pair being Haworth's ethylglucofuranosides.[2] The new α-furanoside, similar to the α-ethylglucofuranoside but unlike the corresponding β-isomers, is not hygroscopic and crystallizes readily from its solvents. It can be isolated in about 2% yield, as a by-product of the main reaction, which gives rise to the β-isomer.

Experimental

Preparation of α-Ethylgalactofuranoside.—To a solution of 28 g. of galactose ethylmercaptal in 250 cc. of absolute ethyl alcohol at 70°, 35 g. of yellow mercuric oxide and 10 g. of powdered drierite were added. The mixture was stirred rapidly, while a solution of 35 g. of mercuric chloride in 150 cc. of absolute ethyl alcohol was added over a period of thirty to forty minutes. After the reaction mixture cooled down to 30° in one hour, it was filtered and 10 cc. of pyridine was added to the filtrate, which was then kept at 0° overnight. After the pyridine–mercuric chloride compound was filtered off, the filtrate was evaporated *in vacuo* at 40° to a sirup, which was dissolved in 100 cc. of water, the solution neutralized with dilute alkali to phenolphthalein, then evaporated to a sirup at 50° *in vacuo*. For removal of water, the substance was taken up in absolute alcohol and the solution evaporated to a thick sirup. This was dissolved in 500 cc. of boiling ethyl acetate, the solution cooled to room temperature, then decanted from oily drops and seeded with β-ethylgalactofuranoside. The crystallization of the β-compound was completed at 0°; yield 10 g. The mother liquor was evaporated to 200 cc. and kept in the ice box for a prolonged time. After several days usually some more β-crystals were precipitated, and possibly some α-crystals, too. The latter were separated mechanically from the β-crystals, as their appearance was that of round translucent buttons, while the β-isomer crystallized in white fragile needles. In some experiments only β-crystals were formed and from the mother liquor, after filtration, the α-compound precipitated as small round buttons all over the wall of the flask. In either case, the crude product ($[\alpha]^{20}D$ 84°) was dissolved in about 100 times its weight of hot ethyl acetate, and, on cooling to room temperature, the solution deposited the pure α-ethylgalactofuranoside in the form of beautiful short needles; yield about 0.40 g.; m. p. 139–140°; $[\alpha]^{20}D$ 92° (0.0500 g. substance, 4 cc. of water solution, 2-dm. semi-micro tube, rotation 2.30° to the right). The substance was devoid of action toward boiling Fehling's solution.

For the determination of the rate of hydrolysis, 0.1087 g. of the substance was dissolved in 20 cc. of hot water, the solution was quickly mixed with 5 cc. of hot 0.05 *N* hydrochloric acid ($t = 0$) and replaced in the boiling water-bath. At intervals of twelve, eighteen, and thirty minutes, respectively, 5-cc. portions were removed and analyzed for free galactose (found: 11.45, 14.25, and 18.33 mg., respectively; calcd. for complete hydrolysis: 18.81 mg.) according to the method of Bertrand. From these data, the average value of $k \times 10^5 = 8000$, calculated from the unimolecular law, was obtained.

Anal. Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.96, 46.23; H, 7.87, 7.90.

(2) Haworth and Porter, *J. Chem. Soc.*, 2796 (1929); Haworth, Porter and Waine, *ibid.*, 2254 (1932).

Summary

α-Ethylgalactofuranoside has been isolated in the crystalline state. Its specific rotation in water solution, 92°, checks with Hudson's rules of isorotation. The rate of hydrolysis in aqueous acid is of the order given by furanosides.

PRINCETON, NEW JERSEY RECEIVED OCTOBER 21, 1937

[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XIII. Analogs of Ephedrine Containing the N-Phenylpiperazine Nucleus

BY BURT L. HAMPTON AND C. B. POLLARD

The effect of several reducing agents on certain of the α-amino ketones derived from N-phenylpiperazine, which have been reported previously by us,[1] forms the basis of this paper. It was desired to prepare certain amino alcohols which were similar in structure to ephedrine and related compounds and which contained the N-phenylpiperazine nucleus. We have been successful in reducing two of these ketones, N-phenyl-N′-phenacylpiperazine, and N-phenyl-N′-*p*-methylphenacylpiperazine, to the corresponding secondary alcohols. Other reductions were not attempted at this time.

The success of this reduction is of interest because of the fact the nitrogen atom is heavily loaded, and, generally, when this is the case most reducing agents tend to split the molecule.

The reduction of N-phenyl-N′-phenacylpiperazine with aluminum amalgam in neutral solution gave N-phenylpiperazine and acetophenone. On reduction with hydrazine in a sealed tube at 185–195° N-phenylpiperazine was the only product isolated and identified, although a strong odor of

(1) Hampton and Pollard, THIS JOURNAL, **59**, 2446 (1937).

acetophenone was present on opening the tube. Sodium and absolute alcohol apparently gave a 25% yield of the corresponding secondary alcohol indicated by the melting point of the product and a mixed melting point with an authentic specimen; however, the main product was a sticky liquid substance which was not identified. Reduction of the ketone with hydrogen and palladinized charcoal in acid solution gave an 85% yield of N-phenyl-N′-β-phenyl-β-hydroxyethylpiperazine, the desired secondary alcohol. This alcohol was also obtained from the ketone in 80% yield by reduction with sodium ethoxide and ethanol in a sealed tube at 185–195°. This latter method was discovered accidentally. It was originally desired to reduce N-phenyl-N′-phenacylpiperazine to the tertiary amine, N-phenyl-N′-phenylethylpiperazine. To accomplish this reduction the well-known method of Wolff[2] was selected. The ketone, hydrazine, sodium ethoxide and ethanol were heated in a sealed tube at 185–195° for eight hours. Two products were obtained, one of which proved identical with the secondary alcohol obtained by the reduction of N-phenyl-N′-phenacylpiperazine by means of hydrogen and palladinized charcoal. The yield of the alcohol was from 75 to 80%. The other product obtained proved to be identical with the compound obtained from phenylethyl bromide and N-phenylpiperazine, the yield being only about 4%. When the hydrazine was mixed intimately with the reactants the yield of the tertiary amine was increased to 50% and the alcohol decreased to about 25%. When the hydrazine was omitted the alcohol was obtained in 80% yield.

N-phenyl-N′-*p*-methylphenacylpiperazine was also reduced to the corresponding secondary alcohol, N-phenyl-N′-β-*p*-tolyl-β-hydroxyethylpiperazine, by the two methods described above.

It is well known that sodium ethoxide and ethanol act as a reducing agent when heated together in a sealed tube. For example, Haller and Minquin[3] have shown that when sodium ethoxide is heated in a sealed tube at 200–210° in the presence of an excess of ethanol, diphenyl ketone is reduced to diphenylcarbinol. However, as far as the authors are able to determine, sodium ethoxide and ethanol have never before been used to reduce an α-amino ketone to the secondary alcohol.

(2) Wolff, *Ber.*, **44**, 2760 (1911); *Ann.*, **394**, 86 (1912).
(3) Haller and Minquin, *Compt. rend.*, **120**, 1105 (1895).

The two secondary alcohols prepared readily react with benzoyl chloride, but the esters formed are sticky oils. However, they readily form the solid dihydrochlorides. The alcohols also yield the dihydrochlorides which are readily soluble in water.

The physiological properties of these compounds are being studied.

Experimental[4]

N-Phenyl-N′-β-phenyl-β-hydroxyethylpiperazine, (I). Method A.—Two grams (0.007 mole) of N-phenyl-N′-phenacylpiperazine hydrochloride was dissolved in 150 ml. of water in a 400-ml. bottle and 4 ml. of concentrated hydrochloric acid was added. Approximately 0.6 g. of palladinized charcoal was suspended in this solution. Hydrogen, under a pressure of about 30 inches (75 cm.) of water, was passed into the solution, the bottle being shaken vigorously by means of a small electric motor. At the end of three hours approximately the theoretical amount of hydrogen had been absorbed. The catalyst was filtered from the solution and an excess of sodium hydroxide solution added to the filtrate. The white precipitate was filtered, washed several times with water, dried between porous plates and recrystallized from ethanol, m. p. 110–111°, yield 85%. This compound is readily soluble in chloroform, slightly soluble in ethanol, ether and insoluble in water.

Anal. Calcd. for $C_{18}H_{22}ON_2$: C, 76.54; H, 7.88; N, 9.96. Found: C, 76.66; H, 8.17; N, 9.90.

Method B.—Three and five-tenths grams (0.012 mole) of N-phenyl-N′-phenacylpiperazine was placed in a high-pressure tube in which 0.5 g. of sodium had been dissolved in 6 ml. of ethanol. The contents of the tube were mixed intimately and the tube sealed. After heating at 185–195° for eight hours the tube was opened and the contents extracted with hot ethanol which was subsequently evaporated on the steam-bath leaving an oil which immediately solidified on cooling. The solid mass was washed several times with water, dried between porous plates and recrystallized from ethanol. The product proved to be identical with the compound prepared by Method A: yield 2.8 g. (80%); m. p. 110–111°; mixed m. p. with compound from Method A 110–111°.

Anal. Calcd. for $C_{18}H_{22}ON_2$: N, 9.96. Found: N, 9.99.

The dihydrochloride of (I) was prepared by dissolving a small amount of the amino alcohol in ethanol and adding an excess of concentrated hydrochloric acid. The salt was precipitated from the solution by the addition of ether. Recrystallized from methanol it melted at 210–212°. In contrast to the salt of the parent ketone the hydrochloride is readily soluble in water.

Anal. Calcd. for $C_{18}H_{24}ON_2Cl_2$: N, 7.88; Cl, 19.93. Found: N, 7.99; Cl, 19.51.

The benzoate of (I) was prepared by dissolving 2 g. of the alcohol in 6 ml. of chloroform and adding 1.1 g. of benzoyl chloride. A vigorous reaction resulted bringing the chloro-

(4) All melting points are corrected.

form nearly to the boiling point. A white precipitate was formed which was filtered from the solution. This precipitate proved to be the hydrochloride of the original amino alcohol. The free benzoate remaining in solution was obtained by evaporating the chloroform. However, the ester proved to be a sticky oil which was analyzed as the dihydrochloride prepared by dissolving the ester in ethanol, adding an excess of concentrated hydrochloric acid and precipitating with ether. The salt was recrystallized from methanol in 77% yield, m. p. 228–230°. This salt is insoluble in water.

Anal. Calcd. for $C_{25}H_{28}N_2O_2Cl_2$: N, 6.09; Cl, 15.44. Found: N, 6.30; Cl, 15.16.

N-Phenyl-N'-β-*p*-tolyl-β-hydroxyethylpiperazine, (II).—This compound was prepared from the hydrochloride of N-phenyl-N'-*p*-methylphenacylpiperazine by Method A. Recrystallized from ethanol the yield was 80%, m. p. 127–128°. This amino alcohol is slightly soluble in ethanol, ether; soluble in chloroform and insoluble in water.

Anal. Calcd. for $C_{19}H_{24}ON_2$: N, 9.45. Found: N, 9.32.

Preparation of this amino alcohol by Method B gave a 77% yield, m. p. 127–128°.

The dihydrochloride of (II) was prepared as described above, yield 94%, m. p. 199–201°. This salt is soluble in water.

Anal. Calcd. for $C_{19}H_{26}ON_2Cl_2$: N, 7.59; Cl, 19.19. Found: N, 7.71; Cl, 18.78.

The dihydrochloride of the benzoate of (II) was prepared as described above. It was recrystallized from methanol in 80% yield, m. p. 219–221°. This salt is slightly soluble in methanol and insoluble in water.

Anal. Calcd. for $C_{26}H_{30}O_2N_2Cl_2$: N, 5.92; Cl, 14.98. Found: N, 6.20; Cl, 14.70.

N-Phenyl-N'-phenylethylpiperazine, (III).—This compound was prepared by refluxing molecular proportions of phenylethyl bromide and N-phenylpiperazine for five hours in butanol solution. The hydrobromide thus obtained was dissolved in hot water and the free base precipitated by the addition of sodium hydroxide. The yield after recrystallization from hexane was 74%, m. p. 77–78°. This compound is soluble in ethanol, chloroform; fairly soluble in ether and insoluble in water.

Anal. Calcd. for $C_{18}H_{22}N_2$: N, 10.74. Found: N, 10.58.

The dihydrochloride of (III) was prepared in 94% yield from 5 g. of the amine in the manner described above. It was recrystallized from ethanol, m. p. 220–222°. This salt is slightly soluble in water.

Anal. Calcd. for $C_{18}H_{24}N_2Cl_2$: N, 8.22. Found: N, 8.35.

Summary

Two new analogs of ephedrine which contain the N-phenylpiperazine nucleus have been synthesized.

The hydrochlorides and benzoates of these amino alcohols have been prepared.

GAINESVILLE, FLORIDA RECEIVED OCTOBER 11, 1937

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

New Alkaloids in Aconitum Napellus[1]

BY WERNER FREUDENBERG AND E. F. ROGERS

An investigation by Schulze and Berger[2] on congeners of aconitine resulted in the isolation and chemical study of a base $C_{32}H_{45}NO_8 \cdot 3H_2O$ which was named neopelline. The relationship of neopelline to aconitine was demonstrated by the fact that on alkaline hydrolysis it yielded an alkamine neoline, $C_{23}H_{39}NO_6$, in addition to one mole each of acetic and benzoic acids. Neither neopelline nor neoline could be obtained in the crystalline state. Neoline hydrobromide was the only crystalline derivative which could be used analytically to set up the empirical formula. Quantitative group determinations led Schulze and Berger to extend the neoline formula as follows: $C_{19}H_{25}O(OH)_2(OCH_3)_3(NCH_3)$.

It appeared promising to reinvestigate these findings inasmuch as neoline appears to be structurally related to aconitine[3–5] or its alkamine aconine. Furthermore its lower oxygen content (six), as compared to aconine (nine) should make neoline a good starting material for structural studies in the aconitine group.

We had available for this study a generous supply of so-called amorphous aconitine which is a mixture of residual bases obtained in the commercial preparation of crystalline aconitine from *tubera aconiti napelli* (Merck). Our procedure as outlined in the following flow sheet, is essentially identical with that of Schulze who used for his studies a similar starting material also secured from E. Merck.

Fraction Ib which corresponds to Schulze's

(1) Fourth communication on aconite alkaloids. Presented at the Rochester meeting of the American Chemical Society, Sept., 1937.

(2) Schulze and Berger, *Arch. Pharm.*, **262**, 353 (1924).

(3) Jacobs and Elderfield, THIS JOURNAL, **58**, 533 (1936).

(4) Freudenberg, *Ber.*, **69**, 1962 (1936).

(5) Majima and Tamura, *Ann.*, **526**, 116 (1936).