prepared. All attempts to convert the cyano group to the amide or carboxyl group, using acidic or basic reagents, failed. Either hydrolysis to the component parts occurred or the substance was recovered unchanged.

Pharmacological Findings

The tertiary amines prepared were active in inhibiting ulcer formation in cats and dogs. The best compound, *N*-(3-pyridylmethyl)dibenzylamine (Ro 2-7983/1) (I), was more active than

khellin, atropine, methantheline and propantheline in the inhibition of ulcer formation in the Shay rat[11] and the histamine-induced ulcer in rats,[12] and prolongation of life of the Mann–Williamson dog.[13] The compound is currently being assessed clinically.

Experimental*

N-(*2-Pyridylmethyl*)*benzylamine.* Benzylamine (50 g) and 2-pyridinecarboxaldehyde (50 g) were added to 500 ml of ethanol containing 10 g of 10 per cent palladium on carbon as a catalyst, and hydrogenated under 1000 lb/in^2 of hydrogen at 25° for 1 h. A theoretical uptake of hydrogen was obtained. The recovered solution was concentrated *in vacuo* to an oil which was distilled at 152–155°/3 mm; yield, 65 g (70 per cent), n_D^{24} 1·5798.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78·7; H, 7·1. Found: C, 79·0; H, 7·4.

N-*Benzyl*-N-(*2-pyridylmethyl*)*benzamide.* Benzoylchloride (110 g) and *N*-(2-pyridylmethyl)benzylamine (136 g) were reacted together in pyridine (750 ml) on a water bath at 80° for 4 h. The pyridine was removed *in vacuo* to yield a solid residue. The residual solid was slurried in water and the aqueous phase carefully saturated with sodium bicarbonate. The suspended amide was extracted with ether. Concentration of the ether solution gave a solid which was recrystallized after carbon decolorization from ethyl acetate in the form of colourless crystals; yield, 87 g (38 per cent), m.p. 95–96°.

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79·4; H, 6·0. Found: C, 79·3; H, 5·6.

N-(*2-Pyridylmethyl*)*dibenzylamine.* Dry *N*-benzyl-*N*-(2-pyridylmethyl)benzamide (87 g) was finely pulverized and introduced into a solution of lithium aluminium hydride (37·5 g) previously dissolved in dry ether (2·3 kg). The solution was stirred for 14 h and the excess $LiAlH_4$ decomposed with ethyl acetate (250 ml). The solution was stirred for 2 h, 150 ml of ice water dropped in, and stirring continued for a further hour. The suspension was filtered and the solid cake obtained was extracted with hot benzene (2 l.). The combined ether–benzene solution was concentrated *in vacuo* and the residual oil distilled. The fraction

* All melting points are corrected.

boiling between 220 and 225°/3–5 mm was dissolved in hot ethyl acetate (50 ml). Colourless crystals were obtained on cooling; yield, 19 g (23 per cent), m.p. 47–48°.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83·3; H, 7·0. Found: C, 83·8; H, 7·2.

N-(3-*Pyridylmethyl*)*benzylamine.* Benzaldehyde (212 g) and 3-pyridylmethylamine (216 g) in ethanol (800 ml) were reduced at 500 lb/in^2 of hydrogen at 60° using 10 per cent palladium on charcoal (20 g) as a catalyst. Concentration of the recovered ethanolic solution gave an oil which distilled at 178–180°/2 mm using a 15-cm Vigreaux column to effect fractionation; yield, 325 g (82 per cent), n_D^{25} 1·5772. A larger experiment gave a 99 per cent yield; n_D^{23} 1·5790.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78·7; H, 7·1. Found: H, 78·1; H, 7·1.

N-(*3-Pyridylmethyl*)-N-*benzylbenzamide.* *N*-(3-Pyridylmethyl)-benzylamine (100 g) was dissolved in pyridine (500 ml) and benzoyl chloride (105 g) added over a period of ½ h. The solution was then heated at reflux temperature for 4 h, cooled, and 100 ml of water slowly added with stirring. The solution was concentrated and the solid residue dispersed in ice water (1·5 l.) and made alkaline with concentrated ammonium hydroxide (28 per cent) (200 ml). The suspended amide was extracted five times with ether using 250 ml for each extraction. The combined ether extracts were washed with ice water (250 ml) and concentrated to 200 ml. The product crystallized and was recrystallized from ether; yield, 80 g (53 per cent), m.p. 75–76°; recrystallization gave a light buff-coloured material, m.p. 78–79°. Larger batches gave up to 70 per cent yields.

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79·6; H, 6·0. Found: C, 80·0; H, 6·2.

N,N-*Dibenzylnicotinamide hydrochloride.* *N*,*N*-Dibenzylnicotinamide[14] (12 g) was dissolved in ethanol (100 ml) and 10 ml of 10 N hydrogen chloride in ethanol added. Ether (50 ml) was added and on cooling a colourless material crystallized. It was recrystallized from ethanol; yield, 10 g, m.p. 175–176°.

Anal. Calcd. for $C_{20}H_{18}N_2O.HCl$: N, 8·3. Found: N, 8·6.

N-(*3-Pyridylmethyl*)*dibenzylamine.* Dry *N*,*N*-dibenzylnicotinamide (209 g) (m.p. 78–79°) was added over a period of ½ h to a

stirred solution of lithium aluminium hydride (290 g) in dry ether (2·3 kg). Stirring was continued for 14 h. Ethyl acetate (450 g) was added to the suspension and stirring was continued for 1 h. Then ice water (150 g) was dropped in and the suspension stirred for 1 h. After filtration the solid residue was extracted with 1·1 kg of hot ethyl acetate. The combined ethyl acetate–ether solution was concentrated to an oil and distilled through a 15-cm Vigreaux column. The fraction boiling between 200 and 220°/1–2 mm was collected; yield, 122 g.

The 122 g of crude product was dissolved in hot ethyl acetate (90 g) and decolorized using 10 g of activated carbon (Norite A). On cooling, the colourless product crystallized; yield, 84 g (42 per cent), m.p. 62–63°. Yields varied from 30–45 per cent.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83·4; H, 7·0. Found: C, 83·6; H, 6·9.

N-(3-Pyridylmethyl)dibenzylamine was also obtained in a yield of 44 per cent by the reduction of *N*-(3-pyridylmethyl)benzylbenzamide using $LiAlH_4$ in ether.

N,N-*Dibenzylthionicotinamide.* *N*,*N*-Dibenzylnicotinamide (246 g) was added to a stirred solution of phosphorus pentasulphide (246 g) and finely powdered potassium sulphide (61·5 g) in dry pyridine (2·7 kg). The solution was heated to the boiling point of pyridine in ½ h and refluxed for 6 h.

The solution was concentrated at 20 mm until 2·3 kg of pyridine was removed. The residual thick solution was poured into 3 kg of ice and 500 ml of ice water with efficient stirring. Concentrated ammonium hydroxide (443 g) was slowly added to the ice water suspension, stirred for 14 h and filtered. The recovered solid was resuspended in cold water (2 l.) and concentrated ammonium hydroxide (50 g) added. The suspension was stirred for 2 h, filtered and the solid residue washed with cold water; yield, 257 g (99 per cent), m.p. 92°. Extraction of the crude thioamide with hot water or dilute ammonium hydroxide followed by recrystallization from hot water or hot ethanol using activated carbon for decolorization, gave a yellow material, m.p. 97–99°.

Anal. Calcd. for $C_{20}H_{18}N_2S$: C, 75·4; H, 5·7; S, 10·1. Found: C, 75·2; H, 5·4; S, 10·1.

N-(*3-Pyridylmethyl*)-N-*benzylthiobenzamide.* *N*-(3-Pyridylmethyl)-*N*-benzylbenzamide was treated with phosphorus

pentasulphide and potassium sulphide in pyridine as for the preparation of the *N*,*N*-dibenzylthionicotinamide described above. The yields of *N*-(3-pyridylmethyl)-*N*-benzylthiobenzamide were 87–99 per cent, m.p. 94–95°, of the crude product which on recrystallization from ethanol gave a yellow material, m.p. 96–97°.

Anal. Calcd. for $C_{20}H_{18}N_2S$: S, 10·1. Found: S, 10·3.

N-(3-*Pyridylmethyl*)*dibenzylamine from* N,N-*dibenzylthionicotinamide.* *N*,*N*-dibenzylthionicotinamide (200 g) was added to a suspension of well drained Raney nickel (1·2 kg) in ethanol (1·92 kg) and water (600 ml). The suspension was stirred by an efficient agitator and heated to reflux for 6 h. The source of heat was removed and the suspension was stirred overnight. After filtration, the pyrophoric Raney nickel was washed on the filter with ethanol (2·4 kg) previously saturated with carbon dioxide (Dry Ice). The combined filtrates were concentrated to an oil and distilled through a 15-cm Vigreaux column. The fraction boiling from 200–220°/2 mm (180 g) was collected and recrystallized from hot ethyl acetate as described above for *N*-(3-pyridylmethyl)dibenzylamine; yield, 82 g (44 per cent), m.p. 62–63°.

The desulphurization of *N*-(3-pyridylmethyl)benzylthiobenzamide with Raney nickel gave 40–45 per cent of recrystallized *N*-(3-pyridylmethyl)dibenzylamine.

N-(*3-Pyridylmethyl*)*dibenzylamine monohydrochloride.* *N*-(3-Pyridylmethyl)dibenzylamine (5 g) was dissolved in 10 N hydrogen chloride in ethanol (50 ml) and concentrated to an amorphous solid *in vacuo*. The amorphous solid was dissolved in ethanol (50 ml) and *N*-(3-pyridylmethyl)dibenzylamine (5 g) added. On cooling, a colourless crystalline monohydrochloride separated; yield, 8 g, m.p. 209–210°.

Anal. Calcd. for $C_{20}H_{20}N_2.HCl$: C, 74·0; H, 6·6; N, 8·6. Found: C, 74·4; H, 6·4; N, 8·0.

N,N-*Dibenzylisonicotinamide.** Dibenzylamine (25 g) was added to a pyridine (300 ml) solution of isonicotinoyl chloride prepared from isonicotinic acid (34 g) using thionyl chloride. The solution was refluxed for 2 h, cooled and concentrated to a small volume. Water (250 ml) was added and 50 g of sodium bicarbonate added

* This compound was also prepared independently by O. Straub of F. Hoffmann-La Roche and Co., Basle, Switzerland. A sample of m.p. 96–98° was obtained from ethanol and petroleum ether.

in small portions (foaming!). After 14 h, the suspension was extracted with ether. The ether solution was decolorized with activated carbon and on concentration deposited colourless crystals; yield, 30 g, m.p. 85–86°.

Anal. Calcd. for $C_{20}H_{18}N_2O$: N, 9·3. Found: N, 9·2.

N,N-Dibenzylisonicotinamide (8 g) in ethanol (100 ml), was treated with 10 ml of 10 N hydrogen chloride in ethanol. On addition of 100 ml of ether and cooling, the colourless hydrochloride crystallized; yield, 6 g, m.p. 185–187°.

Anal. Calcd. for $C_{20}H_{18}N_2O.HCl$: N, 8·3. Found: N, 8·4.

N-(*4-Pyridylmethyl*)*dibenzylamine.* *N,N*-Dibenzylisonicotinamide (28·5 g) was reduced in ether (150 ml) using lithium aluminium hydride (11·4 g) as described for the 2- and 3-isomers. Concentration of the ether layer gave an oil which was crystallized from hexane (Skellysolve B) as a pale yellow compound; yield, 10 g, m.p. 85–86°. Mixed m.p. with the amide, 75–76°.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83·9; H, 7·0. Found: C, 83·6, H, 6·9.

N-(*4-Methoxybenzyl*)-N-*benzylnicotinamide.* *N*-(4-Methoxybenzyl)benzylamine (184 g) was added to a solution of nicotinoyl chloride (160 g) in pyridine (900 ml). The solution became warm, was stirred at 60° for 2 h, concentrated to 300 ml and poured into ice water (4 l.). Sodium bicarbonate was carefully added until the solution became slightly alkaline. The suspension was extracted with ether, the ether removed, and the solid residue dissolved in hot ethyl acetate (500 ml). After decolorization with activated carbon, colourless crystals were obtained; yield, 105 g, m.p. 78–79°.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 75·6; H, 6·0. Found: C, 75·6; H, 5·2.

N-*Benzyl*-N-(*4-methoxybenzyl*)-*3-pyridylmethylamine.* *N*-(4-Methoxybenzyl)-*N*-benzylnicotinamide (100 g) was reduced in ether solution with lithium aluminium hydride (12 g) as described above. On distilling the residue from the ether–ethyl acetate solution, an oil was obtained which did not crystallize; yield, 10 g, b.p. 230°/3–4 mm, n_D^{23} 1·5892.

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79·2; H, 7·0. Found: C, 79·4; H, 7·1.

N,N-*Bis*(*3-pyridylmethyl*)*benzylamine.* Crude, amorphous, dry

N-(3-pyridylmethyl)-*N*-benzylnicotinamide (300 g), prepared by treating *N*-(3-pyridylmethyl)benzylamine with nicotinoyl chloride in pyridine, was treated in pyridine (3 l.) with phosphorus pentasulphide (300 g) and finely powdered potassium sulphide (75 g) at reflux for 6 h. The solution was concentrated to half-volume and poured into ice and water. Concentrated ammonium hydroxide was added to pH 9 and a red, amorphous solid separated. The thioamide so obtained did not crystallize from the usual organic solvents or hot water. The amorphous material was dissolved in 80 per cent ethanol–water (2·5 l.) and desulphurized with drained Raney nickel (1600 g) by refluxing for 6 h. The catalyst was removed as previously described and the aqueous ethanolic filtrate concentrated to an oily residue. The residue was extracted with ether and concentration of the ether gave a crude product which was fractionated through a 15-cm Vigreaux column. The fraction boiling at 190–225°/2–3 mm (45 g) was refractionated at 5 mm, b.p. 225°; yield, 25 g, n_D^{20} 1·5910. The light-yellow amorphous material solidified at 4°, and liquified at 35–37°.

Anal. Calcd. for $C_{19}H_{19}N_3$: C, 78·9; H, 6·6. Found: C, 79·5; H, 6·9.

N,N-*Bis(3-pyridylmethyl)nicotinamide.* Bis(3-pyridylmethyl)-amine[15] (95 g) was dissolved in pyridine (500 ml) and treated with nicotinoyl chloride (99 g). The solution spontaneously warmed to 70° and was heated at 80° for 4 h. It was concentrated to 100 ml, poured into ice water (2 l.) and brought to pH 9 with sodium bicarbonate. The amide could not be extracted with ether, and therefore the neutralized solution was evaporated to dryness and the solid residue extracted with hot ethanol. Concentration of the ethanolic solution gave a solid which crystallized from ethyl acetate in very pale yellow crystals; yield, 32 g (22 per cent), m.p. 99–100°. Using the experience gained from the above experiment, the yield was raised to 67 per cent on a second try under identical reaction conditions.

Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 71·0; H, 5·3. Found: C, 71·1; H, 5·0.

This compound was soluble in water and was not reduced to the tertiary amine using lithium aluminium hydride.

α-*Cyano-tribenzylamine.* Dibenzylamine (378 g) and mandelonitrile (250 g) in ethanol (250 ml) were heated at reflux for

2 h. The solution was kept at 4° for 4 days. An oil separated which crystallized. The colourless crystals were filtered off and recrystallized from ethanol; yield, 278 g, m.p. 102–104°.

Anal. Calcd. for $C_{22}H_{20}N_2$: N, 9·0. Found: N, 9·0.

N-(α-*Cyanobenzyl*)-N-(*3-pyridylmethyl*)*benzylamine.* A solution of mandelonitrile (420 g) and *N*-(3-pyridylmethyl)benzylamine (615 g) in ethanol (415 ml) was heated at reflux for 2 h. On cooling, an amorphous precipitate separated. Repeated solution in ethanol and cooling gave a crystalline, colourless product; yield, 450 g, m.p. 80–81°.

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80·5; H, 6·1; N, 13·4. Found: C, 80·8; H, 6·3; N, 13·3.

Summary. A number of pyridylmethylbenzylamines were prepared by the reduction of the *N*,*N*-disubstituted amides, using lithium aluminium hydride. Conversion of the amides to the thioamides by phosphorus pentasulphide and potassium sulphide in pyridine, followed by desulphurization using Raney nickel, was also used to prepare some of the pyridylmethylbenzylamines. One compound, *N*-(3-pyridylmethyl)-dibenzylamine, was active in the prophylaxis of ulcer formation in the Shay rat, and the histamine-induced ulcer in the rat, and prolonged the life of the Mann–Williamson dog to a greater extent than a number of commercial antiulcer compounds used as controls.

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