Ethyl 2-Keto-4-phenylnipecotate, V.—A mixture of 130 g. of cinnamonitrile, 160 g. of ethyl malonate and a solution of 23 g. of sodium in 450 ml. of ethanol was boiled for four hours and then neutralized with dilute acetic acid. The resulting **ethyl α-carbethoxy-γ-cyano-β-phenylbutyrate (IV)** boiled at 190–195° at 0.5 mm. and melted at 43–45°; yield 241 g. (83%).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6. Found: C, 66.5; H, 6.5.

This cyano ester (100 g.) was reduced in an equal weight of alcohol at 155°, using Raney nickel and hydrogen at a pressure of 2000 lb. Removal of the alcohol and solution of the products in benzene gave 50 g. of an uncrystallizable, easily soluble sirup and 17 g. of crystalline **4-phenylpiperidone-2.** The latter substance was also obtained from the sirup by dissolving it in boiling sodium hydroxide solution, acidification, and subsequent distillation of the precipitate under reduced pressure. The lactam formed colorless plates from benzene; m. p. 137–139°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.4. Found: C, 75.7; H, 7.5.

Twenty grams of 4-phenylpiperidone-2, reduced in butyl alcohol with 20 g. of sodium, gave 11.2 g. of 4-phenylpiperidine, b. p. 137–147° at 21 mm., m. p. 57–60° (reported[3] 57–58°). The hydrochloride of 4-phenylpiperidine sintered at 110° and melted at 164–165° when it was heated slowly; placed in a bath at 150° it melted with effervescence. With the base just described, there was also obtained 2.9 g. of a base that boiled at 160–220° at 18 mm. and melted at 137° after it had been crystallized from benzene; it was not investigated further.

When 8 g. of 4-phenylpiperidine hydrochloride was heated for thirty hours at 100° with an excess of formalin, there was obtained 1.8 g. of a non-volatile base, colorless needles from alcohol, m. p. 101–103° (methylene-bis-4-phenylpiperidine ?), together with 3.1 g. of **1-methyl-4-phenylpiperidine,** a colorless liquid, b. p. 138–140° at 17 mm. The methylated base was analyzed as its **hydrochloride,** colorless plates from a mixture of alcohol and ether, m. p. 185–187°.

Anal. Calcd. for $C_{12}H_{18}ClN$: C, 68.1; H, 8.5. Found: C, 67.9; H, 8.4.

The author thanks Mr. C. H. Stratton for most of the analyses reported in this paper.

(3) Bally, *Ber.*, **20**, 2590 (1887).

Summary

Catalytic reduction of β-phenyl-γ-cyanobutyric esters is accompanied by cyclization and leads to the formation of 4-phenylpiperidones. These lactams can be reduced to 4-phenylpiperidines by treatment with sodium and butyl alcohol.

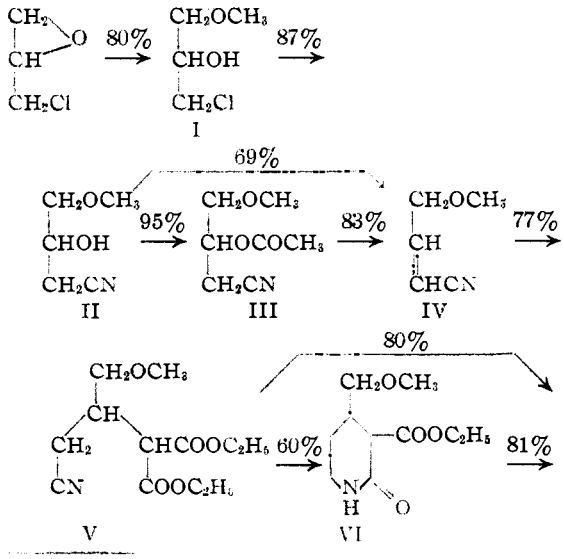
MINNEAPOLIS, MINNESOTA RECEIVED SEPTEMBER 7, 1943

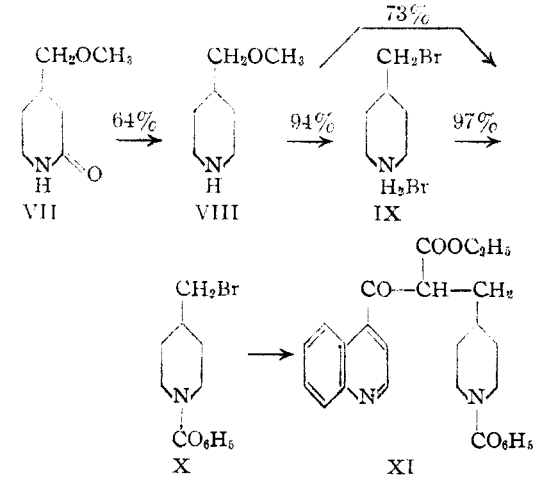
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Two New Syntheses of 1-Benzoylpiperidine-4,β-propionic Acid

BY C. F. KOELSCH

Part I.—The piperidine synthesis described in previous papers[1] can be applied to the preparation of 4-bromomethylpiperidine, and it appeared likely that this halide could be condensed with ethyl quinoline-4,β-ketopropionate to form a compound which occupies a key position in Rabe's[2] synthesis of rubanol-9. The reactions involved and yields realized are summarized in the accompanying chart.

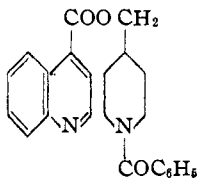




Considerable study was devoted to the determination of the optimum conditions for carrying out each reaction, and satisfactory yields were obtained in each step except the last. Compound X was recovered unchanged after it had been boiled for three hours with the sodium derivative of ethyl quinoline-4,β-ketopropionate in alcohol, and when the period of boiling was prolonged or when ethyl carbonate was used in place of alcohol as the solvent, tarry unworkable products were

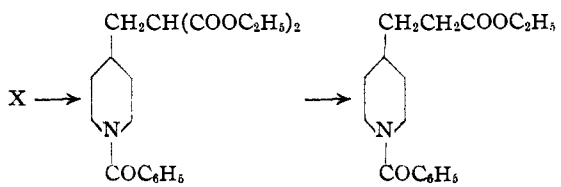
(1) Koelsch, THIS JOURNAL, **65**, 2093 (1943); **65**, 2459 (1943).
(2) Rabe, Kindler and Wagner, *Ber.*, **55**, 536 (1922).

obtained. Compound X reacted with the silver derivative of the β-ketoester, but the product was 1-benzoyl-4-piperidylmethyl cinchoninate (XII), a substance also formed from X and silver cinchoninate.



XII

Although X could not be transformed directly into XI, it was possible to carry out the following reactions and it has been shown by Rabe that

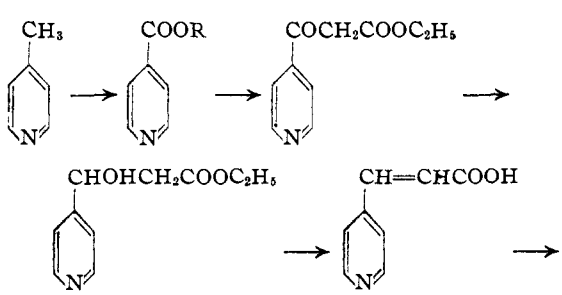


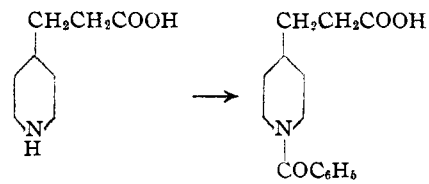
XIII

XIII will condense with ethyl cinchoninate to form XI. Unfortunately the route from X to XIII could be followed with only moderate success (over-all yield 28%), a circumstance which removes the present series of reactions from consideration as a practical synthesis of rubanol.

Since, however, alkyl groups can be introduced into the 3-position of VI or into the corresponding position of V,[3] the series of reactions offers a means of obtaining rubanols analogous to hydroquinine but bearing substituents on C-3 different from the ethyl group of the natural alkaloid. Experiments in this direction will be reported in future papers. It is of interest that whereas hydroquinine is a potent antimalarial, the ethyl-free analog, 6-methoxyrubanol-9, is inactive.[4]

Part II.—For comparison with the 1-benzoylpiperidine-4,β-propionic acid synthesized in Part I, the compound was prepared by a second method, through the reactions indicated in the accompanying formulas.





It was hoped that the reduction of ethyl isonicotinoylacetate to ethyl piperidine-4,β-propionate could be done in one operation, for similar transformations have been reported[5] using a platinum catalyst. However, with Raney nickel, the only catalyst available to the author, the direct reduction could not be carried beyond ethyl pyridine-4,β-hydracrylate. The necessity of isolating each of the various intermediates renders the present synthesis less practical than those which have been used heretofore.[6]

Experimental

1-Chloro-3-methoxypropanol-2 (I).[7]—A solution of 40 g. of sulfuric acid in 1600 ml. of methanol contained in a five-liter flask fitted with a reflux condenser and a stirrer was heated to boiling, and 1100 g. of epichlorohydrin was added at such a rate that the mixture boiled gently. The solution was allowed to stand for four hours, and then 40 g. of finely ground dry sodium carbonate was added with stirring. After thirty minutes the sodium sulfate and carbonate were removed by filtration, and the filtrate was concentrated by distillation from a water-bath. The residue was distilled, giving 1208 g. (81.5%) of a colorless liquid, b. p. 75–78° at 12 mm. (reported, 95° at 20 mm.). Yields in other preparations carried out similarly were 78, 75, 79, 80, and 85%.

On keeping, the sirupy distillation residue solidified; washing it with alcohol and ether then left a very deliquescent substance, pearly white plates that contained sodium, chlorine and sulfur. The salt appeared to be $ClCH_2CHOHCH_2OSO_3Na$.

Anal. Calcd. for $C_3H_6ClNaO_6S$: Na, 10.8. Found: Na, 11.6.

β-Hydroxy-γ-methoxybutyronitrile (II).—A three-liter flask was fitted with a thermometer reaching nearly to the bottom and with a mechanical stirrer, and was supported so that it could be immersed in a bath of ice water at varied depths. Water (225 ml.) and granulated sodium cyanide (225 g., calcd. 210 g.) were placed in the flask, stirred for ten minutes, and then treated with 530 g. of I, in one portion. The cooling bath was placed so that the reaction temperature was held at 44–46° for one hour, while the mixture was stirred. The temperature was then allowed to rise to 47–49° for one hour, and finally to 50° for thirty minutes. The cooling bath was then removed, and the mixture was stirred for six hours. It was then neutralized with concd. hydrochloric acid (Hood. If the neutralization is omitted, subsequent distillation of the product is often accompanied by partial dehydration). The sodium chloride was removed and washed well with methanol. The combined filtrate and washings were concentrated and finally distilled under reduced pressure, giving 33 g. of a fore-run, b. p. less than 125°, and 414 g. (85%) of II, a colorless liquid b. p. 125–135° at 21 mm. Yields obtained in other similar preparations were 77, 86, 91, 90 and 92%. The pure compound boiled at 133° at 18 mm.

Anal. Calcd. for $C_5H_9NO_2$: C, 52.2; H, 7.8. Found: C, 51.7; H, 7.8.

The hydroxynitrile was soluble in water and in ether in all proportions; small quantities could be distilled at

(3) Koelsch, THIS JOURNAL, **65**, 2458 (1943).

(4) Rabe and Hagen, *Ber.*, **74**, 636 (1941); *cf.* Prelog and coworkers, *ibid.*, page 647.

(5) *Cf.* Strong and McElvain, THIS JOURNAL, **55**, 816 (1933).

(6) Prelog and Cerkovnikov, *Ann.*, **532**, 83 (1937); also Part I of this paper, and ref. 2.

(7) *Cf.* Fourneau and Ribas, *Bull. soc. chim.*, **39**, 1584 (1926).

atmospheric pressure with darkening but only slight decomposition; when it was boiled with zinc chloride, the compound became dark and gave off an acrolein-like odor, but the residue was completely soluble in water; when the hydroxynitrile was boiled with aqueous potassium hydroxide, it darkened rapidly and was converted partly into IV.

γ-Methoxycrotononitrile (IV).—Dehydration of III by distilling it from phosphorus pentoxide, the classical[8] method for dehydrating β-hydroxynitriles, yielded IV in only small amount. Satisfactory results were obtained, however, (a) by carrying out the dehydration of II with anhydrous potassium carbonate, or (b) by converting II into the acetate III and then pyrolyzing this over potassium acetate.

(a) A mixture of 100 g. of II with 4 g. of anhydrous potassium carbonate was distilled slowly from a 200-ml. flask using a free flame. The distillates from four such operations were combined and distilled to 185°; the residue was mixed with 2 g. of potassium carbonate and distilled. The total distillates were combined and saturated with dry potassium carbonate, and the organic layer was separated and fractionated, yielding 27 g. of a fore-run and 236 g. (70%) of practically pure IV, b. p. 175–185°. For analysis, a sample whose b. p. was 182° was selected. One gram of the nitrile was soluble in about 19 g. of water at 25°.

Anal. Calcd. for C_5H_7NO: C, 61.8; H, 7.2. Found: C, 61.3; H, 7.3.

(b) A mixture of 400 g. of the hydroxynitrile II with an equal weight of acetic anhydride was boiled for thirty minutes. The acetic acid formed was then distilled through a column (to 85° at 55 mm.), and the residue was fractionated. There was obtained 525 g. (96%) of pure **β-acetoxy-γ-methoxybutyronitrile (III)**, a colorless liquid, b. p. 128–130° at 21 mm., that was difficultly soluble in water. When the compound was boiled for one minute with 0.1 *N* sodium hydroxide, the acetyl group was removed.

Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.5; H, 7.1; sapon. equiv., 157. Found: C, 53.6; H, 7.25; sapon. equiv., 156.

The acetate was distilled in portions of 100 g. from potassium acetate (4 g.), and several combined distillates were fractionated repeatedly, acetic acid being finally removed from the intermediate fractions by treatment with potassium carbonate. Yields of IV in this step averaged 83%, and the product did not become brown on standing as did the nitrile prepared by the direct dehydration of II.

γ,γ-Dicarbethoxy-β-methoxymethylbutyronitrile (V).—Attempts to condense ethyl malonate or ethyl cyanoacetate with the hydroxynitrile II by Ingold's method[9] or to condense ethyl malonate with IV using a catalytic amount of sodium ethoxide were not successful. But yields of V averaging 77% were obtained in the following way.

To a solution of 46 g. of sodium in 550 ml. of dry alcohol was added 320 g. of ethyl malonate, and then 194 g. of IV was run into the hot solution in a thin stream, the heat evolved in the reaction causing gentle boiling. The mixture was boiled for thirty minutes, then cooled and treated with 120 g. of acetic acid followed by 200 ml. of water. Most of the alcohol was removed by distillation from an oil-bath at 135°, and the residue was separated while it was still hot. The lower layer was diluted, cooled, and extracted once with ether. The ether extract and the upper layer were combined, washed with water, and then distilled twice under reduced pressure. There was obtained 383 g. (74.5%) of V, a colorless liquid, b. p. 180–185° at 20 mm.

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.0; H, 7.4. Found: C, 55.8; H, 7.5.

Ethyl 2-Keto-4-methoxymethylnipecotate (VI).—The reduction of V (in portions as large as 400 g.) in three-fourths of its volume of 95% alcohol with hydrogen at 2500 lb. in the presence of Raney nickel usually began at 140° and was rapid at 155°, the theoretical quantity of hydrogen being taken up in less than one hour. The product, freed of alcohol by heating it at 100° under 20 mm., formed a thick colorless oil, soluble in water in all proportions. It boiled at 220–225° at 20 mm., but could be distilled only in small quantities (15–20 g.) and then with some decomposition; only 60% of the material submitted to distillation could be recovered.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.8; H, 7.9. Found: C, 55.5; H, 7.9.

4-Methoxymethylpiperidone-2 (VII).—A solution of 66 g. of 85% potassium hydroxide in 240 ml. of water was shaken with 200 g. of crude alcohol-free VI. The mixture rapidly became homogeneous, and its temperature rose to 80°. After thirty minutes, it was cooled (a crystalline salt was obtained if the solution was concentrated under reduced pressure) and treated with a cold solution of 50 g. of sulfuric acid in 50 ml. of water. The potassium sulfate was removed, the filtrate was distilled to a sirup under reduced pressure at 85°, and the resulting second crop of potassium sulfate was removed and washed with acetone. The organic product was heated at 100° and then distilled under reduced pressure, giving 111 g. (83% yield) of VII, b. p. 179–181° at 21 mm. The compound crystallized readily, m. p. 59–62°, but it was too soluble to be recrystallized.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.7; H, 9.1. Found: C, 58.4; H, 9.3.

4-Methoxymethylpiperidine (VIII).—Small scale (0.05 mole) reductions of VII were carried out in the usual way,[1] using 2.5–3 times the calculated amount of sodium in 10 times its weight of butyl alcohol. The desired product was obtained in yields of 60–65%, but because of the large volumes of dry butyl alcohol required, the procedure was inconvenient for reducing large quantities of the piperidone. Experiments were therefore carried out to determine how efficiently the sodium was consumed, and two of these are summarized in Table I.

TABLE I

REDUCTION WITH SODIUM IN BUTYL ALCOHOL

Expt.	Na added g.[c]	Na added at.[d]	H_2 evolved[a] ml.[d]	H_2 evolved[a] moles	Lactam[b] present, moles	Efficiency in increment %	Efficiency over-all %
A[e]	..	...	..	...	0.1	..	..
	1.65	0.072	258	0.012	.088	68	68
	2.40	.176	516	.023	.068	76	74
	2.15	.270	1290	.058	.061	28.5	58
	3.48	.420	2320	.104	.047	36.8	50.5
	2.45	.528	3360	.150	.043	1.5	43.2
	4.18	.710	5080	.228	.037	1.3	35
B	..	...	..	...	.1	..	..
	9.65	.418	1290	.058	.024	72.4	72.4
	6.05	.684	3960	.177	.018	10.2	48

[a] Collected over water; corrected for water vapor, pressure, and temperature. [b] All hydrogen not evolved was assumed to be used in reduction of the lactam VII. [c] In increment. [d] Total. [e] Each experiment involved 0.1 mole of VII in 200 ml. of butyl alcohol which had been dried by distillation from butyl phthalate and sodium butoxide.

From experiment **A** it is seen that an excess of sodium over the calculated amount (0.4 atom) is utilized poorly if it is added in small increments, and by comparing **A** with **B**, it appears that a much greater amount of reduction is achieved if the sodium is added in large increments. Also it is indicated that little is gained by using more than 1.5 times the calculated amount of sodium.

Based on the quantitative experiments, large scale reductions were carried out as follows. **A solution of 72 g.** of the piperidone VII in 800 ml. of butyl alcohol (dried by dis-

(8) Moureu, *Ann. chim.*, [7] **2**, 191 (1894); Lespieau, *Bull. soc. chim.*, [3] **33**, 468 (1905).

(9) Ingold, *J. Chem. Soc.*, **119**, 329 (1921).

tillation through a 1.5-meter column packed with glass helices) was placed in a three-liter three-necked flask fitted with a water-jacketed reflux condenser, the inner tube of which was 1.7 meters long and 4 cm. in diameter. The solution was warmed to about 50°, then 80 g. of sodium in large pieces was added at once, and the side necks of the flask were stoppered. When the extremely vigorous reaction had moderated, the large condenser was removed and a motor driven stirrer was inserted in its place. A small reflux condenser was fitted to a side neck of the flask, the stirrer was started, and the mixture was heated with a free flame until the remaining globules of sodium had reacted. The mixture was then cooled and treated with 300 ml. of water. The aqueous layer was separated and discarded. The organic layer was acidified to Congo red with concd. hydrochloric acid, and the butyl alcohol was removed by distillation, small portions of water being added when necessary to prevent bumping and to allow the last of the butyl alcohol to be removed with steam. Sixty grams of solid sodium hydroxide was added to the aqueous residue, together with enough water to dissolve inorganic salts. The oil was separated, and the aqueous layer was extracted with three 50-ml. portions of ether; the extracts and the oil were combined, treated with solid potassium hydroxide, and distilled. The product boiling at 60–95° at 28 mm. (45 g., 68%; yields in other similar experiments were 60 and 62%) was quite pure and was suitable for conversion into the hydrobromide. Pure VIII, obtained by drying the crude product over barium oxide, boiled at 80–81° at 27 mm., and melted at about 0°. It had a pronounced but not characteristic odor, was hygroscopic and completely miscible with cold water or ether.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.1; H, 11.6. Found: C, 65.0; H, 11.8.

The **picrate** formed yellow prisms from water, m. p. 146–148°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.6; H, 5.0. Found: C, 43.8; H, 5.3.

The **hydrochloride**[10] formed colorless prisms, m. p. 150°.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50.5; H, 9.7. Found: C, 50.7; H, 9.4.

The **hydrobromide** crystallized from a mixture of alcohol and ether in the form of colorless slightly hygroscopic plates, m. p. 143°.

Anal. Calcd. for $C_7H_{16}BrNO$: Br, 38.1. Found: Br, 38.1.

The *p*-nitrobenzoyl derivative, prepared from the hydrobromide with *p*-nitrobenzoyl chloride and aqueous sodium carbonate, formed colorless plates from alcohol, m. p. 84–86°.

With sodium nitrite and aqueous hydrochloric acid, the hydrobromide yielded 83.5% of 1-**nitroso-4-methoxymethylpiperidine**, a bright yellow oil which had an odor similar to that of nitrosopiperidine and hypochlorous acid; it was only slightly soluble in water, b. p. 158–160° at 23 mm.

Anal. Calcd. for $C_7H_{14}N_2O_2$: C, 53.2; H, 8.9. Found: C, 53.3; H, 8.7.

Reduced with zinc and sulfuric acid at 55–60°, the **nitroso derivative** (19 g.) gave 60% of **1-amino-4-methoxymethylpiperidine**, a hygroscopic oil, b. p. 100–115° at 25 mm., which smelled strongly of ammonia and formed no solid derivative with anisaldehyde or *m*-nitrobenzaldehyde. It was analyzed as its **hydrobromide**, colorless plates from a mixture of alcohol and ether, m. p. 102–104°.

Anal. Calcd. for $C_7H_{17}BrN_2O$: Br, 35.6. Found: Br, 36.3.

4-Bromomethylpiperidine Hydrobromide (IX).—When a solution of 4-methoxymethylpiperidine hydrobromide in 48% hydrobromic acid was heated to the boiling point, a rapid effervescence set in, and within ten minutes the calculated amount of methyl bromide (collected over saturated aqueous sodium chloride) was evolved. Evaporation of the reaction mixture at 100° under reduced pressure left a solid which melted at 150–151° after it had been crystallized from dry alcohol. This salt was not the desired IX, but was **4-hydroxymethylpiperidine hydrobromide.**

Anal. Calcd. for $C_6H_{14}BrNO$: total Br = ionic Br, 40.7. Found: total Br, 41.4; ionic Br, 39.9.

A series of experiments in which similar residues were analyzed for bromine after the reaction mixtures had been boiled for varying lengths of time led to the following optimum conditions for preparing IX from VIII.

A mixture of 130 g. of 4-methoxymethylpiperidine hydrobromide with 700 ml. of 47% hydrobromic acid was boiled gently for ten minutes, and the methyl bromide evolved (55 g., 94%) was collected in a trap cooled with dry-ice. The reaction mixture was then boiled for seven hours, and finally the excess hydrobromic acid and water were removed under reduced pressure at 100°. The remaining sirup was stirred with ether, and the crystalline 4-bromomethylpiperidine hydrobromide (151 g., 94%) was removed by filtration and then dried over sulfuric acid. The crude salt was very hygroscopic, and no significant melting point was obtained; analysis indicated that the crude salt was rather impure.

Anal. Calcd. for $C_6H_{13}Br_2N$: Br, 61.5. Found: Br, 57.0.

A mixture of 78.5% of IX with 21.5% of hydroxymethylpiperidine hydrobromide would have a bromine content of 57%.

When IX was warmed with an excess of 5% sodium hydroxide, it was converted into 1-azabicyclo[1,2,2]heptane, identified through its picrate, m. p. 270°, (dec.), (uncor.) (reported 274°, dec.[11a]; 285°, (dec.), (cor.[11b])).

1-Benzoyl-4-bromomethylpiperidine (X).—A small scale benzoylation of a pure sample of IX (2.5 g.) gave X in a yield of 97%. Larger scale experiments in which a crude IX was used gave poorer yields. The hydrobromide IX (151 g.) described in the preceding section was dissolved in 150 ml. of water at 0°, and the solution was stirred vigorously while 200 g. of benzoyl chloride and then 2000 ml. of 10% aqueous sodium carbonate were added. After two hours the semi-solid product was removed and triturated with ether. Part (88 g.) of the benzoyl derivative remained undissolved, and the remainder (31.6 g.) was obtained from the mother liquor after the benzoic anhydride had been removed by stirring for several hours with dilute sodium carbonate.

The total yield was 73%, and the product separated from alcohol in the form of colorless prisms that melted at 88–90°.

Anal. Calcd. for $C_{13}H_{16}BrNO$: C, 55.3; H, 5.7; Br, 28.3. Found: C, 55.4; H, 5.7; Br, 27.8.

Ethyl Quinoline-4,β-ketopropionate and its Reaction with X.—A suspension of sodium ethoxide (from 4.5 g. of powdered sodium and 9.5 g. of ethanol) in 100 ml. of ether was mixed with ethyl cinchoninate[12] and 17.5 g. of ethyl acetate. The mixture was boiled for twenty hours, and the resulting **sodio derivative**, fine white needles, was removed by filtration and washed with ether.

Anal. Calcd. for $C_{14}H_{12}NNaO_3$: Na, 8.7. Found: Na, 8.5.

The sodio derivative gave a clear solution in water, and it was not changed when it was boiled with 10% sodium hydroxide. The free ketoester was an oil[13] which formed

(10) This salt was prepared by Mr. S. T. Rolfson.

(11) (a) Clemo and Metcalf, *J. Chem. Soc.*, 1523 (1937); (b) Clemo and Prelog, *ibid.*, 400 (1938).

(12) 2-Chlorocinchoninic acid was prepared according to Thielepape [*Ber.*, **55**, 127 (1922)] and dehalogenated with hydrogen (35 lb. pressure) and Raney nickel in aqueous sodium hydroxide (twelve hours shaking; yield >90%). The resulting cinchoninic acid was esterified according to the method of Cohen and King [*Proc. Roy. Soc.* (London), **B125**, 49 (1938)]. Ethyl cinchoninate gave a bright yellow picrate, difficultly soluble in alcohol, m. p. 183–185°.

(13) Rabe and Pasternack, *Ber.*, **46**, 1026 (1913).

a sulfate that melted sharply at 150° with decomposition,[14] and a **picrate,** yellow plates from alcohol, insoluble in water, m. p. 160–163°.

Anal. Calcd. for $C_{20}H_{16}N_4O_{10}$: C, 50.9; H, 3.4. Found: C, 51.0; H, 3.3.

Ethyl sodioquinoline-4,β-ketopropionate (5.3 g.) gave a yellow solution in alcohol (25 ml.) containing 5.7 g. of X. This solution was still alkaline after it had been boiled for seven hours; and when it was worked up in an appropriate way, it yielded 3.7 g. of the picrate of ethyl quinoline-4,β-propionate, 4.8 g. of unchanged X, and a small amount of resinous material. A similar mixture boiled for twenty-five hours yielded 0.9 g. of the same picrate, 1.3 g. of the picrate of ethyl cinchoninate, 4.6 g. of ether-soluble resin, and some ether-insoluble resin. Only resinous substances were isolated from a similar reaction mixture prepared in ethyl carbonate and boiled for four hours.

The **silver derivative** of ethyl quinoline-4,β-ketopropionate was obtained by mixing aqueous silver nitrate with a solution of the sodio derivative. It formed a tan powder, insoluble in water, alcohol, or ether, which yielded ethyl quinoline-4,β-ketopropionate (identified through its picrate) when it was treated with dilute acetic acid.

Anal. Calcd. for $C_{14}H_{12}AgNO_3$: Ag, 30.8. Found: Ag, 30.7.

A mixture of 3.5 g. of the silver derivative with 2.8 g. of X reacted slowly at 100°, giving silver bromide and a viscous brown oil after six hours. The oil was separated into 1.2 g. of X and 1.8 g. of **1-benzoylpiperidine-4-methyl cinchoninate (XII),** purified through its picrate. Recrystallized from dilute alcohol, the base formed faintly tan micro prisms that melted at 132–133°.

Anal. Calcd. for $C_{23}H_{22}N_2O_3$: C, 73.9; H, 5.9. Found: C, 74.0; H, 6.0.

The **picrate,** deep yellow micro crystals from ethyl acetate, was insoluble in water or alcohol. It sintered at 165° and melted at 170–172°.

Anal. Calcd. for $C_{29}H_{25}N_5O_{10}$: C, 57.7; H, 4.2. Found: C, 57.7; H, 4.2.

The base XII was obtained in fair yield when a mixture of silver cinchoninate and X was heated for six hours at 100°. Mixed melting point determinations (free base; picrate) showed the identity of the compound with that obtained from the silver derivative of the ketoester.

Ethyl 1-Benzoylpiperidine-4,β-propionate (XIII).—To a solution of 2.3 g. of sodium in 30 ml. of alcohol was added 16 g. of ethyl malonate and then 28 g. of X. The mixture was boiled for two hours, filtered, and treated with water and ether. Removal of the ether left 35.2 g. (calcd. 36 g.) of syrupy alkylation product. This was warmed for thirty minutes with 4.5 g. of sodium hydroxide in 5 ml. of water and 25 ml. of 95% alcohol. The crystalline salt which precipitated was removed by filtration, but gave no useful product on further treatment. The solution was heated at 100° under 25 mm. to remove solvents, and the residue was treated with water. An oil (10.4 g., probably a mixture of mono- and dialkylated malonic ester) remained undissolved and was not further examined. Acidification of the aqueous solution gave 15.6 g. of a glassy substance from which no crystalline material could be isolated. When this glass was heated at 185° it lost 2.3 g. of carbon dioxide, leaving a residue which was separated by means of aqueous sodium carbonate into 5.2 g. of 1-benzoyl-piperidine-4,β-propionic acid and 7.7 g. of the corresponding ethyl ester (XIII).

The **acid** separated from benzene or from water in the form of clear prisms that melted at 145–147°; its solution in aqueous soda decolorized permanganate only very slowly at the boiling point.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.3; neut. equiv., 261. Found: C, 68.6; H, 7.1; neut. equiv., 259.

(14) A sulfate of unstated m. p. was described by Rabe and Pasternack[13] as being difficultly soluble in water. The 150° compound of the present investigation was too soluble to be useful for semi-quantitative isolation of the ester.

The ester (XIII) boiled at 240–245° at 6 mm. (reported[2] 240° at 8 mm.), and when it was boiled for one minute with 2% sodium hydroxide in 30% alcohol it was saponified, giving benzoylpiperidinepropionic acid quantitatively.

Ethyl Pyridine-4,β-ketopropionate (Ethyl Isonicotinoylacetate).—A mixture of 46 g. of γ-picoline[15] with 750 ml. of water was heated to boiling under a reflux condenser and stirred while 190 g. of potassium permanganate was added in portions of about 20 g. The mixture was then boiled for fifteen minutes and filtered with suction; the manganese dioxide was washed with 200 + 100 ml. of hot water. The combined filtrates were distilled to about 275 ml., the distillate being saved and used in place of water in subsequent oxidations. The residue was acidified with 75 ml. of acetic acid and cooled to 20°; isonicotinic acid was removed by filtration and washed with cold water. The yield in the first experiment was 25.4 g. (45%), and in subsequent ones was 55.0, 62.4, 56.4, and 60.1%.

A mixture of 46 g. of isonicotinic acid, 180 ml. of absolute alcohol, and 45 g. of concd. sulfuric acid was boiled for ten hours. There was obtained 37.5 g. (67%) of ethyl isonicotinate.

A suspension of sodium ethoxide from 5.7 g. of powdered sodium and 11.5 g. of alcohol in 50 ml. of ether was treated with a mixture of 37.5 g. of ethyl isonicotinate and 24 g. of ethyl acetate. The mixture was boiled for four hours and then shaken with 250 ml. of water. Acidification of the aqueous layer with 15 ml. of acetic acid gave 25.8 g. (53.5%) of crystalline ethyl isonicotinoylacetate.[16]

Reduction.—A solution of 25 g. of ethyl isonicotinoylacetate in 25 ml. of dry alcohol absorbed one equivalent of hydrogen rapidly at 100° and 2200 lb. in the presence of Raney nickel, but no more hydrogen was taken up even at 200°. The product, **ethyl pyridine-4,β-hydracrylate,** was a yellow oil, which was analyzed in the form of its **hydrochloride,** shining colorless prisms from alcohol–ether that sintered at 153° and melted at 155–157°.

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: Cl, 15.4. Found: Cl, 15.4.

When the ester was boiled for thirty minutes with four times its weight of 1:1 hydrochloric acid, and the resulting solution was then distilled to dryness at 20 mm., there was obtained **pyridine-4,β-hydracrylic acid hydrochloride** colorless crystals from alcohol–ether that sintered at 170° and melted at 173–175°.

Anal. Calcd. for $C_8H_{10}ClNO_3$: Cl, 17.4. Found: Cl, 17.4.

A solution of 2.9 g. of ethyl pyridine-4,β-hydracrylate and 1.4 g. of potassium hydroxide in 5 ml. of water was warmed to 60° for twenty-five minutes, then cooled and acidified with acetic acid. No acid separated, but the addition of a slight excess of copper acetate gave a precipitate of 2.95 g. of **copper pyridine-4,β-hydracrylate,** blue crystals that melted at 207–208° with decomposition. The salt was anhydrous after it had been dried over sulfuric acid at room temperature; it was easily soluble in hot glacial acetic acid.

Anal. Calcd. for $C_{16}H_{16}CuN_2O_6$: Cu, 15.3. Found: Cu, 15.4.

Decomposition of the copper salt with hydrogen sulfide in hot water gave the **free acid,** which separated from alcohol in the form of a fine white crystalline powder. It sintered at 193° and then melted with evolution of gas at 201–202°, forming a violet liquid.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.5; H, 5.4. Found: C, 57.6; H, 5.4.

The acid was easily soluble in warm glacial acetic acid, and was not precipitated when such a solution was diluted with water.

(15) This substance was kindly furnished by the Barrett Division of the Allied Chemical and Dye Corporation, New York City. The commercial substance required no further purification for the present purpose.

(16) *Cf.* Pinner, *Ber.*, **34**, 4249 (1901); Kolloff and Hunter, THIS JOURNAL, **63**, 490 (1941).

Pyridine-4,β-acrylic Acid.—A mixture of 13.5 g. of ethyl pyridine-4,β-hydracrylate with 26 ml. of water and 26 ml. of concd. sulfuric acid was boiled (130°) for forty-five minutes and then diluted with 50 ml. of water. The resulting pyridine-4,β-acrylic acid precipitated (yield, 4 g.) when the strongly acid solution was treated with sodium acetate. The pure substance was easily soluble in warm glacial acetic acid, but it precipitated when such a solution was diluted with water. It became brown at 190° and melted with decomposition at 280–285° (reported[17] 296°, (cor.)).

The **copper salt** was a deep green crystalline powder, insoluble in water; it became brown at 235° and melted with effervescence at 255°.

Anal. Calcd. for $C_{16}H_{12}N_2O_4Cu$: Cu, 17.6. Found: Cu, 17.4.

Four grams of pyridine-4,β-acrylic acid in 100 ml. of *n*-butyl alcohol was reduced with 10 g. of sodium[17]; the product was isolated as the crystalline hydrochloride[18] (0.9 g.) Benzoylation of the reduction product (200 mg.) in excess 10% sodium hydroxide gave 250 mg. of an oil which crystallized completely when it was seeded with 1-benzoylpiperidine-4,β-propionic acid (Part I). The m. p. of the benzoylation product could not be raised above 135–140°, and it was found that traces of unsaturated substances were present. When these were removed (potassium permanganate in cold sodium carbonate solution), the product melted at 145–147° alone or mixed with the acid obtained in Part I.

(17) Rabe and Kindler, *Ber.*, **52**, 1848 (1919).

(18) *Cf.* Prelog and Cerkovnikov, *Ann.*, **532**, 83 (3197).

Analyses for carbon and hydrogen reported in the present paper were performed by Mr. Stanley T. Rolfson, those for hetero elements by the author.

Summary

A series of reactions leading from epichlorohydrin to 1-benzoyl-4-bromomethylpiperidine in an over-all yield of >12% is described. This halide could not be coupled successfully with ethyl quinoline-4,β-ketopropionate, but it was converted into 1-benzoylpiperidine-4,β-propionic acid, an intermediate in Rabe's synthesis of "vinyl-free quinine." The reactions are of importance in that they point a way to the synthesis of certain analogs of quinine.

MINNEAPOLIS, MINNESOTA RECEIVED SEPTEMBER 7, 1943

NOTES

2-Chloroacetylpyrrole[1]

BY F. F. BLICKE, J. A. FAUST, J. E. GEARIEN AND R. J. WARZYNSKI

The interaction of phenylmagnesium bromide with aceto-, propio-, butyro- or valeronitrile was shown by Shriner and Turner[2] to yield an acyl benzene in 70–90% yield.

When Majima and Hoshino[3] allowed indolylmagnesium bromide to react with chloroacetonitrile, they did not obtain the ketone, 3-chloroacetylindole, but isolated 3-indolylacetonitrile in 50% yield[4]; similarly, β-(3-indolyl)-propionitrile was obtained from β-chloropropionitrile.

In order to determine whether or not pyrrylmagnesium bromide would react in a manner analogous to that of indolylmagnesium bromide, we treated pyrrylmagnesium bromide with chloroacetonitrile. The only product which could be isolated was 2-chloroacetylpyrrole. The latter compound was obtained also from pyrrole, chloroacetonitrile and hydrogen chloride in 20% yield. 2-Chloroacetylpyrrole was converted into 2-iodoacetylpyrrole, and the latter into 2-acetoxyacetylpyrrole.

From pyrrylmagnesium iodide and chloroacetonitrile, we obtained 2-acetylpyrrole in very small amount.[5]

Experimental Part

2-Chloroacetylpyrrole. (a) From Pyrrylmagnesium Bromide and Chloroacetonitrile.—A solution of ethylmagnesium bromide, prepared from 15.3 g. of magnesium, 69.0 g. of ethyl bromide and 125 cc. of ether, was cooled in an ice-bath and 40.2 g. of pyrrole, dissolved in 35 cc. of ether, added. Then 45.0 g. of chloroacetonitrile,[6] dissolved in 30 cc. of ether, was dropped slowly into the mixture. The latter was refluxed for one-half hour, cooled to 0° and kept at this temperature while 46 g. of acetic acid, which had been diluted with 200 cc. of water, was added. The ether layer was separated and the aqueous layer extracted with ether. The combined ether solutions were shaken with sodium bicarbonate solution and then submitted to steam distillation in order to remove unchanged pyrrole and acetonitrile. When the solution in the steam distillation flask was cooled, long colorless needles formed. In order to dissolve the latter, benzene was added and the mixture heated on a steam-bath. The hot benzene layer was separated, the solvent removed and the residue distilled under 2 mm. pressure; 20 g. (23%) of crystalline material was obtained. After recrystallization from carbon tetrachloride, the 2-chloroacetylpyrrole (14 g. or 16%) melted at 118–119°.[7]

Anal. Calcd. for C_6H_6ONCl: N, 9.76. Found: N, 9.54.

When this experiment was repeated with the substitution of ethyl iodide for ethyl bromide, we obtained only a small

(1) This compound was prepared incidentally during an extensive study of pyrrole derivatives which was supported by grants from Parke, Davis and Company, Eli Lilly and Company and the Board of Governors of the Horace H. Rackham School of Graduate Studies.

(2) Shriner and Turner, THIS JOURNAL, **52**, 1267 (1930).

(3) Majima and Hoshino, *Ber.*, **58**, 2042 (1925). See also Hoshino and Kobayashi, *Ann.*, **520**, 20 (1935).

(4) This experiment was confirmed by Jackson (*J. Biol. Chem.*, **88**, 659 (1930)).

(5) In this connection it is of interest to mention that Salway (*J. Chem. Soc.*, **103**, 354 (1913)) found that 2-methylindolylmagnesium bromide reacted with chloroacetyl chloride to yield 2-methyl-3-chloroacetylindole. However, when 2-methylindolylmagnesium iodide was employed, he obtained a mixture of 2-methyl-3-chloroacetyl- and 2-methyl-3-acetylindole.

(6) Steinkopf, *Ber.*, **41**, 2541 (1908).

(7) Prepared by a different procedure, Oddo and Moschini (*Gass. chim. ital.*, **42**, II, 257 (1912)) found 115°.