The Chemistry of the Benzylpyridines. V. β-Phenyl-β-pyridyl-β-hydroxypropionic Acids and Derivatives as Antispasmodic Agents[1]

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The Reformatsky reaction of ethyl bromoacetate and 2-, 3-, and 4-benzoylpyridine yielded the expected ethyl β-phenyl-β-pyridyl-β-hydroxypropionates. Catalytic hydrogenation of the 2-pyridyl ester gave a mixture of 1-keto-3-phenyl-3-hydroxyoctahydroindolizine and β-phenyl-β-(2-piperidyl)-β-hydroxypropionic acid. Hydrogenolysis of the tertiary hydroxyl group and reduction of the pyridine ring occurred on catalytic hydrogenation of ethyl β-phenyl-β-(3-pyridyl)-β-hydroxypropionate. Catalytic hydrogenation of the 4-pyridyl Reformatsky ester and subsequent methylation yielded the desired ethyl β-phenyl-β-(N-methyl-4-piperidyl)-β-hydroxypropionate. The compounds showed little biological activity.

The availability of 2-, 3-, and 4-benzoylpyridine, and the corresponding N-methylated 3- and 4-benzoylpiperidines,[2] prompted a program directed to the conversion of these ketones into derivatives having possible pharmacological action. This report is concerned with the Reformatsky reaction of these ketones and the preparation and characterization of various derivatives. These compounds, I and II, are related to the series of potent antispasmodic and antihistaminic tertiary carbinols, IIIa, and their unsaturated derivatives, IIIb,[3] the carboxy or carbethoxy group replacing the dialkylamino methylene group of IIIa and IIIb.

$C_6H_5C(OH)RCH_2COOR^1$

Ia, R = 2-pyridyl, $R^1 = C_2H_5$
b, R = 3-pyridyl, $R^1 = C_2H_5$
c, R = 4-pyridyl, $R^1 = C_2H_5$
d, R = 2-pyridyl, $R^1 = H$
e, R = 3-pyridyl, $R^1 = H$
f, R = 4-pyridyl, $R^1 = H$

$C_6H_5CR{=}CHCOOH$

IIa, R = 2-pyridyl
b, R = 3-pyridyl
c, R = 4-pyridyl

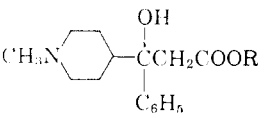
$C_6H_5CR(OH)CH_2CH_2NR'_2$ IIIa

$C_6H_5CR{=}CHCH_2NR'_2$ IIIb

The reaction of the benzoylpyridines with ethyl bromoacetate and zinc proceeded as expected and the corresponding ethyl β-phenyl-β-pyridyl-β-hydroxypropionates (Ia, b, c) were isolated in about 50% yield. To minimize quaternization of the pyridine nitrogen by the bromoester, a solution of the latter was added to the mixture of zinc and the pyridyl ketone in anhydrous benzene. Preliminary experiments indicated that the yields of the desired hydroxy ester were substantially increased if fresh portions of zinc metal were added during the course of the reaction. The benzoylpyridines did not exhibit the usual exothermic reaction characteristic of most ketones in the Reformatsky reaction. The hydroxy esters were saponified to the hydroxy acids, which upon reaction with thionyl chloride and subsequent alkaline treatment were converted into the acrylic acids (II).

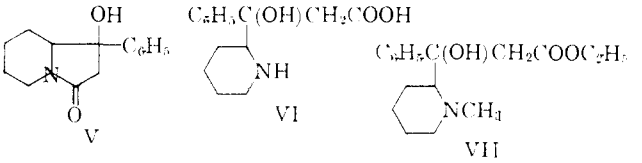
Several attempts to effect the Reformatsky reaction with N-methyl-4-benzoylpiperidine gave the desired hydroxy ester in very poor yield (2–4%). Compounds containing the piperidine ring, however, were prepared by the catalytic hydrogenation of the pyridine esters with varied results depending on the position of the nitrogen in the pyridine ring.

Catalytic hydrogenation of Ic in the presence of a platinum catalyst and one equivalent of hydrochloric acid, with subsequent methylation of the resulting piperidine derivative gave the expected ethyl β-phenyl-β-(N-methyl-4-piperidyl)-β-hydroxypropionate (IVa), in 84% yield.



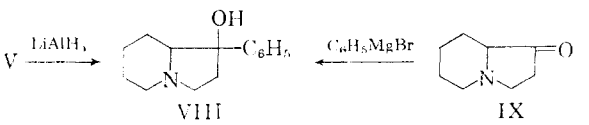
IVa, R = C_2H_5
b, R = H

Ethyl β-phenyl-β-(2-pyridyl)-β-hydroxypropionate (Ia) yielded, under similar reduction conditions, a mixture of 1-keto-3-phenyl-3-hydroxyoctahydroindolizine (V) and β-phenyl-β-(2-piperidyl)-β-hydroxypropionic acid (VI), probably formed by the hydrolysis of V.



Compound VI was converted into V in almost quantitative yield by heating in aqueous solution with hydrochloric acid.

The structure of V was established as follows. Reduction of V with lithium aluminum hydride gave 3-phenyl-3-hydroxyoctahydroindolizine (VIII), identical with the compound prepared by the Grignard addition of phenylmagnesium bromide to 3-keto-octahydroindolizine (IX). When the nitrogen atom of compound Ia was quaternized with dimethyl sulfate, and the latter hydrogenated in the presence of a platinum catalyst, the expected compound VII was obtained.



Catalytic hydrogenation of the 3-pyridyl ester (Ib) resulted in the uptake of approximately 4 moles of hydrogen and the isolation of ethyl β-phenyl-β-(3-piperidyl)-propionate (X).[4] N-Methylation of X with

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(2) (a) F. J. Villani, M. S. King, and D. Papa, *J. Org. Chem.*, **17**, 249 (1952); (b) F. J. Villani and M. S. King, *Org. Syntheses*, **37**, 6 (1957).

(3) (a) D. W. Adamson, *J. Chem. Soc.*, 5144 (1949); (b) D. W. Adamson and J. W. Billinghurst, *ibid.*, 1039 (1950).

(4) This compound contains a small amount of an unsaturated ester, XI. Evidence for the presence of XI was obtained by (a) the ultraviolet absorption spectrum which showed a maximum of low intensity at 242 mμ (ϵ_{max} = 3800–4200) and a shoulder at 240 mμ, and (b) by the poorly resolved infrared spectrum which showed a weak peak in the 1650 $cm.^{-1}$ region characteristic of a >C=CH grouping.

TABLE I

X
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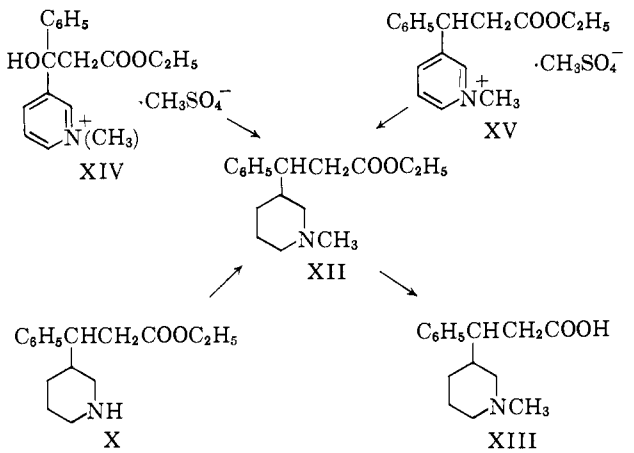
$C_6H_5CRCH_2COOR^1$

R	R^1	X	Method	Yield, %	M.p., °C.	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
2-C_5H_4N	C_2H_5	OH	A	55	63–64[a]	$C_{16}H_{17}NO_3$	70.82	70.51	6.31	6.17	5.16	5.22
3-C_5H_4N	C_2H_5	OH	A	56[b]	77–78[c]	$C_{16}H_{17}NO_3$	70.82	70.69	6.31	6.12	5.16	4.82
4-C_5H_4N	C_2H_5	OH	A	49	99–100[c]	$C_{16}H_{17}NO_3$	70.82	70.55	6.31	6.27	5.16	4.68
2-C_5H_4N	H	OH	B	84	159–159.5[d]	$C_{14}H_{13}NO_3$	69.12	68.98	5.39	5.47	5.76	5.47
3-C_5H_4N	H	OH	B	78	186–187[d]	$C_{14}H_{13}NO_3$	69.12	68.85	5.39	5.12	5.76	5.28
4-C_5H_4N	H	OH	B	87	266–267[d]	$C_{14}H_{13}NO_3$	69.12	68.78	5.39	5.47	5.76	5.38
3-C_5H_4N	H	H	[e]	90	171–172	$C_{14}H_{13}NO_2$	73.99	73.89	5.77	5.83		
3-C_5H_4N	C_2H_5	H	[f]	80	59–60[g]	$C_{16}H_{17}NO_2$	75.27	75.72	6.71	6.74		
4-N-Me-C_5H_9N	C_2H_5	OH	[h]	84	[i,j]	$C_{17}H_{25}NO_3$	70.07	70.45	8.65	8.33	4.81	4.79
4-N-Me-C_5H_9N	H	OH	B	50	249–250[d]	$C_{15}H_{21}NO_3 \cdot H_2O$	64.03	64.37	8.24	8.60	4.98	4.89
2-N-Me-C_5H_9N	C_2H_5	OH	C	33	[k]	$C_{17}H_{25}NO_3$	70.07	70.50	8.65	8.38	4.81	5.23
3-N-Me-C_5H_9N	C_2H_5	H	C	80	[l]	$C_{17}H_{25}NO_2$	74.14	74.00	9.15	8.87		
3-N-Me-C_5H_9N	H	H	B	39	273–274[d]	$C_{15}H_{21}NO_2 \cdot H_2O$	67.89	67.40	8.74	8.43		

[a] B.p. 160–170° (2 mm.), recrystallized from petroleum ether. [b] When fresh portions of zinc were not added, the yield of this product was 23%. [c] Recrystallized from hexane. [d] Recrystallized from ethanol. [e] Reduction of sodium β-phenyl-β-3-pyridylacrylate in ethanol using Raney nickel. [f] Esterification of acid with ethanol–sulfuric acid. [g] B.p. 187–190° (10 mm.). [h] See Experimental section. [i] B.p. 166–169° (1.5 mm.). [j] Hydrochloride salt, m.p. 258–259° (from methanol). *Anal.* Calcd. for $C_{17}H_{25}NO_3 \cdot HCl$: C, 62.27; H, 7.99; N, 4.24. Found: C, 62.39; H, 8.19; N, 4.25. [k] B.p. 163–165° (4 mm.), $n^{25}D$ 1.5215. [l] B.p. 167–170° (6 mm.), $n^{26}D$ 1.5207.

formaldehyde and formic acid yielded a product, in poor yield, which on the basis of ultraviolet and infrared spectral determinations was assigned the structure XII. Saponification of XII gave the acid XIII. To demonstrate that hydrogenolysis was the prime reaction in the reduction of Ib, the reactions of X–XV were employed. Quaternization of Ib with dimethyl sulfate and subsequent hydrogenation gave compound XII, which was identical with the product obtained by reduction of the quaternary salt of ethyl β-phenyl-β-(3-pyridyl)-propionate (XV). The infrared and ultraviolet spectra of the compounds obtained by these methods were identical and there was no depression in the melting point of the mixture of the acids (XIII) obtained by saponification.



The compounds prepared were subjected to a variety of pharmacological testing procedures, including the *in vivo* antispasmodic,[5a] anticonvulsant and parasympathetic blocking activity,[5b] and the *in vitro* guinea pig ileum antihistamine and antiacetylcholine screens. In general, the compounds showed little biological activity. Compounds VI, V, and X showed some activity in the maximal electroshock procedure at doses of 180, 220 and 230 mg./kg., respectively, when administered orally to rats. Compared to trimethadione (ED_{50} 350 mg./kg., orally in rats) these compounds showed approximately 1.9, 1.6 and 1.5 times, respectively, the activity of the standard in this test procedure. Compound X showed an oral *in vivo* antispasmodic activity equal to 6/7 the activity of atropine sulfate, (ED_{50} 220 mg./kg. orally in mice) but the compound was toxic at this dose level. It is interesting to note that X exhibits antispasmodic activity in spite of the fact that the polarity characteristics of the side chain in this compound are different from that of IIIa and IIIb.

(5) (a) D. I. Macht and J. Barba-Gose, *J. Am. Pharm. Assoc.*, **20**, 558 (1931); (b) A. Makovsky and S. Margolin, *Fed. Proc.*, **13**, 382 (1954).

Experimental[6]

Method A. General Reformatsky Reaction Procedure.—To a refluxing mixture of 48 g. of clean, dry zinc metal (20 mesh), 109.8 g. (0.6 mole) of the benzoylpyridine, 180 ml. of anhydrous benzene and a crystal of iodine was added dropwise with stirring, a solution of 120 g. of ethyl bromoacetate in 200 ml. each of anhydrous benzene and toluene. After one half of the bromoester was added, an additional portion (120 g.) of zinc was added then in 1 hr. a second portion of zinc. The reaction was heated on the steam bath for 3 hr. and allowed to cool to room temperature. The red-brown mixture was made acid to litmus by the addition of dilute acetic acid and extracted with benzene. The combined benzene–toluene solution was extracted several times with 10% hydrochloric acid, and the acid solution, after an ether wash, was made neutral with ammonium hydroxide and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and the ether was removed by evaporation of the steam bath.

Method B. General Saponification Procedure.—The ester (10 g.), potassium hydroxide (10 g.), 100 ml. of ethanol and 50 ml. of water was refluxed for 3 hr. on the steam bath. The solvents were removed *in vacuo* on the steam bath and the residue was dissolved in a small amount of water, washed with ether and made neutral with acetic acid.

General Preparation of Acrylic Acids (II).—Ten grams of the hydroxy acid was heated under reflux on the steam bath for 2 hr. with 150 ml. of freshly distilled thionyl chloride, the excess thionyl chloride was removed *in vacuo* and the residue was heated for 1 hr. with 100 ml. of 10% sodium hydroxide solution. After cooling, the water solution was made neutral with acetic acid and allowed to crystallize by cooling in an ice bath (slow process). The precipitated acid was crystallized from ethanol (see Table II).

(6) All melting points are corrected. Microanalyses were performed by Mr. Edwin Conner of the Microanalytical Laboratory of the Schering Corporation. The authors express their gratitude to the Physical Analytical Chemistry Department of the Schering Corporation for the ultraviolet and infrared spectra determinations, and to the Department of Pharmacology of the Schering Corporation for the biological data.

TABLE II

$C_6H_5CR{=}CHCOOH$

R	Yield, %	M.p., °C.	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
2-C_5H_4N	53	203–204	$C_{14}H_{11}NO_2$	74.64	75.01	4.93	4.98
3-C_5H_4N	56	201–202[a]	$C_{14}H_{11}NO_2$	74.64	74.50	4.93	4.69
4-C_5H_4N	78	241–242	$C_{14}H_{11}NO_2$	74.64	74.77	4.93	4.62

[a] log $\epsilon_{270m\mu}$ 4.17.

Ethyl β-Phenyl-β-(N-methyl-4-piperidyl)-β-hydroxypropionate (IVa).—Thirty grams (0.11 mole) of Ic, in 200 ml. of absolute ethanol containing 9.0 ml. of concd. hydrochloric acid, was hydrogenated in the presence of 0.5 g. of platinum oxide catalyst and an initial hydrogen pressure of 3.5 kg./cm.². The theoretical amount of hydrogen (0.33 mole) was absorbed in 1.5 hr. The catalyst was filtered off, and the alcoholic filtrate was concentrated *in vacuo* on the steam bath. The residue was dissolved in water, made basic with ammonium hydroxide and extracted with chloroform. The chloroform extracts were washed with water and the chloroform was removed by evaporation on the steam bath. The residue, a yellow oil, was dissolved in 29 g. of 90% formic acid and 25 ml. of formalin (37%) was added. After warming on the steam bath for 8 hr., 50 ml. of 20% hydrochloric acid was added and the solution was concentrated to dryness *in vacuo*. The residue was dissolved in water, made basic with ammonium hydroxide and extracted with chloroform.

Hydrogenation of Ethyl β-Phenyl-β-(2-pyridyl)-β-hydroxypropionate.—The ester Ia (32 g., 0.12 mole) in 200 ml. of absolute ethanol containing 10 ml. of concd. hydrochloric acid was reduced in the presence of 0.5 g. of platinum oxide in a Parr hydrogenator at an initial pressure of 3.5 kg./cm.². The theoretical amount of hydrogen was absorbed in 3 hr. The catalyst was filtered off and the alcohol was removed by concentration *in vacuo* on the steam bath. The residue was dissolved in water and was neutralized with ammonium hydroxide, cooled and filtered. There was obtained 4.5 g. (16.5%) of a white solid (V). The filtrate was extracted with chloroform and after removal of the chloroform, 25 g. (78.1%) of a white solid (VI) was obtained. Compound V was recrystallized from benzene; m.p. 159–159.5°.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 73.11; H, 7.49.

Compound VI was recrystallized from benzene; m.p. 161–162° dec.

Anal. Calcd. for $C_{14}H_{19}NO_3{\cdot}H_2O$: C, 62.90; H, 7.92. Found: C, 62.72; H, 8.02.

Conversion of VI to V.—A solution of 0.6 g. of VI in a small amount of water and 5 ml. of concd. hydrochloric acid was boiled vigorously for 2 min. under reflux. The clear solution was cooled and made alkaline with ammonium hydroxide solution. An immediate precipitate formed which was filtered and recrystallized from benzene, m.p. 157–158°. A mixture melting point with V showed no depression, whereas a mixture melting point with VI showed a marked depression.

3-Phenyl-3-hydroxyoctahydroindolizine (VIII) from (V).—Seven grams (0.03 mole) of V was reduced with 3 g. of lithium aluminum hydride employing the Soxhlet technique.[7] After 20 hr. the mixture was decomposed with ice water and 150 ml. of 10% sodium hydroxide was added. The ether layer was separated and the solvent removed on the steam bath. The crude residue was recrystallized from petroleum ether: m.p. 107–108°; yield 4 g. (62%).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.24; H, 8.84.

3-Phenyl-3-hydroxyoctahydroindolizine (VIII) from 3-Keto-octahydroindolizine (IX).—The ketone (IX) was prepared in 49% yield by the Dieckmann cyclization of ethyl (N-β-carbethoxyethyl)-pipecolinate,[8] b.p. 95–97° (17 mm.); $n^{30}D$ 1.4785; reported b.p.[8] 93° (18 mm.).

To a cooled ethereal solution of Grignard reagent prepared from 50 g. of bromobenzene and 7.7 g. of magnesium turnings was added a solution of 25 g. of IX in 50 ml. of anhydrous ether. The mixture was permitted to stand overnight at room temperature and was decomposed by addition of dilute hydrochloric acid. The acid solution was made basic with ammonium hydroxide, causing the precipitation of a cream colored solid which was filtered off and recrystallized from petroleum ether; m.p. 107–108°; yield 25 g. (71%).

The *methiodide* was recrystallized from a mixture of absolute methanol and absolute ether; m.p. 198–199°.

Anal. Calcd. for $C_{14}H_{19}NO{\cdot}CH_3I$: N, 3.90. Found: N, 3.58.

Method C. Ethyl β-Phenyl-β-(N-methyl-2-piperidyl)-β-hydroxypropionate (VII).—The ester Ia (10 g., 0.036 mole) in 50 ml. of anhydrous benzene and 5 g. of dimethyl sulfate was heated on the steam bath under reflux for 3 hr. The benzene was decanted from the precipitated oily product which was washed thoroughly with anhydrous ether. The oily salt was dissolved in 200 ml. of absolute ethanol and hydrogenated in a Parr hydrogenator in presence of 0.5 g. of platinum oxide catalyst. Within 15 min. 80% of the theoretical quantity of hydrogen was absorbed. The reduction was allowed to proceed for 1 hr. The catalyst was removed and the solvent was evaporated off on the steam bath. The residue was dissolved in water, made basic and extracted with ether. The product was isolated by distillation.

Reduction of Ethyl β-Phenyl-β-(3-pyridyl)-β-hydroxypropionate (Ib).—The ester Ib (27.1 g., 0.1 mole) dissolved in 250 ml. of ethanol containing 8.0 ml. of concd. hydrochloric acid was hydrogenated in a Parr hydrogenator in the presence of 0.5 g. of platinum oxide. After 24 hr., the catalyst was filtered off and the filtrate was concentrated to dryness and processed as above; b.p. 171–174° (2 mm.); $n^{24}D$ 1.5423; yield 17 g.; $\epsilon_{242\ m\mu}$ 3800–4200.

Anal. Calcd. for compound X, $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.24; H, 8.57; N, 5.52.

Compound XII from XV.—Ethyl β-phenyl-β-(3-pyridyl)propionate was quaternized with dimethyl sulfate and hydrogenated as in Method C; b.p. 170–172° (4 mm.); $n^{24}D$ 1.5130; yield 15 g. (75%).

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.47; H, 9.26; N, 5.48.

(7) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947).

(8) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 2969 (1932).