

ANTIHISTAMINE AGENTS. V. 2-SUBSTITUTED ETHYLAMINES

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At the time these compounds were prepared, the most active known anti-histamine agents were 2-dimethylaminoethyl benzohydril ether (Benadryl) (1), and N,N-dimethyl-N'-benzyl-N'-2-pyridylethylenediamine (Pyribenzamine) (2). Consequently, the structures of these compounds bear varying degrees of resemblance to those established agents. Each of the eleven compounds prepared has the general formula $R-CH_2-CH_2-NR_1R_2$ in which R_1 and R_2 may be methyl, benzyl, or hydrogen. The R group includes 2-pyrazylamino-, 2-pyrazyl-oxy-, 2-amino-4-pyrimidyloxy-, 5-chloro-2-pyrimidyloxy-, 5-chloro-2-pyrimidyl-mercapto-, 2-pyridyloxy-, *o*-nitranilino-, 2-benzothiazolyloxy-, N-benzyl-2-pyridylamino-, and benzohydryloxy-.

Most of the compounds were prepared using the Williamson ether synthesis. Each of the dimethylaminoethoxy compounds was made by dissolving sodium metal in an excess of commercial dimethylaminoethanol and treating the resulting solution with the appropriate aromatic halide. In those cases where the reagent alcohol was less readily obtained, it was dissolved in toluene, where it was converted to the sodium salt and thence etherified. A modification of this for the preparation of substituted amines involves the use of a substituted sodamide, sodio-2-benzylaminopyridine, after the method used by Whitmore (3). In two cases 2,5-dichloropyrimidine was used as the halide. The product is designated as 5-chloro-2-pyrimidyl because English (4) prepared 5-chloro-2-methylaminopyrimidine in 87% yield by a similar reaction. English's compound was identified by an independent synthesis. Two secondary amines were prepared in good yields by the direct action of amines on halogen compounds, and one was prepared by treatment of a primary amine with benzaldehyde and subsequent hydrogenation of the Schiff's base formed.

None of the compounds was more active than Benadryl when tested *in vitro* against histamine spasm of guinea pig gut.

EXPERIMENTAL

All melting points are corrected. All analyses except the neutral equivalents are the average of two or more determinations. Combustion analyses were carried out under the direction of Dr. J. A. Kuck; the pharmacology was studied under the supervision of Dr. J. T. Litchfield, Jr.

2-(2-Dimethylaminoethyl)aminopyrazine. When 3.5 g. of chloropyrazine and 5.3 g. of 2-dimethylaminoethylamine were heated for three hours in a bath at 130-140° and then treated with 40% sodium hydroxide, an oil formed. When this was removed by washing with ether, it gave an oil, 2.6 g. of which distilled 120-124° at 4 mm., a 51% yield. The picrate from this, after repeated crystallization from ethanol, melted 157-159°.

Anal. Calc'd for $C_{14}H_{17}N_7O_7$: C, 42.53; H, 4.33; N, 24.80.

Found: C, 43.12; H, 4.77; N, 24.54.

2-(2-Dimethylaminoethoxy)pyrazine. A solution of 4 g. of sodium in 125 cc. of 2-dimethylaminoethanol was treated with 20 g. of chloropyrazine and stirred on the steam-bath for ninety minutes. The cooled liquid was filtered and vacuum distilled. A 21.7-g. cut boiling 80–89° at 5 mm. was collected (74%). The picrate melted at 136–138°.

Anal. Calc'd for $C_{14}H_{16}N_6O_8$: N, 21.21. Found: N, 21.54.

4-(2-Dimethylaminoethoxy)-2-aminopyrimidine. A solution of 4.6 g. of sodium in 200 cc. of 2-dimethylaminoethanol was treated with 25.9 g. of 2-amino-4-chloropyrimidine and then stirred on a steam-bath for an hour. The cooled, filtered, vacuum-concentrated product was continuously extracted with ethyl acetate. Three crystallizations from ethyl acetate gave 14.5 g. (40%) of tan crystals melting at 110–111°.

Anal. Calc'd for $C_8H_{14}N_4O$: N, 30.75. Found: N, 30.51.

2-(2-Dimethylaminoethylmercapto)-5-chloropyrimidine. Using essentially the method of Suter (5), 2-dimethylaminoethylmercaptan was made in 38% yield. The product distilled at 40–50° at 10–20 mm. pressure, and it gave a monohydrochloride which melted at 159–161° after recrystallization from isopropanol.

A mixture of 0.43 g. of sodium and 2 g. of 2-dimethylaminoethylmercaptan was stirred for seventeen hours at room temperature in toluene. The white suspension was then treated with 2.8 g. of 2,5-dichloropyrimidine and heated two hours on the steam-bath. Cooling, filtration, and vacuum distillation produced 2.22 g. (50%) of a light yellow oil boiling at 110–120° at 2 mm. The hydrochloride of this, recrystallized from isopropanol, melted at 188–190°. The picrate melted at 177–179°.

Anal. Calc'd for $C_8H_{14}Cl_2N_2S$: C, 37.80; H, 5.15; N, 16.53.

Found: C, 37.83; H, 6.03; N, 15.29.

2-(2-Dimethylaminoethoxy)-5-chloropyrimidine. A solution of 1.23 g. of sodium in 50 cc. of 2-dimethylaminoethanol was treated with 8 g. of 2,5-dichloropyrimidine and heated on a steam-bath for an hour. The product was chilled, filtered and concentrated by evaporation *in vacuo*. The hydrochloride was formed by passing dry hydrochloric acid into an alcoholic solution of the crude product followed by precipitation by dilution with ether. Recrystallization from isopropanol gave 8 g. (62%) of shiny white crystals melting 180–182°. The picrate melts 160–161°.

Anal. Calc'd for $C_8H_{14}Cl_2N_2O$: C, 40.35; H, 5.50; N, 17.65.

Found: C, 41.39; H, 6.18; N, 17.32.

2-(2-Benzylaminoethoxy)pyridine. A solution of 15.1 g. of 2-benzylaminoethanol and 15.8 g. of 2-bromopyridine in 50 cc. of toluene was added dropwise to a suspension of 5.5 g. of potassium in toluene. The reaction was run hot, and ammonia evolved rapidly. After twenty hours at reflux temperature the mixture was cooled, filtered, and extracted with 5% hydrochloric acid. When this was made alkaline again and extracted and distilled, two separate products were obtained. One was 2.8 g. of oil boiling 115–120° at 0.5 mm. which is probably N-benzyl-N-(2-pyridyl)aminoethanol. It did not form a hydrochloride with pentachloroethane but did react with sodium. A second cut was 8.2 g. (35%) boiling 135–137° at 0.5 mm. This was heated with 40 cc. of pentachloroethane for thirty minutes on the steam-bath to produce 6.0 g. of white crystals. These were recrystallized four times from ethyl acetate to produce colorless plates melting at 174–175°.

Anal. Calc'd for $C_{14}H_{17}ClN_2O$: C, 63.51; H, 6.47; N, 10.58.

Found: C, 63.63; H, 6.73; N, 10.26.

2-(2-Dimethylaminoethoxy)pyridine. This product was prepared in 40% yield by the action of 5 g. of 2-bromopyridine on a solution of 0.73 g. of sodium in 30 cc. of 2-dimethylaminoethanol. The product was 2 g. of oil boiling 80–90° at 0.3 mm. This was made into the dipicrate which melted at 155°.

Anal. Calc'd for $C_{21}H_{20}N_8O_{15}$: C, 40.32; H, 3.22; N, 17.92.

Found: C, 40.38; H, 3.54; N, 17.81.

Bis-(2-N-benzyl-N-2-pyridylaminoethyl) ether. Sodamide, prepared from 1.3 g. of sodium in liquid ammonia containing a trace of ferric nitrate, was treated with 10.4 g. of ben-

zyl-2-pyridylamine. The liquid ammonia was replaced with dry toluene and 4.0 g. of bis-(2-chloroethyl) ether was added at room temperature. This was heated for four hours on the steam-bath before hydrolysis. Many unsatisfactory ways of purifying the product were tried before it was found that the difficult impurities were removed by prolonged steam distillation. The oil remaining behind was recrystallized from ethanol and a little Darco to give 0.61 g. of white crystals melting at 99–100° (5.5%).

Anal. Calc'd for $C_{23}H_{30}N_4O$: C, 76.68; H, 6.90; N, 12.78.

Found: C, 76.29; H, 7.03; N, 12.97.

2-Dimethylaminoethyl-o-nitraniline. When 52.5 g. of *o*-chloronitrobenzene, 29.3 g. of 2-dimethylaminoethylamine, and 70 g. of sodium carbonate were refluxed together for four hours, an orange mixture, largely solid, resulted. The product was steam distilled, and the red oil so obtained was vacuum distilled; 57 g. (83%) was collected, boiling 129–135° at 2 mm. A hydrochloride was prepared from this and recrystallized from ethyl acetate. After sublimation at 1 mm. pressure the salt melted at 186–188°.

Anal. Calc'd for $C_{16}H_{16}ClN_2O_2$: C, 48.88; H, 6.51; N, 17.10; N.E. 246.

Found: C, 48.77; H, 6.87; N, 16.71; N.E., 239.

2-(2-Dimethylaminoethoxy)benzothiazole. A solution of 0.68 g. of sodium in 30 cc. of 2-dimethylaminoethanol was treated with 5 g. of 2-chlorobenzothiazole during ten minutes. The mixture was heated for an hour on a steam-bath, then chilled and filtered. The excess solvent was evaporated *in vacuo*, and the light yellow, oily residue was separated from an insoluble gum by extraction with ether. Concentration of the ether solution and distillation yielded 4.05 g. (62%) boiling from 147–155° at 4 mm. A solution of 3.39 g. of this liquid in alcohol was treated with dry hydrogen chloride, and the hydrochloride was precipitated by the addition of ether. Crystallization of the precipitate from alcohol gave 1.54 g. of glistening plates, m.p. 189–191°.

Anal. Calc'd for $C_{11}H_{13}ClN_2OS$: C, 51.05; H, 5.84; N, 10.83.

Found: C, 51.20; H, 6.09; N, 10.76.

2-Aminoethyl benzohydril ether. A hot solution of 1.6 g. of sodium in 50 cc. of ethanolamine was treated with 17.0 g. of bromodiphenylmethane. The resulting solution was kept hot for an hour and then concentrated *in vacuo* to 38 cc. volume. This was drowned in 200 cc. of water and extracted with ether. The ether extract was vacuum distilled to yield 11.3 g. (72%) of a yellow oil boiling at 150–153° at 0.3 mm. This oil crystallized in ether and was recrystallized from ether-ligroin mixtures, m.p. 73–74°. Pharmacology, but no chemistry of this compound has been reported (6).

Anal. Calc'd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; N.E., 227.

Found: C, 79.26; H, 7.66; N, 5.89; N.E., 232.

2-Benzylaminoethyl benzohydril ether. When 23 g. of 2-aminoethyl benzohydril ether and 10.6 g. of benzaldehyde were heated overnight in 100 cc. of boiling toluene, 1.8 cc. of water was produced and collected in a Dean trap. Attempts to reduce the product at 3 atm. hydrogen pressure failed over platinum oxide and over palladium on charcoal. When the mixture was heated to 115° and shaken over two teaspoonsful of Raney nickel with high pressure hydrogen it absorbed 70% of the theoretical hydrogen. The product was filtered and distilled to give two cuts. The first was 12.1 g. boiling 62–147° at 0.1 mm., and it is unidentified. The second was 10.1 g. (25%) of yellow oil boiling 182–204° at 0.4–0.6 mm.; n_D^{20} 1.5912. This was converted to the hydrobromide by treatment with alcoholic hydrobromic acid. It was recrystallized from absolute alcohol, m.p. 181–182°.

Anal. Calc'd for $C_{22}H_{24}BrNO$: C, 66.33; H, 6.07; N, 3.52; N.E., 398.

Found: C, 66.29; H, 6.26; N, 3.59; N.E., 406.

SUMMARY

The preparation and some properties of eleven new 2-substituted ethylamines are recorded.

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