REACTIONS OF (-)-PHYSOSTIGMINE AND (-)-N-METHYLPHYSOSTIGMINE IN REFLUXING BUTANOL AND AT HIGH TEMPERATURE : FACILE PREPARATION OF (-)-ESEROLINE +

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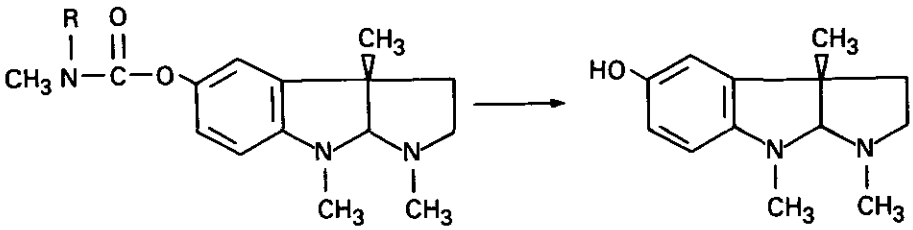
Abstract — (-)-Physostigmine (1), when refluxed in 1-butanol in the presence of sodium butylate afforded (-)-eseroline (3) in high yield, isolated as fumarate salt. Butyl N-methylcarbamate (4) was obtained from the mother liquor. (-)-N-Methylphysostigmine (2), prepared from 3 and dimethylcarbamoyl chloride, underwent under these conditions, similar decomposition suggesting that formation of 3 from 1 and 2 is the result of a nucleophilic substitution. Subliming, or distilling 1, in high vacuum afforded (-)-eseroline (3) and methyl isocyanate trapped by 1-butanol as butyl N-methylcarbamate (4). Compound 2 distilled without decomposition. It is suggested that pyrolysis of 1, therefore, proceeds by fragmentation, forming N-methylisocyanate and (-)-eseroline (3) as reaction products.

(-)-Eseroline (3) is an intermediate in the total synthesis of (-)- physostigmine (1)[1,2], exhibits morphine-like analgesic effects,[3,4,5,6] and represents a valuable compound to prepare ester and ether analogs. (-)-Physostigmine (1) is a natural alkaloid[7] and commercially available[8], and therefore represents a convenient source to prepare 3. Eseroline (3) is extremely sensitive to air-oxidation[2,4], and alkaline[9] or acid hydrolysis of 1[10] to make 3 require neutralization and work-up from aqueous solutions, and proved tedious when carried out on a larger scale. Facile decomposition of (1-phenylethyl)-ureas taking place in refluxing alcohols in the presence of catalytic amounts of sodium[11], suggested that similar reaction could occur with urethanes having an -O-CO-NH-CH_3 group instead of an -$\overset{|}{N}$-CO-NH-R group and 1 served as a model compound to test this hypothesis.

+Dedicated to Professor Dr. Bernhard Witkop, Laboratory of Chemistry, NIDDK, National Institutes of Health, Bethesda, Maryland 20892, USA, at the occasion of his 70th birthday.



1 R=H
2 R=CH_3

3

+ $CH_3-NH-CO_2C_4H_9$

4

We now report facile conversion of 1 into 3 in refluxing 1-butanol in the presence of a catalytic amount of sodium, affording 3 as fumarate salt in 98% yield, besides butyl N-methylcarbamate (4) identified by comparision with a standard sample. The fumarate salt of 3 can readily be crystallized from ethanol-ether, and afforded the free base from its aqueous solution after addition of sodium carbonate and extraction with ether. Reaction of 3 with dimethylcarbamoyl chloride in pyridine in the presence of triethylamine afforded the N-methyl derivative 2 in 80% yield, isolated as a crystalline solid, which so far did not give crystalline salts with a variety of acids, including fumaric acid and salicyclic acid, but could be crystallized from hexane-ether[12]. Pure compound 2 distilled in high vacuum without decomposition,[13] in contrast to 1, which afforded by sublimation or high vacuum distillation 3, and N-methylisocyanate trapped as 4. Formation of amines and urethanes from (1-phenylethyl)-ureas in refluxing alcochols was greatly enhanced when methanol was replaced by 1-butanol or 1-hexanol, and the reaction further accelerated by addition of a catalytic amount of sodium.[2,11] It was, therefore, speculated that (1-phenylethyl)-ureas with an acidic hydrogen on nitrogen fragmented into amines and isocyanates. That N-methylphysostigmine (2), with no hydrogen on the nitrogen of carbamate group, easily cleaved in refluxing 1-butanol after addition of a catalytic amount of sodium suggests, that formation of the products isolated may well be the result of a nucleophilic substitution. The finding that physostigmine (1), but not N-methylphysostigmine (2), decomposed when heated in high vacuum into eseroline and methylisocyanate, however, supports the hypothesis that *R-NH-carbamates and possibly ureas with one R-NH-group pyrolyse when heated*[14] to volatile

isocyanates and phenols or amines respectively. Further research will be necessary to determine the exact mechanisms of these highly practical reactions.

EXPERIMENTAL

Melting points were determined on Fisher-Johns melting point apparatus, and optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. ^{1}H-nmr spectra were measured on a Varian HR 220 (220 MHz) spectrometer, and mass spectra were taken on a Finnigan 1015D instrument (CI). GC analyses were performed with a Hewlett Packard 5880A instrument. Silica gel GHLF plates were from Analtech, Inc., were used for TLC. Column chromatography was done with Kieselgel 60 (Merck), 40-63 m (flash chromatography). Extraction of an aqueous solution with an organic solvent included washing of the combined organic extracts with a saturated aqueous NaCl solution. Drying was done with anhydrous Na_2SO_4.

(-)-Eseroline (3) from (-)-Physostigmine (1): (-)-Physostigmine (1) (2.0 g, 7.3 mmol) was dissolved in 20 ml of 1-butanol and a slight piece of sodium (less than 0.1 mg) added. After refluxing for 25 min in nitrogen atmosphere a hot butanol solution (16 ml) of fumaric acid [1g (8.7 mmol)] was added. The reaction mixture was left in the refrigerator overnight to crystallize. Filtration gave crystal 2.2g of (-)-eseroline fumarate. From the mother liquid a second crop of fumarate salt was obtained which was recrystallized from EtOH. The total amount of (-)-eseroline fumarate was 2.4g (97.8%): mp 198-200°C [lit.[15] mp 197-199°C]; $[\alpha]_D$ -109.0° (c=1, MeOH); TLC, Rf 0.3 (MeOH CH_2Cl_2=1:9). Anal. Calc. for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38. Found: C, 60.99; H, 6.67; N, 8.36.

(-)-Eseroline Base: (-)-Eseroline fumarate (100 mg) was dissolved in 1 ml of distilled water, the pH adjusted to 7-8 by addition of 10% sodium bicarbonate. Extraction with ether (3x4 ml) gave a gum which crystallized by the addition of ether to give 50.2 mg (93.6%) of base: mp 125-126°C; $[\alpha]_D$ -109.7° (c=1, MeOH) [lit.[13] mp 127-128°C; $[\alpha]_D$ -107.2° (c=1, MeOH)].

The mother liquid was concentrated in vacuo and butyl N-methylcarbamate (4) identified by GC analysis by comparison with a standard sample.

Butyl N-Methylcarbamate (4): 1-Butanol (14.8 g, 0.2 mol) and methylisocyanate (2.3 g, 0.04 mol) were left for 1 hr. Distillation over a short column to remove butanol and distillation under vacuum gave 4.5 g (93%) of butyl N-methylcarbamate (4): bp 95°C/10 mm, MS(CI); m/z 132 (M^++1); ^{1}HNMR (CCl_4): δ 0.95 (3H, t, J=7, $-CH_3$), 1.37 (2H, m, $-CH_2-$), 1.52 (2H, m, $-CH_2-$), 2.83 (3H, d, J=5, -NH-$\underline{CH_3}$), 3.93 (2H, t, J=7, $-O-CH_2-$), 5.19 (1H, br s, -NH-).

Sublimation and Distillation of (-)-Physostigmine (1) in High Vacuum: Compound 1 (1 g, 3.6 mmol) was placed on the bottom of sublimation apparatus, heated under high vacuum to 180°C to give a glass-like product (350 mg). The product was dissolved in 8 ml of ether, and added to 6 ml of alcoholic solution of fumaric acid (130 mg). Crystallization gave crude fumarate salt which was recrystallized from alcohol to give 320.5 mg (32%) of TLC-pure material identical with the material described above. The butanol solution from the pump trap was concentrated under reduced pressure. 1-Butanol and butylester 4 were identified by GC analysis and comparison with standard samples.

Compound 1 (955 mg, 3.5 mmol) when distilled in high vacuum gave 497 mg of a glass-like crude product. Recrystallization of the fumarate salt from ethanol gave TLC-pure (-)-eseroline fumarate 439 mg (45%), identical with material prepared before. Butylester 4 obtained from the butanol solution in the pump trap was identified by GC analysis by comparison with a standard sample.

(-)-N-Methylphysostigmine (2). Compound 3 (356 mg, 1.6 mmol) was dissolved in 5 ml of pyridine (dryed over NaOH), and 876 mg (8.1 mmol) of dimethylcarbamoyl chloride added. The reaction mixture was stirred at 50°C overnight, and after addition of 0.2 ml of Et_3N kept for an additional 3 h at 50°C. Solvent was evaporated in high vacuum and the residue was flash chromatographed on a silica gel column (CH_2Cl_2/CH_3OH) to give, after evaporation of solvent a glass-like residue, which was dissolved in ethyl acetate, the solution washed with sodium bicarbonate and saturated aqueous NaCl and dried. The residue obtained after evaporation of solvent crystallized from hexane-ether to give crystalline 2 (380 mg, 80.5%): mp 73.5-74°C; $[\alpha]_D$ -74.2° (c=1, $CHCl_3$); TLC, Rf 0.7 (CH_2Cl_2 MeOH=9:1). Anal. Calc. for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.29; H, 8.04; N, 14.47. When heated to 180°C in high vacuum, under conditions applied for the thermal decomposition of 1, compound 2 sublimed unchanged, giving colorless crystals which were identical with starting material (TLC, mp).

Hydrolysis of 2 in Butanol: Refluxing compound 2 (80 mg, 0.07 mmol) in 1 ml of 1-butanol and a small amount of sodium for 25 min in N_2-atmosphere afforded quantitatively 3, isolated as fumarate salt and identical with material prepared before (mp, [α], TLC). From the mother liquor butyl N-dimethylcarbamate was obtained and identified by MS (m/z 146, M^+ +1).

REFERENCES

1. P. L. Julian, and J. Pikl, J. Am. Chem. Soc., 1935, 57, 755.

2. A. Brossi, J. Nat. Prod., 1985, 48, 878.

3. A. Galli, G. Renzi, R. Bartolini, and P. Malmberg-Aiello, J. Pharm. Pharmacol., 1979, 31, 784.

4. A. Galli, P. Malberg-Aiello, G. Renzi, and A. Bartolini, ibid. 1984, 37, 42.

5. S. Furst, T. Friedmann, A. Bartolini, R. Bartolini, P. Aiello-Malmberg, A. Galli, G. Somogyi, and J. Knoll, Eur. J. Pharmacol., 1982, 83, 233.

6. B. Schönenberger, A. E. Jacobson, A. Brossi, R. Streaty, W. A. Klee, J. L. Flippen-Anderson, and R. Gilardi, J. Med. Chem., 1986, 29, 2268.

7. B. Robinson, "The Alkaloids" (ed. Manske, R. H. F.), Academic Press, New York, 1971, Vol. 13, pp 213-226. See also Vols. 8, pp 27-46 and 10, pp 363-401 of "The Alkaloids".

8. Aldrich, Chemical Co., Milwaukee, USA and Fluka, AG., Buchs, Switzerland.

9. M. Polonovsky, Bull. Soc. Chim. Fr., 1915, 17 239.

10. M. Polonovsky, ibid. 1916, 19, 28.

11. B. Schonenberger, and A. Brossi, Helv. Chim. Acta, 1986, 69, 1486.

12. A. Brossi, B. Schönenberger, O. E. Clark, and R. Ray, FEBS Letters, 1986, 201, 190. Compound 2 was described here as an oil.

13. A. Straus, Liebigs Ann. Chem., 1913, 401, 361.

14. R. B. Woodward, "Recent Advances in the Chemistry of Natural Products", Pure & Appl. Chemistry 1968, 524. No experimenal details are available.

15. Fetherstone & Co., Canadian Patent, 1982, 1,137,489.

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