A NEW PROCESS FOR THE SYNTHESIS OF FENTANYL

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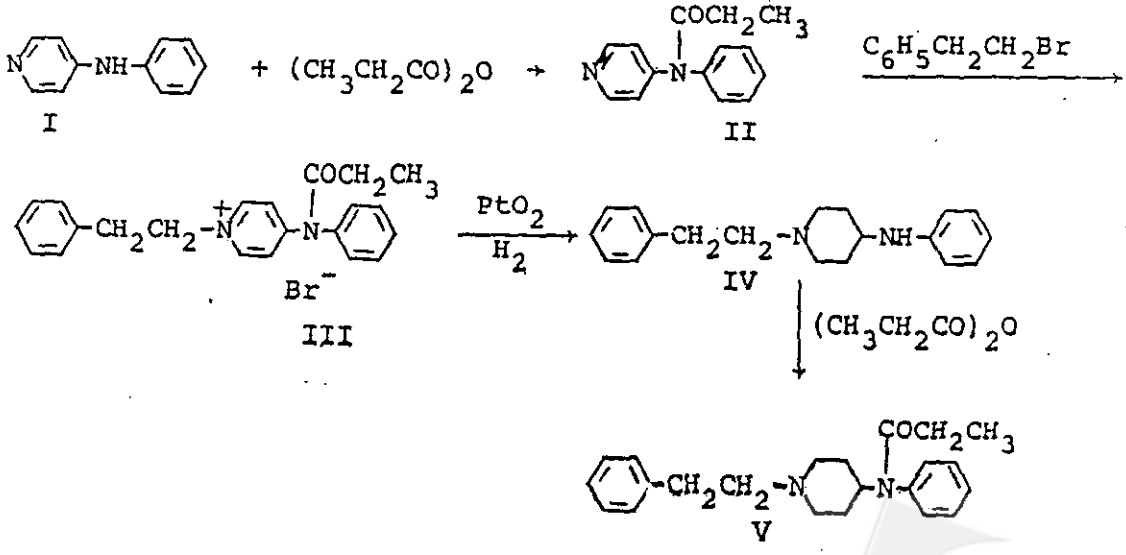
Catalytic hydrogenation of pyridinium derivative for the preparation of analgesic Fentanyl, (*N*-(1-phenethyl-4-piperidyl)-propionanilide) is reported. This constitutes a novel synthesis for the analogs of Fentanyl type compounds.

In 1963 Janssen reported in his patents the preparations of 1-arylalkyl-4-arylacyl-aminopiperidines[1~5]. These compounds have the properties of Morphine. The citrate of one of these compounds, *N*-(phenethyl-4-piperidyl)-propionanilide, or Fentanyl by trade name showed the most potent narcotic analgesic. Benke and his coworker prepared the Fentanyl by a different synthetic route[6].

In 1952 Truitt *et al.*[7] reported the reduction of 4-alkyl-1-phenacylpyridinium halide with Adams catalyst over hydrogen to give the corresponding 4-alkyl-1-phenacyl piperidine. The reduction took place selectively at pyridinium moiety without affecting the phenyl group. This type of reduction was thought to provide an excellent method for the preparation of Fentanyl type compounds. It was decided to synthesize Fentanyl by this selective reduction[8].

4-Anilinopyridine (I) which was prepared according to the method of Jarchel[9,10] was acylated using propionic anhydride, the propionyl group was at the anilino nitrogen, and the resulting *N*-(4-pyridyl)propionanilide (II) was *N*-alkylated by allowing it to react with β-phenethylbromide. The resulting 1-phenethyl-4-propionanilino pyridinium bromide (III) was reduced in the presence of platinum oxide at 20 *lb* pressure of hydrogen. Under such reaction condition, the propionyl group was lost and 1-phenethyl-4-anilinopiperidine (IV) was obtained. Acylation of (IV) with propionic anhydride gave the desired compound Fentanyl, *N*-(1-phenethyl-4-piperidyl) propionanilide (V). The overall yield from the preparation of 4-anilinopyridine from pyridine to V is 27%.



Acknowledgement-We are indebted to National Science Council of Republic of China for financial support of this project.

EXPERIMENTAL*

4-Anilinopyridine (I). Was prepared by the methods of Koenigs[9] and Jarchel[10]. Thionyl chloride (406 *gm*, 3.14 *mole*) was added dropwise to an ice cold pyridine (135 *gm*, 1.70 *mole*). The reaction mixture was stirred at ice temperature for several hours and then was kept at room temperature for seven days. The unreacted thionyl chloride was removed by rotary evaporator. The dark residual mass was treated with 95% ethanol (50 *ml.*). An yellowish brown mass was collected by filtration. This yellowish brown mass was treated with methanol (400 *ml.*), the insoluble material was removed by filtration, the methanol solution was concentrated to give crude pyridylpyridinium chloride (124 *gm*, 64%). Crystallization by 95% ethanol gave slight yellow crystals, m. p. 158-160°(lit. 158-160°)[11].

A mixture of pyridylpyridinium chloride (23.0 *gm*, 0.10 *mole*) and aniline hydrochloride (26.0 *gm*, 0.20 *mole*) was heated on an oil bath to 180-200° for 1.5 *hours*. On cooling, the mixture was dissolved in water (250 *ml.*), the aqueous solution was basified to *p*H 8-9 with 20% sodium hydroxide solution. An orange yellow solid as crude 4-anilinopyridine (I) (16.0 *gm*, 94%) was isolated and collected by filtration. Crystallization by methanol gave colorless crystals, m. p. 173-174° (lit. m. p. 175°)[10], ν_{N-H} 3220 w, $\nu_{C=O}$ 1450 *s* cm^{-1} in KBr. $\delta^{CDCl_3}_{TMS}$=2.63 (—NH, broad, 1H),6.9 (3, 5-Py-H, *d*, J=4.5 *Hz*, 2H), 7.10-7.55 (benzene proton, *m*, 5H), 8.17 (2.6-Py-H, *d*, J=4.5 *Hz*, 2H) *ppm*.

N-(4-pyridyl) propionanilide (II). A mixture of propionic anhydride (5.6 *gm*, 0.43 *mole*) and 4-anilinopyridine (7.2 *gm*, 0.42 *mole*) was stirred at room temperature until becoming homogeneous. The solution was heated at 100° for 1 *hour*. The resulting solution was poured into 50 *ml* of ice water and adjusted to *p*H 10 with 10% aqueous sodium hydroxide. The precipitate was collected by filtration. Recrystallization from 95% ethanol gave the pure product (9.0 *gm*, 95%), m. p. 110-111°, $\nu_{C=O}$ 1649 *s* cm^{-1} in KBr. $\delta^{CDCl_3}_{TMS}$=1.06 (-C<u>H</u>$_3$, *t*, J=7 *Hz*, 3H), 2.15(-C<u>H</u>$_2$-, *q*, J=7 *Hz*, 2H) 7.20(—C$_6$<u>H</u>$_5$, 3, 5-Py-H, *m*, 7H), 8 05 (2, 6-Py-H, *d*, J=4 *Hz*, 2H). *ppm*. Mass (75 *ev*) 226(M^+), 170 (base peak). *Anal. Calcd* for $C_{14}H_{14}N_2O$: C, 74.34; H, 6.19; N, 12.39. *Found*: C, 74.64; H, 6.27; N, 12.32.

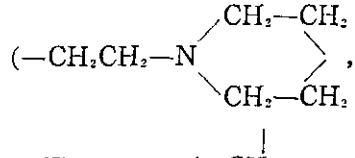
1-Phenethyl-4-propionanilino Pyridinium bromide (III). A mixture of *N*-(4-pyridyl) propionanilide (9.8 *gm*, 0.043 *mole*) and phenethyl bromide (10.4 *gm*, 0.056 *mole*) in dry toluene (100 *ml*) was refluxed with stirring for 17 *hrs*. The white precipitate (15.0 *gm*, 84%) was collected by filtration. Recrystallization from 95% ethanol gave colorless crystals, m. p. 201-202°. $\nu_{C=O}$ 1704 cm^{-1} in KBr. Mass (12 *ev*) M^+, 274, 170, 78, 56. C^{13} NMR. $\delta^{CDCl_3}_{TMS}$=8.85; 31.22; 37.35; 60.40; 117.06; 126.98; 128.43; 128.98; 130.34; 131.26; 135.15; 137.92; 144.63; 154.46; 175.03 *ppm*. *Anal. Calcd*. for $C_{22}H_{23}N_2OBr$: C, 64.24; H, 5.64; N, 6.81; Br, 19.43. *Found*: C, 64.16; H, 5.79; N, 6.49; Br, 19.33.

1-Phenethyl-4-anilino-piperidine (IV). A solution of 1-phenethyl 4-propionanilino pyridinium bromide (III) (1 *gm*, 0.00243 *mole*) in anhydrous ethanol (20 *ml*) with 2-drops

* All melting point were not corrected.

of glacial acetic acid were hydrogenated at 20 *psi* over platinum oxide (0.05 *gm*) in a Parr apparatus for 4 *hrs*. The catalyst was filtered off and the filtrate was concentrated on rotary evaporator. The concentrated solution was dilute with 10 *ml* of water and was added with 10% sodium hydroxide to *p*H 9. The alkaline solution was extracted with chloroform. The chloroform extract was dried over sodium sulfate and was concentrated to give white solid (0.41 *gm*, 62%). Recrystallization from methanol gave colorless flacklets. m.p. 98-100°. lit. m.p. 99°[6] ν_{N-H} 3270 cm^{-1} in KBr. Mass (12 *ev*) 280 (M^+), 189 (100%), 146, 96. C^{13} NMR. $\delta^{CDCl_3}_{TMS}$=32.49; 33.85; 49.80; 52.33; 60.45; 112.97; 116.92; 125.72; 128.05; 128.34; 128.98; 140.06; 146.73 *ppm*. *Anal. Calcd* for $C_{19}H_{24}N_2$: C, 81.37; H, 8.63; N, 9.99. *Found*: C, 81.27; H, 8.70; N, 9.87

Fentanyl (V). A solution of 1-phenethyl -4-anilino piperidine (5.2 *gm*, 0.019 *mole*) in toluene (20 *ml*) was added dropwise to a solution of propionic anhydride (3.1 *gm*, 0.024 *mole*) in toluene (10 *ml*). The reaction mixture was stirred at reluxing temperature for 5 *hrs*. it was cooled to 5°*C* and alkalied to *p*H 9 with 10% sodium hydroxide solution. The organic layer was separated, washed with water (30 *ml*×2), dried with anhydrous sodium sulfate. Solvent was removed by rotary evaporator, the brown oily residue solidified on cooling (5.80 *gm*, 93%). Crystallization by methanol *n*-hexane (1:1) mixture gave light brown crystals of Fenfanyl base V, m.p. 81-83C (lit 84-85)[6] ν_{D-O} 1607*s*, $\delta_{\phi-H}$ 766*s*, 753*s*, 738*s*, 710*s*, cm^{-1} in KBr. Mass 245 (base peak, $M^+ - \langle\bigcirc\rangle-CH_2 =$ 336-91) no M^+. H^1 NMR. $\delta^{CCl_4}_{TMS}$= 0.7~3.0



, NH, CH_2CH_3, *m*, 17H) 4.1-4.7 (—CH—, *m*, 1H), 6.7~7.4 (2—C_6H_5, *m*, 10H) *ppm*. C^{13} NMR. $\delta^{CDCl_3}_{TMS}$=9.73; 28.59; 30.64; 33.93; 52.21; 53.14; 60.47; 125.86; 128.20; 128.44; 129.08; 130.25; 138.69; 140.04; 173.20 *ppm*.

The IR and NMR spectra were identical with Fentanyl and did not depress the melting point on admixture with authentic sample.

The overall yield (27%) of this process started from preparation of pyridylpyridinium chloride from pyridine is much better than any other known process.

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(Received February 14, 1980)