[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Pyridinium Analogs of the Pressor Amines. I. The Benzene Series[1]

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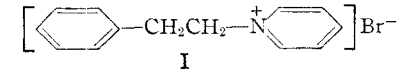
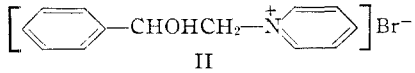
The interesting observation of Kröhnke[3] that certain pyridinium compounds possess both pressor and ergot-like activity prompted the preparation and subsequent physiological testing of a series of pyridinium compounds possessing the carbon skeletons considered desirable for pressor activity. Formulas I-IV indicate the compounds with unsubstituted aromatic nuclei which were deemed most capable of proving physiologically interesting. In this series of compounds the side chain analogs to those found in tyramine, epinephrine, benzedrine and ephedrine have been reproduced.



I



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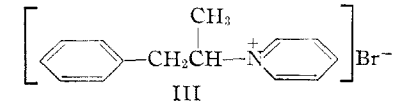
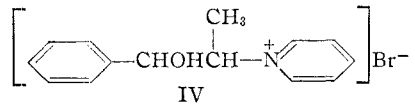


III



IV

Although β-phenylethylpyridinium bromide (I) has been reported,[4] it has not previously been characterized, nor have yields been indicated. Kröhnke[5,6] has prepared β-hydroxy-β-phenylethylpyridinium bromide (II) and β-hydroxy-β-phenylisopropylpyridinium bromide (IV) by a condensation reaction. A new and direct synthesis has been developed which involves the high pressure, platinum-catalyzed reduction of phenacylpyridinium bromide and propiophenonylpyridinium bromide, respectively. It is indeed interesting to note that the ordinary pressures employed by Kröhnke and Fasold[6] for the reduction of phenacylpyridinium bromide yielded only a minute portion of the desired alcohol, a substantial yield of piperidinium compounds resulting. By the simple expedient of using elevated pressures for a very short period of time, it was found that the absorption of one mole of hydrogen led to the formation of a fair amount of the desired pyridinium carbinol. Crystallization from absolute ethanol effected separation from undesirable by-products.

(1) From the Ph.D. thesis by Harold Wittcoff, June, 1943.

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(3) F. Kröhnke, *Ber.*, **72**, 2000 (1939).

(4) S. Sugasawa and N. Sugimoto, *Ber.*, **72**, 977 (1939); *Proc. Imp. Acad. Tokyo*, **15**, 49 (1899).

(5) F. Kröhnke, *Ber.*, **66**, 604 (1933).

(6) F. Kröhnke and K. Fasold, *ibid.*, **67**, 656 (1934).

β-Hydroxy-β-phenylethylpyridinium bromide (II) was also prepared by an alternative method indicated by Kröhnke and Fasold[6] which involved the direct interaction of styrene bromohydrin and pyridine. It is interesting to note that a melting point of 239–240° was observed in this Laboratory in contrast to that of 231.5° reported by previous investigators. On the other hand, the melting point of the material obtained by the catalytic reduction of phenacylpyridinium bromide agreed well with that reported by the German workers. Because of the polar characteristics of these compounds, their melting points cannot be considered too indicative of purity.

The reduction of propiophenonylpyridinium bromide to obtain β-hydroxy-β-phenylisopropylpyridinium bromide (IV) led to the isolation of only one of the two racemic mixtures demanded by stereochemical considerations. Here again a discrepancy in melting point was observed, the product obtained in this Laboratory melting at 223–224° in contrast to the value of 199–200° reported by Kröhnke and Fasold[6] for their higher melting product. This variance in melting point necessitated an alternative synthesis of the compound, for which there was employed the direct interaction of pyridine with α-hydroxy-β-bromopropylbenzene. This more direct reaction yielded an oil from which there was finally obtained a small amount of crystalline product melting at 230–232°. The two samples on admixture melted at 225–227°.

β-Phenylisopropylpyridinium bromide (III) was obtained as a characterizable oil by the action of pyridine on the requisite bromide. The formation of pyridinium salts of secondary halides proceeds with difficulty due to a marked tendency toward dehydrohalogenation which, of course, obviates the use of elevated temperatures.

The pharmacological investigation of these materials is under way.

Grateful thanks are due to the Smith, Kline and French Laboratories for the financial aid which made possible this investigation.

Experimental[7]

β-Phenylethylpyridinium Bromide (I).—This product was prepared in a 24% yield similarly to the previously employed procedure,[4] save that toluene was employed as a solvent instead of xylene. Treatment of an aqueous solution of the salt with Norit followed by crystallization of the solid product from absolute ethanol yielded short white needles melting at 125–126°.

Anal. Calcd. for $C_{13}H_{14}BrN$: Br, 30.3. Found: Br, 30.7.

β-Hydroxy-β-phenylethylpyridinium Bromide (II).—(A) A 59% yield of this product resulted when the

(7) All melting points are corrected.

method of Kröhnke and Fasold,[6] *i. e.*, the direct interaction of styrene bromohydrin and pyridine, was modified by the use of toluene as a solvent and by extending the time of refluxing to sixteen hours. Treatment of an aqueous solution with Norit followed by crystallization from water yielded a product melting at 239–240°. Styrene bromohydrin was prepared either by the direct addition of hypobromous acid to styrene[7] or by the aluminum isopropoxide catalyzed reduction of phenacyl bromide.[8]

(B) In the second procedure, a solution of 4.2 g. of phenacylpyridinium bromide[5] in 9 ml. of water in a glass-lined steel bomb was subjected to a pressure of 850 pounds of hydrogen in the presence of 200 mg. of platinum oxide.[10] After a short period of time, 1 mole of hydrogen was absorbed whereupon the reaction mixture was freed from catalyst by filtration. Treatment of the solution with Norit and removal of the solvent *in vacuo* yielded an oil which crystallized on standing in the cold room. The solid mass was treated with 10 ml. of boiling absolute ethanol, after which the insoluble portion was crystallized from water and washed with ether to obtain 1.2 g. (30%) of product melting at 230–231°. A m. p. of 228–230° was obtained when it was mixed with the product from procedure A.

Careful addition of ether to the ethanol extract caused the precipitation of 2 g. of a white solid which melted over a range of 170–182°. This was probably a mixture of starting material and the other possible products of hydrogenation such as the piperidinium salts of phenacyl bromide and styrene bromohydrin.

Anal. Calcd. for $C_{13}H_{14}BrNO$: Br, 28.5. Found: Br, 28.9.

β-Bromopropylbenzene.—Although this compound had been prepared previously by Carter[11] by the addition of aqueous hydrobromic acid to allylbenzene, it was decided to employ an alternative procedure. The induction of a rapid stream of hydrogen bromide into a solution of 10 g. of allylbenzene in 25 ml. of glacial acetic acid over a period of two hours led to the formation of two layers which were subsequently dispelled by the addition of 20 ml. more of solvent. The reaction mixture, having been subjected to low temperatures overnight, was poured into ice water to yield a heavy bromide which was taken up in ether and combined with the solution which resulted from the ether and benzene extraction of the aqueous layer. The solution, having been washed with dilute bicarbonate and with water, was dried over sodium sulfate. Thereupon, the solvent was evaporated to obtain a reddish oil which on fractionation yielded 12 g. (71%) of a colorless liquid which distilled at 77–80° at 1 mm.

β-Phenylisopropylpyridinium Bromide (III).—From the admixture of 16 g. of β-bromopropylbenzene and 6.4 g. of anhydrous pyridine with 100 ml. of dry ether there gradually precipitated a yellow oil. After twenty-five days at room temperature the oil was taken up in water, whereupon the aqueous solution was subjected to the action of Norit and extracted with ether to remove organic impurities. Removal of the solvent *in vacuo* yielded a light yellow oil (10 g., 45%) which decomposed on attempted distillation at 10^{-5} mm. and which resisted all attempts to induce crystallization; $n^{24}D$ 1.6038, d^{27} 1.043.

Anal. Calcd. for $C_{14}H_{16}BrN$: Br, 28.7. Found: Br, 30.1.

β-Hydroxy-β-phenylisopropylpyridinium Bromide (IV).—(A) Propiophenonylpyridinium bromide was prepared in 67% yield by the direct interaction of α-bromopropiophenone with pyridine in anhydrous ether. The resulting product exhibited a melting point of 153–157° in contrast to the value of 130–131° noted by Schmidt.[12]

To a solution of 2.2 g. of propiophenonylpyridinium bromide in 10 ml. of water was added 200 mg. of platinum oxide catalyst. Under a pressure of 900 pounds, 1 mole of hydrogen was readily absorbed. Evaporation of the solvent yielded an oil which, covered with ether, gave rise to a mass of sticky crystals (1.9 g.) after several days in the cold room. The sticky mass having been washed with ether and with absolute ethanol, was crystallized from water to obtain a product (0.5 g., 23%) which melted at 223–224°. Evaporation of the mother liquor yielded an oil which may have been a lower melting racemic mixture together with other possible reduction products.

Anal. Calcd. for $C_{14}H_{16}BrNO$: Br, 27.2. Found: Br, 27.8.

(B) The interaction of 27 g. of α-hydroxy-α-phenyl-β-bromopropane[13] with 10 g. of dry pyridine in 50 ml. of anhydrous ether was allowed to proceed for many months in the ice chest to yield about 15 g. of a dark oil. Crystallization was accomplished by allowing a very dilute ethanolic solution of the oil to evaporate spontaneously at room temperature. The well-formed crystal which resulted after several weeks was added to an ethanolic solution of the oil which previously had been treated with Norit. Crystallization, however, proceeded only very slowly to yield finally about 500 mg. of product which was purified by several crystallizations from water, m. p. 230–232°. On admixture, this product together with the one prepared by the reduction of propiophenonylpyridinium bromide (m. p. 223–224°) melted at 225–227°.

Anal. Calcd. for $C_{14}H_{16}BrNO$: Br, 27.2. Found: Br, 27.6.

Summary

1. A series of pyridinium analogs of the pressor amines without substituents in the aromatic nucleus has been prepared.

2. The high pressure catalytic reduction of phenacylpyridinium bromide and propiophenonylpyridinium bromide has been studied.

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(9) H. Lund, *Ber.*, **70**, 1520 (1937).

(10) The authors are grateful to Prof. Robert H. Baker for his kind assistance and advice which led to the accomplishment of the high pressure catalytic reductions.

(11) H. E. Carter, *J. Biol. Chem.*, **108**, 619 (1935).

(12) E. Schmidt, *Arch. Pharm.*, **247**, 141 (1909); *Chem. Zentr.*, **13** [1], 1705 (1909).

(13) P. G. Stevens, O. C. W. Allenby and A. S. DuBois, THIS JOURNAL, **62**, 1424 (1940).