[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Tetrahydropyranyl Amino Alcohols

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Morphine has often been interpreted as a tertiary amino alcohol derived from the various polycyclic ring systems which can be discerned in the molecule of the alkaloid.[2] The study of condensed cyclic aryl ethers[3] and sulfides[4] carrying alkamine side-chains has been based on the assumption that these groups may be responsible, in part, for the analgesic action of morphine.

A simplification of this principle would lead to monocyclic ethers containing amino alcohol chains. The closest analogy to the ether ring present in morphine could be reached in hydrofuran derivatives. Two compounds of this type, 1,4-bis-(3-diethylaminopropyl)-1,4-dimethyltetrahydrofuranol-3, and 1-(3-diethylaminopropyl)-1,4,4-trimethyltetrahydrofuranol-3, were prepared by Henecka,[5] but they showed none of the properties associated with the opium alkaloid. The lack of analgesic action of these derivatives may have been due to the δ- and ϵ-spacing of the alcohol and tertiary amino groups. It seemed of interest to study α- or β-amino alcohols derived from saturated cyclic ether systems, since these relative positions of the alcohol and amino groups have generally proved to be more effective. This article deals with an investigation of tetrahydropyranyl alkamines, and will be followed by a report on analogous tetrahydrofuran derivatives.

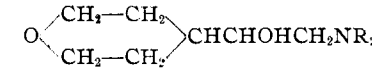
4-Tetrahydropyranoyl chloride (I) was treated with diazomethane, and the resulting diazoketone converted into 4-bromoacetyltetrahydropyran (II). Secondary amines were condensed with the bromoketone, and the tertiary amino ketones (III) were reduced catalytically to the corresponding alcohols (IV).

$$C_5H_9OCOCl \xrightarrow[2.\ HBr]{1.\ CH_2N_2} C_5H_9OCOCH_2Br \longrightarrow$$

I II

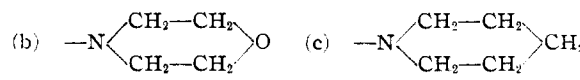
$$C_5H_9OCOCH_2NR_2 \longrightarrow$$

III



IV

$-NR_2$: (a) $-N(C_2H_5)_2$



Attempts to prepare tertiary β-aminoketones of the type $C_5H_9OCOCH_2CH_2NR_2$ from 4-acetyltetrahydropyran[6] and secondary amines by the Mannich reaction under a variety of conditions were unsuccessful. 4-Acetyltetrahydropyran was obtained from 4-cyanotetrahydropyran and methylmagnesium iodide under conditions similar to those used recently by Henze and McKee.[7] The nitrile was prepared most conveniently by dehydration of 4-tetrahydropyran carbonamide, or by the method of Gibson and Johnson.[7,8]

We also attempted to change the positions of the alcohol and amino groups in tetrahydropyranyl-α-amino alcohols. The 4-bromo-4-acyl derivatives needed in the synthesis of such compounds should be formed by substitution of the tertiary hydrogen atom in 4-acyltetrahydropyrans. Bromination of 4-acetyltetrahydropyran was slow and yielded no homogeneous bromoketone although this reaction was expected to take a course analogous to the halogenation of methyl isopropyl ketone.[9] On the other hand, bromination of 4-benzoyltetrahydropyran[7] (b. p. (20 mm.) 175–177°) in carbon tetrachloride solution proceeded rapidly. The oily 4-bromo-4-benzoyltetrahydropyran reacted sluggishly with secondary amines. Since none of the resulting amino ketones, or their salts, could be crystallized, the oily hydrochloride of 4-piperidino-4-benzoyltetrahydropyran was hydrogenated in ethanol solution in the presence of platinum oxide catalyst. Hydramine fission occurred during the reduction, and piperidine was the only basic reaction product.

In working up tetrahydropyranyl-α-bromoketones it was observed that these compounds were quite soluble in acids and could not be removed

(1) Smith, Kline and French Research Fellow.

(2) Small, Eddy, Mosettig and Himmelsbach, *Studies on Drug Addiction*, U. S. Public Health Service Reports, Supplement No. 138, Washington, D. C. (1938).

(3) Mosettig and Robinson, THIS JOURNAL, **57**, 2186 (1935); **58**, 688 (1936); Kirkpatrick and Parker, *ibid.*, **57**, 1123 (1935).

(4) Burger and Bryant, *ibid.*, **63**, 1054 (1941).

(5) Henecka, *Medicine in its Chemical Aspects*, Bayer, Leverkusen, 1938, Vol. III, p. 380.

(6) Prelog, Cerkovnikov and Heimbach, *Collection Czechoslov. Chem. Commun.*, **10**, 399 (1938).

(7) Henze and McKee, THIS JOURNAL, **64**, 1672 (1942).

(8) Gibson and Johnson, *J. Chem. Soc.*, 2525 (1930).

(9) Faworskiy, *J. prakt. Chem.*, [2] **88**, 641 (1913).

completely from this medium by ether extraction. Likewise, 4-benzoyltetrahydropyran was soluble in dilute hydrobromic acid to a considerable extent. These compounds were not readily soluble in water, and precipitated when their acid solutions were made alkaline. Apparently, these tetrahydropyran derivatives form stable water soluble oxonium salts.

The amino alcohols IV a, b and c are being tested for analgesic action by Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School. 4-(1-Hydroxy-2-piperidinoethyl)-tetrahydropyran hydrochloride (IVc) exhibits an analgesic effect in rats in a large proportion of the animals tested. In this connection it is interesting to note that certain tetrahydropyranyl hydantoins cause a mild anti-convulsant but no hypnotic action.[7]

We are deeply grateful to Smith, Kline and French Laboratories for generous financial aid in this investigation.

Experimental

Tetrahydropyran-4-carboxylic Acid.—Gibson and Johnson[8] attained an over-all yield of 33.2% based on 2,2′-dichlorodiethyl ether. The modifications introduced in our directions increase this yield to 52%.

To a solution of 46 g. of sodium in 500 cc. of absolute ethanol, placed in a three-neck flask fitted with a reflux condenser, a stirrer and a dropping funnel, 304 cc. of diethyl malonate was added, and the mixture stirred for five minutes. Dichlorodiethyl ether (238.5 cc.), purified by distillation of the commercial product, was added. and the mixture was refluxed with stirring overnight. After cooling, another 46 g. of sodium dissolved in 500 cc. of absolute ethanol was added, and refluxing continued for forty-eight hours. The precipitated sodium chloride was filtered, the alcohol driven off on a steam-bath, the residue treated with water and extracted with three 200-cc. portions of ether. After drying over sodium sulfate, the ether was evaporated, and the diethyl tetrahydropyran-4,4-dicarboxylate distilled. The yield of the fraction of b. p. (23 mm.) 140–170° was 272 g.

The ester was hydrolyzed by boiling with a solution of 202 g. of potassium hydroxide in 440 cc. of water and 1900 cc. of ethanol for fifteen hours. The alcohol was distilled off, and water was added to increase the total volume to 1400 cc. The clear solution was acidified with concentrated hydrochloric acid. Although a small portion of the dicarboxylic acid precipitated, the major portion was obtained only after three days of continuous extraction with ether. The ether extract was dried over sodium sulfate, the solvent evaporated, and the solid residue decarboxylated without further purification.

Thirty-gram portions of tetrahydropyran-4,4-dicarboxylic acid were heated in a sausage flask at 175–185° for about twenty minutes until the evolution of carbon dioxide ceased, and the tetrahydropyran-4-carboxylic acid was purified by distillation. The yield of the acid boiling at 18 mm. and 145–150° was 136 g.

An attempt to prepare 2,6-dimethyl-tetrahydropyran-4-carboxylic acid from 2,2′-dichlorodiisopropyl ether by an analogous series of reactions was unsuccessful. Dichlorodiisopropyl ether could not be condensed with sodium diethyl malonate, nor could it be converted to 2,2′-diiododiisopropyl ether with sodium iodide in acetone solution as in the case of 2,2′-dichlorodiethyl ether.[8]

4-Tetrahydropyranoyl Chloride.—A mixture of 153 g. of tetrahydropyran-4-carboxylic acid and 240 cc. of thionyl chloride was refluxed for two hours, and fractionated under reduced pressure. The acid chloride boiled at 93–95° under 21 mm. pressure, the yield was 143 g.

4-Diazoacetyltetrahydropyran.—A solution of 27 g. of 4-tetrahydropyranoyl chloride in 30 cc. of dry ether was dropped slowly into an ice-cold solution of 16 g. of diazomethane in 1500 cc. of ether which had been dried over solid potassium hydroxide. Nitrogen was evolved vigorously, and the solution was allowed to warm to room temperature. After one hour it was concentrated to 300 cc. and used directly in the preparation of the bromoketone. The diazoketone crystallized on cooling of its concentrated solution in ether, and was recrystallized from ether–petroleum ether. The yellow needles melted at 42–45° (dec.).

Anal. Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54. Found: C, 54.61; H, 6.96.

4-Bromoacetyltetrahydropyran.—The ether solution of the crude diazoketone was cooled in an ice-bath, and treated slowly with a solution of 55 cc. of 48% aqueous hydrobromic acid in 55 cc. of ether. After completion of the addition the solution was allowed to stand for thirty minutes, and then solid sodium carbonate was added until the mixture reacted alkaline. This was necessary because the bromoketone was readily soluble in dilute aqueous hydrobromic acid. The ether layer was separated, the solution extracted three times with ether, the combined extracts were dried over sodium sulfate, and the solvent was removed by distillation. The oily residue weighed 40 g. and was used directly in the reaction with secondary amines. Pure 4-bromoacetyltetrahydropyran crystallized on cooling of the crude oily product, and was purified by sublimation at 50° and 1 mm. pressure. The colorless needles melted at 50–53°. The compound acted as a strong lachrymator.

Anal. Calcd. for $C_7H_{11}BrO_2$: C, 40.60; H. 5.36. Found: C, 40.74; H, 5.09.

Preparation of Tertiary 4-Aminoacetyltetrahydropyran Derivatives.—A solution of 0.1 mole of the crude oily bromoketone in 150 cc. of dry ether was allowed to stand with 0.25 mole of the secondary amine for five hours; the hydrobromide of the amine precipitated from the solution. The mixture was washed with water, the ether layer dried over sodium sulfate. the solvent evaporated. and the oily residue heated at 95° and 20 mm. pressure for one hour in order to remove any unreacted secondary amine. The bases were dissolved in acetone and neutralized with ethereal hydrogen chloride. The hydrochlorides were recrystallized from ethanol or acetone and ether. In order to isolate the morpholino ketone, the reaction mixture had to be made alkaline and extracted exhaustively with ether.

TABLE I

Hydrochlorides of tetrahydropyran derivatives	M. p., °C. cor.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-Diethylaminoacetyl	152–155	$C_{11}H_{22}ClNO_2$	56.04	55.89	9.41	9.27
4-Piperidinoacetyl	177–179	$C_{12}H_{22}ClNO_2$	58.17	58.58	8.95	9.06
4-Morpholinoacetyl	214–219	$C_{11}H_2ClNO_3$	52.90	53.42	8.07	7.89
4-(1-Hydroxy-2-diethylamino ethyl)	140.5–142	$C_{11}H_{24}ClNO_2$	55.56	55.80	10.17	10.73
4-(1-Hydroxy-2-piperidino ethyl)	208–210	$C_{12}H_{24}ClNO_2$	57.70	57.37	9.69	9.99
4-(1-Hydroxy-2-morpholino ethyl)	213–216	$C_{11}H_{22}ClNO_3$	52.48	52.48	8.81	9.07
4-(1-Acetoxy-2-piperidino ethyl)	211–213	$C_{14}H_{26}ClNO_3$	57.62	57.26	8.98	9.30
4-(1-Acetoxy-2-morpholino ethyl)	223–225	$C_{13}H_{24}ClNO_4$	53.14	53.41	8.23	8.51

Preparation of Tetrahydropyran Alkamines.—A 15% alcoholic solution of the respective dialkylaminoacetyl tetrahydropyran hydrochloride was hydrogenated in the presence of platinum oxide under one atmosphere pressure. Absorption of hydrogen was complete after about six hours. The catalyst was filtered, the solvent removed under reduced pressure, and the crystalline hydrochloride recrystallized from alcohol and acetone. The salts appeared as colorless powders and were readily soluble in water.

Acetyl derivatives of the amino alcohols were prepared by warming the hydrochlorides with an excess of acetic anhydride in pyridine solution at 60° for eight hours. The solvents were distilled under reduced pressure, the residues treated with sodium carbonate solution, the oily esters extracted into ether and converted to the hydrochlorides.

4-Cyanotetrahydropyran.—Since 4-tetrahydropyran carbonamide is readily soluble in water,[8] it was advantageous to prepare it by bubbling dry ammonia into an ether solution of 4-tetrahydropyranoyl chloride. The mixture of the amide and ammonium chloride was used directly for the following dehydration.

A mixture of 27.4 g. of the crude amide thus obtained (containing 19.3 g. of the pure amide) and 32 g. of phosphorus pentoxide was heated in a Claisen flask at 180–200° under 20 mm. pressure; almost all of the crude nitrile distilled and the reaction was completed by raising the temperature of the bath to 280°. On redistillation the product boiled at 91–95° (17 mm.), or at 100–102° (25 mm.). The yield was 12.8 g.

In the alternative preparation of the nitrile by the method of Gibson and Johnson[8] the boiling point of ethyl 4-cyanotetrahydropyran-4-carboxylate was found to be 130–134° at 23 mm. This is in better agreement with the observation of these authors (b. p. (16 mm.) 125°) than with that of Henze and McKee[7] who recorded b. p. (16 mm.) 135°.

Summary

In order to test the significance of saturated monocyclic ether systems in analgesics, several tertiary tetrahydropyranyl amino alcohols were synthesized. One of them caused analgesia in the rat.

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Molecular Weights and Intrinsic Viscosities of Polyisobutylenes[1]

BY PAUL J. FLORY

Introduction

The extensive investigations carried on by Staudinger and co-workers during the past thirteen years have done much to stimulate interest in one of the most important phases of high polymer chemistry, namely, the assignment of molecular weight values to these substances. Early in the course of these investigations, and on the basis of extremely meager experimental evidence, Staudinger[2,3] proposed his well-known relationship of proportionality between the molecular weight of a linear polymer and the ratio of the viscosity increment ($\eta_r - 1$) to concentration. With appropriate revisions introduced by Kraemer and Lansing,[4,5] this may be written

$$[\eta] = K_S \overline{M}_w \qquad (1)$$

where $\overline{M}_w$ is the weight average molecular weight, K_S is a constant and $[\eta]$ is the intrinsic viscosity,[4] or limiting ratio of viscosity increment to concentration, defined by

$$[\eta] = [(\eta_r - 1)/c]_{c=0} \equiv [(\ln \eta_r)/c]_{c=0} \qquad (2)$$

η_r is the relative viscosity and c is the concentration in g. of solute per 100 cc. of solution. Staudinger and co-workers proceeded to determine the

(1) Presented before the Division of Rubber Chemistry at the Buffalo meeting of the American Chemical Society, September 11, 1942.

(2) H. Staudinger and W. Heuer, *Ber.*, **63**, 222 (1930); H. Staudinger and R. Nodzu, *ibid.*, **63**, 721 (1930).

(3) H. Staudinger, "Die hochmolekularen organischen Verbindungen," Verlag von Julius Springer, Berlin, 1932.

(4) E. O. Kraemer and W. D. Lansing, *J. Phys. Chem.*, **39**, 153 (1935).

(5) E. O. Kraemer, *Ind. Eng. Chem.*, **30**, 1200 (1938).