[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

α-Aminophenacylpyridines and Quinolines[1]

BY JAMES M. SMITH, JR., HUGH W. STEWART, BARBARA ROTH AND ELMORE H. NORTHEY[2]

In 1943 Dodds, Lawson and Williams[3] reported that 1,2-diphenylethylamine and certain related compounds had an analgesic action in cancer patients suffering from "pain due to pressure on nerve." One of the compounds which they prepared was α-(dimethylamino)-α-phenylacetophenone. In the course of a search for new analgesics, we have prepared a series of similar compounds in which the α-phenyl group is replaced by a pyridyl or quinolyl group.

The general method of synthesis involves the preparation of the corresponding phenacyl heterocycles (V) by the method of Scheuing and Winterhalder,[4] halogenation in the α-position (VI), and subsequent replacement of the halogen atom by the appropriate secondary amine.

The styrylpyridines (I) and -quinolines were prepared by heating the methylheterocycles with a benzaldehyde in an excess of acetic anhydride[5] or by a high temperature condensation with zinc chloride as catalyst.[6] The styryl compounds were then brominated in a solvent to give the α,β-dibromophenethylheterocycles (II). In our investigation, it was observed that in some instances the reaction is complicated by the formation of more or less stable N-perbromides. In three series, only the α (or β-)-bromostyrylheterocycle hydrobromides (III) could be isolated, which, however, were converted to the phenethynylheterocycles (IV) by treatment with alcoholic potassium hydroxide under the same conditions as those used for the dibromoethane (II) by Scheuing and Winterhalder. The phenacyl compounds (V) were then obtained by hydration of the acetylenes (IV) in 65% sulfuric acid at the boil.

$$R_1{-}CH_3 + O{=}CHR_2 \longrightarrow R_1CH{=}CHR_2 \quad (I)$$

$$R_1{-}CH{=}CHR_2 + Br_2 \longrightarrow R_1CHBrCHBrR_2 \quad (II)$$

$$II \longrightarrow \underset{(III)}{\left\{\begin{matrix} R_1{-}CH{=}CBrR_2 \\ \text{or} \\ R_1CBr{=}CHR_2 \end{matrix}\right\}} \longrightarrow R_1C{\equiv}CR_2 \quad (IV)$$

$$R_1C{\equiv}CR_2 \longrightarrow R_1CH_2COR_2 \quad (V)$$

$$R_1CH_2COR_2 \longrightarrow R_1CHBrCOR_2 \quad (VI)$$

$$R_1CHBrCOR_2 \longrightarrow R_1CHCOR \quad (VII)$$
$$\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\quad N(R)_2$$

$-N(R)_2$ = diethylamino, piperidyl, or morpholinyl

R_1 = pyridyl or quinolyl

R_2 = phenyl or *p*-chlorophenyl

In the hydration of an unsymmetrical acetylene to the methylene ketone, two isomers are possible. From the hydration of 2-phenethynylpyridine, only 2-phenacylpyridine was isolated. The structure of the latter has been demonstrated[7] by the conversion of the oxime to 2-pyridylacetanilide by the Beckmann rearrangement and hydrolysis to 2-pyridylacetic acid. 4-Phenacylpyridine[8] and 2- and 4-phenacylquinoline[9] have been prepared by a synthesis which leaves no doubt as to their structure. This method of synthesis consists of condensing the methylheterocycle with a benzoic acid ester in the presence of an alkali metal or amide to give the phenacyl derivative. The properties described are identical with those of our products. Therefore it seems probable that the major product of the hydration of arylethynylheterocycles under the conditions we have used is the isomer having the carbonyl adjacent to the aryl group.

The α-aminophenacylheterocycles are generally rather unstable in the form of the free bases. The hydrochloride salts are relatively stable but may decompose on standing, particularly in aqueous solution. For example, 4-[α-(1-piperidyl)-phenacyl]-pyridine dihydrochloride, on standing at room temperature for a few days in a dilute water solution, slowly hydrolyzed as evidenced by precipitation of benzoic acid.

Preliminary tests in animals have shown that some of the α-aminophenacylheterocycles have moderate analgesic activity approximately of the order of codeine. The effect on analgetic potency of changes in the molecule, such as varying the amine, the heterocycle, and placing a substituent on the benzene ring, has been investigated. Among the more active compounds are 4-[α-(1-piperidyl)-phenacyl]-pyridine dihydrochloride and 2-[4-chloro-α-(1-piperidyl)-phenacyl]-pyridine hydrochloride. The pharmacological data will be reported in detail elsewhere.

Experimental[10,11]

A. Styrylheterocycles (I). 4-Styrylpyridine.[12,13]—The procedure used was essentially that of Shaw and Wag-

(1) A portion of the material in this paper forms the subject matter of U. S. Patent 2,414,398, Smith to American Cyanamid Company; *C. A.*, **41**, 5904 (1947).

(2) Present address: Stamford Laboratories, American Cyanamid Company, Stamford, Connecticut.

(3) Dodds, Lawson, and Williams, *Nature*, **151**, 614 (1943); *ibid.*, **154**, 514 (1944).

(4) Scheuing and Winterhalder, German Patent 594,849, March 15, 1934; *Friedländer*, **19**, 1147.

(5) Shaw and Wagstaff, *J. Chem. Soc.*, 77 (1933).

(6) Ainley and King, *Proc. Roy. Soc.* (*London*), **B125**, 72 (1938).

(7) Oparina, *Khim. Farm. Prom.*, 12–15 (1934); *C. A.*, **29**, 1820 (1935). *J. Gen. Chem.* (*U. S. S. R.*), **5**, 1699–1706 (1935); *C. A.*, **30**, 2567 (1936).

(8) Tchitchibabine, *Rec. trav. chim.*, **57**, 582 (1938).

(9) Bergstrom and Moffat, THIS JOURNAL, **59**, 1494 (1937); P. M. Foreman, "The Acylation and Aroylation of α- and γ-Alkylquinolines," Thesis, Stanford University, December, 1939, p. 35; Bergstrom, *Chem. Revs.*, **35**, 184 (1944).

(10) All melting points are corrected.

(11) We are indebted to Mr. O. Sundberg and assistants for the microanalyses.

(12) Wagstaff, *J. Chem. Soc.*, 276 (1934).

(13) (a) Bailey and McElvain, THIS JOURNAL, **52**, 1636 (1930); (b) Friedlander, *Ber.*, **38**, 159 (1905); (c) Oparina and Smirnov, *Khim. Farm. Prom.*, 15–16 (1934); *C. A.*, **29**, 1820 (1935).

staff[5] for the preparation of 2-styrylpyridine using acetic anhydride as the condensing agent. Other preparations mentioned in the literature used zinc chloride under pressure at a high temperature which was not very convenient for the preparation of large quantities. Recrystallization of the hydrochloride of the crude 4-styrylpyridine from water was found to be a useful method of purification. Neutralization of a water solution of the hydrochloride gave a free base in a form suitable for bromination. The yield was 65.7% of the theoretical amount; m. p. 129.5–130°; b. p. 208–210° at 33 mm. A sample of this material was recrystallized to a constant melting point of 130–130.5° from aqueous ethyl alcohol.

A sample of 4-styrylpyridine hydrochloride[13b] was recrystallized from water and dried at 50°; m. p. 229.5–231.5° with sintering at 170°. The approximate solubility in water was 5.9 g./100 ml. at 28°; *p*H of a 1% water solution was 3.6 at 28°.

Anal. Calcd. for $C_{13}H_{11}N \cdot HCl \cdot {}^1/_3H_2O$: C, 69.82; H, 5.71; Cl, 15.86; N, 6.27; H_2O, 2.57. Found: C, 70.20; H, 6.10; Cl, 15.90; N, 6.41; H_2O, 2.59 (Karl Fischer).

Other styrylheterocycles were prepared in a similar manner. Those not previously reported in the literature are given in Table I, Section A.

B. α,β-Dibromophenethylheterocycles (II); and C. α(or β-)-Bromostyrylheterocycles (III).—Bromination of the styryl compounds presumably gave N-perbromides which rearranged to the α,β-dibromophenethylheterocycles on heating (see Table I, Section B). This was usually accomplished in boiling chloroform or carbon tetrachloride.[4] When, as in the case of 4-styrylpyridine perbromide, the temperature necessary for the rearrangement was about 117° or higher, hydrogen bromide split out instead and the α(or β-)-bromostyrylheterocycle hydrobromides were the products isolated. In the 4-quinoline series, protecting the nitrogen atom of 4-styrylquinoline by formation of a hydrochloride salt followed by bromination gave the desired dibromo derivative. When 4-styrylquinoline base was used, the products were indeterminate but probably consisted largely of the N-perbromide. Bromination of 4-(4-chlorostyryl)-quinoline by the methods above gave only a product which was apparently the N-perbromide.

4-Styrylpyridine Perbromide.—To a solution of 18.1 g. of 4-styrylpyridine (0.1 mole) in 100 ml. of dry chloroform was added slowly a solution of 16.0 g. of bromine (0.1 mole) in 35 ml. of dry chloroform at 5° with stirring. A bright orange precipitate formed immediately. After twenty minutes, the solid was isolated by filtration, washed with chloroform and dried at room temperature. The yield was 31.9 g. (93.5% of the theoretical amount). Since this compound decomposes on melting to give 4-[α (or β-)-bromostyryl]-pyridine hydrobromide (see below), the melting point was taken by immersing a series of freshly filled melting point tubes in the bath, held at a constant temperature, at one degree intervals. It sintered at 92°, became wet at 110° and completely melted at 117° before it solidified (compare reference 13b).

Anal. Calcd. for $C_{13}H_{11}Br_2N$: C, 45.76; H, 3.26; Br, 46.85; N, 4.10. Found: C, 45.5; H, 3.3; Br, 46.7; N, 4.19.

This perbromide, when added to alcoholic potassium hydroxide solution at 30° and the mixture refluxed for one hour, gave a 96% yield of 4-styrylpyridine. Treatment in glacial acetic acid at 40° with 2-naphthol gave 1-bromo-2-naphthol and a 75% yield of 4-styrylpyridine. One sample after standing for one month in the dark in a stoppered bottle decomposed and developed an odor of benzaldehyde. Attempts to crystallize the perbromide by heating in various solvents led to the production of the bromoethylene hydrobromide (see below).

4-[α-(or β)-Bromostyryl]-pyridine Hydrobromide.—A quantity of 543.6 g. of 4-styrylpyridine (3.0 moles) was dissolved in 2100 ml. of glacial acetic acid at room temperature. To this solution was added slowly with cooling and stirring at 25–30° a solution of 479.4 g. of bromine (3.0 moles) in 300 ml. of glacial acetic acid. A precipitate of 4-styrylpyridine perbromide was obtained. The reaction was heated to the refluxing temperature (119°). At 110°, all of the perbromide had dissolved. After refluxing for one-half hour the reaction was cooled to room temperature while stirring. At 117°, the product began to crystallize. It was isolated by filtration and was washed with glacial acetic acid until the filtrate was colorless, and then with petroleum ether to remove the acetic acid. It was dried at 50°. The yield was 841 g. (82.4% of the theoretical amount). Sharp melting points may be obtained ranging from 247 to 255° depending upon the rate of heating. A sample was recrystallized from glacial acetic acid for analysis. The approximate solubility in water was 2.6 g./100 ml. at 25°.

Anal. Calcd. for $C_{13}H_{10}BrN \cdot HBr$: C, 45.76; H, 3.26; Br, 46.85; N, 4.10. Found: C, 45.1; H, 2.8; Br, 46.7; N, 4.16.

See Table I, Sections B and C for other compounds of this class.

D. Phenethynylheterocycles (IV).—The α,β-dibromophenethyl- and α(or β)-bromostyrylheterocycles were converted to the acetylenes by boiling alcoholic potassium hydroxide according to the method of Scheuing and Winterhalder.[4] The crude products were purified by distillation or crystallization from a solvent such as alcohol.

4-(Phenethynyl)-pyridine.—To 2100 ml. of absolute ethanol containing 477 g. of 88% potassium hydroxide (7.5 moles) there was added 1023 g. of crude 4-[α(or β)-bromostyryl]-pyridine hydrobromide at 40° with stirring. The thick slurry was then refluxed with stirring for one hour, and poured into 9 l. of cold water. The brown product was isolated by filtration, washed with water until the washings were neutral, and dried at 50°. The yield was 531 g. (98.9% of the theoretical amount); m. p. 92.5–94.5°. Considerable decomposition took place when heated to 180°; b. p. 109–110° (0.5 mm.) with some decomposition. Using hot 55% aqueous ethyl alcohol and a Darco treatment, a portion was recrystallized to a constant melting point to give white flakes, m. p. 95–95.5°.

Anal. Calcd. for $C_{13}H_9N$: C, 87.10; H, 5.06; N, 7.81. Found: C, 86.6; H, 4.9; N, 7.77.

Other phenethynylheterocycles are described in Table I, Section D.

E. Phenacylheterocycles (V). 4-Phenacylpyridine.[8] 1. From 4-Phenethynylpyridine.—The process used is similar to that described for 2-phenacylpyridine.[4] To 2160 g. of 65% sulfuric acid at 120° there was added 716.8 g. of crude 4-phenethynylpyridine (4.0 moles) while stirring. It dissolved readily with the evolution of some heat. The reaction was heated at the refluxing temperature (143°) for one hour and then cooled slowly with stirring to 10°. The precipitated 4-phenacylpyridine sulfate was isolated by filtration through glass cloth and washed with glacial acetic acid until the washings were colorless. The cake was then washed with petroleum ether and dried at 50°. The yield was 956 g. (80.1% of the theoretical amount); m. p. 194–198°. A small amount was recrystallized from glacial acetic acid to a constant melting point of 203.5–204.5°.

Anal. Calcd. for $C_{13}H_{11}NO \cdot H_2SO_4$: C, 52.88; H, 4.44; N, 4.74; S, 10.86. Found: C, 52.8; H, 4.4; N, 4.86; S, 10.8.

The 4-phenacylpyridine sulfate from above was dissolved in 15 l. of water, and the solution was made alkaline to phenolphthalein with concentrated ammonium hydroxide solution. (Sodium hydroxide solution apparently gave a ketonic cleavage.) The pale yellow 4-phenacylpyridine was isolated by filtration and was washed with water and dried at 50°. The yield was 618 g. (78.4% from 4-phenethynylpyridine); m. p., 111.5–114.5°. It may be sublimed under reduced pressure. A small amount was crystallized from benzene to a constant melting point of 113–115°.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.9; H, 5.7; N, 7.34.

TABLE I

STYRYL-, DIBROMOPHENETHYL-, PHENETHYNYL-, PHENACYL- AND α-AMINOPHENACYLPYRIDINES AND QUINOLINES

R_1	R_2	R_3	Yield, %	M. p., °C.	Empirical formula	Calcd. Carbon, %	Found Carbon, %	Calcd. Hydrogen, %	Found Hydrogen, %	Calcd. Chlorine, %	Found Chlorine, %	Calcd. Nitrogen, %	Found Nitrogen, %
A. Styrylheterocycles (I) $R_1CH{=}CHR_2$													
2-C_5H_4N–	4-ClC_6H_4–		55[a]	193–195[b]	$C_{13}H_{10}ClN\cdot HCl\cdot H_2O$	57.77	58.4	4.85	5.65	26.26	26.1	5.19	5.70
4-C_5H_4N–	4-ClC_6H_4–		63	248–250[b,c]	$C_{13}H_{10}ClN\cdot HCl$	61.90	61.4	4.40	4.43	28.14	27.6	5.56	5.38
2-C_9H_6N–	4-ClC_6H_4–		65.4	142.8–143.2[d]	$C_{17}H_{12}ClN$	76.8	77.2	4.55	4.52	13.31	12.7	5.27	5.46
4-C_9H_6N–	4-ClC_6H_4–		45	127–128.1	$C_{17}H_{12}ClN$							5.27	5.19
B. α,β-Dibromophenethylheterocycles (II) $R_1CHBrCHBrR_2$													
2-C_5H_4N–[e]	4-ClC_6H_4–		84	183–184[b]	$C_{13}H_{10}Br_2ClN\cdot HCl$	37.88	38.3	2.69	2.73	77.62[f]	75.1[f]	3.40	3.49
4-C_9H_6N–[g]	C_6H_5–		82.5	189–190[b]	$C_{17}H_{13}Br_2N\cdot HCl$					55.58[f]	57.3[f]	3.27	3.39
C. α(or β-)-Bromostyrylheterocycles (III) $R_1CBr{=}CHR_2$ or $R_1CHCBrR_2$													
4-C_5H_4N–[h]	4-ClC_6H_4–		95	275–280[p]	$C_{13}H_9BrClN\cdot HBr$	41.56	41.3	2.69	2.85	63.87[f]	63.4[f]	3.73	3.72
2-C_9H_6N–[i]	4-ClC_6H_4–		69	199–199.9[p]	$C_{17}H_{11}BrClN\cdot HBr$							3.29	3.38
D. Phenethynylheterocycles (IV) $R_1C{\equiv}CR_2$													
4-C_9H_6N–	C_6H_5–		86.5[j]		$C_{17}H_{11}N$								
2-C_5H_4N–	4-ClC_6H_4–		52.5[k]	99–100.5	$C_{13}H_8ClN$	73.06	72.4	3.78	3.8	16.60	17.1	6.56	6.49
4-C_5H_4N–	4-ClC_6H_4–		69[l]	119.5–122	$C_{13}H_8ClN$	73.06	73.5	3.78	3.89	16.60	16.4	6.56	6.52
2-C_9H_6N–	4-ClC_6H_4–		78	135.4–135.9	$C_{17}H_{10}ClN$	77.4	77.5	3.8	3.85	13.5	13.6	5.31	5.42
E. Phenacylheterocycles (V) $R_1CH_2COR_2$													
4-C_9H_6N–	C_6H_5–[a]		95	113.4–117.3	$C_{17}H_{13}NO$	82.5	82.9	5.3	5.4			5.67	5.58
2-C_5H_4N–	4-ClC_6H_4–		95	176.6–180[n]	$C_{13}H_{10}ClNO\cdot HCl\cdot H_2O$	54.54	54.6	4.58	4.72	24.79	24.7	4.90	5.14
4-C_5H_4N–	4-ClC_6H_4–		100	94.5–96	$C_{13}H_{10}ClNO$	67.37	67.2	4.35	4.38	15.31	15.1	6.05	6.1
2-C_9H_6N–	4-ClC_6H_4–		81	145.2–146	$C_{17}H_{12}ClNO$	72.5	73.5	4.29	4.70	12.5	13.2	4.97	4.99
2-(5-C_2H_5)-C_5H_3N–	C_6H_5–[o]			68–69.4	$C_{15}H_{15}NO$	79.95	79.2	6.72	6.7			6.22	6.2
F. α-Bromophenacylheterocycles (VI) $R_1CHBr(CO)R_2$													
4-C_9H_6N–	C_6H_5–		36	116–121	$C_{17}H_{12}BrNO$	62.6	62.4	3.69	3.8	24.5[p]	24.3[p]	4.3	4.5
2-C_5H_4N–	4-ClC_6H_4–		95[q]	172–175[p]	$C_{13}H_9BrClNO\cdot HBr$								
4-C_5H_4N–	4-ClC_6H_4–		100	223–228[p]	$C_{13}H_9BrClNO\cdot HBr$	39.86	40.2	2.58	2.1			3.58	3.6
G. α-Aminophenacylheterocycles (VII) $R_1CHR_3(CO)R_2$													
2-C_5H_4N–	C_6H_5–	1-C_4H_8NO–	50	110–111	$C_{17}H_{18}N_2O_2$	72.3	72.3	6.4	6.38			9.92	9.92
2-C_5H_4N–	C_6H_5–	$(C_2H_5)_2N$–	47.5	161–165[b,r]	$C_{17}H_{20}N_2O\cdot HCl\cdot H_2O$	63.3	64.9	7.17	7.12	11.0	10.5	8.68	8.73
4-C_5H_4N–	C_6H_5–	1-$C_5H_{10}N$–[s]	93	170–180 dec.[b]	$C_{18}H_{20}N_2O\cdot 2HCl\cdot 0.5H_2O$	59.67	59.1	6.4	6.4	19.57	19.5	7.73	7.58
4-C_5H_4N–	C_6H_5–	1-C_4H_8NO–[t]	69.5	110–118 dec.[b]	$C_{17}H_{18}N_2O_2\cdot 2HCl\cdot 0.5H_2O$	56.04	56.2	5.81	5.9	19.46	18.3	7.69	7.5
2-C_5H_4N–	4-ClC_6H_4–	1-$C_5H_{10}N$–	87	195–205[b,u]	$C_{18}H_{19}ClN_2O\cdot HCl$	61.52	60.8	5.74	5.88	20.2	20.0	7.98	8.03
4-C_5H_4N–	4-ClC_6H_4–	1-$C_5H_{10}N$–	70	199–203[b]	$C_{18}H_{19}ClN_2O\cdot HCl$	61.52	60.8	5.74	5.87	20.2	19.5	7.98	8.07
4-C_9H_6N–	C_6H_5–	1-$C_5H_{10}N$–	11	219–219.5[b]	$C_{22}H_{24}N_2O\cdot HCl$	72.0	71.3	6.32	5.8	9.66	10.0	7.64	7.66
2-C_9H_6N–	4-ClC_6H_4–	1-$C_5H_{10}N$–	29	135–136.6	$C_{22}H_{21}ClN_2O$							7.68	7.69

[a] Crude, m. p. 76–79°; b. p. 173–180° (5–7 mm.); m. p. 83–84°. [b] Hydrochloride. [c] M. p. free base 110°. [d] M. p. hydrochloride, 234–236°. [e] Bromination in boiling C. P. chloroform; m. p. 173–175°. [f] Total halogen calculated as Br. [g] From 4-styrylquinoline hydrochloride (see ref. 6); bromination in boiling C. P. chloroform. [h] Bromination in acetic acid at 25–30° followed by refluxing at 119°. [i] Bromination in *o*-dichlorobenzene at 25–30°, followed by refluxing two hours at 180–190°. [j] Used in the next step without further purification or analysis; b. p. 205–210° (3 mm.). [k] The product crystallized directly from the alcoholic solution after a hot filtration to remove the potassium bromide; hydrochloride, m. p. 138–141°, hydrolyzes almost completely in water. [l] The product crystallized directly from the alcoholic solution after a hot filtration to remove the potassium bromide. [m] Foreman reports a m. p. 114.8–115.8° for 4-phenacyl quinoline made from methyl benzoate and lepidine with potassium amide as condensing agent; compare Ref. 9. [n] M. p. free base 86–87°. [o] From the crude acetylene derivative from 2-(α,β-dibromophenethyl)-5-ethylpyridine; Plath, *Ber.*, **21**, 3086 (1888). This yielded unstable products on bromination and attempted reaction with amines. [p] Bromine. [q] Used in the next step without further purification or analysis. [r] M. p. free base 65.8–66.9°. [s] Calcd.: H_2O, 2.49; found: H_2O, 2.62 (Karl Fischer reagent). The product is very hygroscopic and the melting point varied from 156 to 195° depending upon the degree of hydration. It was dried to constant weight in a vacuum oven at 50°. [t] Calcd.: H_2O, 2.47; found: H_2O, 2.98 (Karl Fischer reagent.) The crude product, which was probably anhydrous, melted at 191–196°. After purification, it was dried to a constant weight in a vacuum oven at 50°. [u] M. p. free base 104–106.8°; found: C, 68.9; H, 6.6; Cl, 12.3; N, 9.26. [v] Hydrobromide.

The **hydrochloride** salt was prepared in absolute ethyl alcohol and crystallized from the same solvent to a constant melting point of 207–209.5°. It sintered at 175°. The approximate solubility in water at 27° was 69 g./100 ml. The *p*H of a 1% water solution was 3.2 at 27°.

Anal. Calcd. for $C_{13}H_{11}NO\cdot HCl$: C, 66.80; H, 5.18; Cl, 15.17; N, 5.99. Found: C, 66.6; H, 5.3; Cl, 15.1; N, 6.07.

2. From 4-Picoline, Ethyl Benzoate and Phenyllithium.—A low yield of 4-phenacylpyridine was obtained by a method similar to one described in the literature[8] except that phenyllithium[14] was used as condensing agent. The melting point was 110–114°. A mixture melting point with that made from 4-phenethynylpyridine (see above) gave no depression.

In the preparation of certain other phenacylheterocycles, the sulfuric acid solution was diluted and neutralized with ammonia, and the base then was purified by distillation or recrystallization from a suitable solvent (see Table I, Section E).

(14) "Organic Syntheses," **23**, 83 (1943).

F. α-Bromophenacylheterocycles (VI). 2-(α-Bromophenacyl)-pyridine.—A solution of 67.2 g. (0.34 mole) of 2-phenacylpyridine[4] in 600 ml. of glacial acetic acid was treated with 54.5 g. (0.34 mole) of bromine dissolved in 500 ml. of acetic acid, added over a period of two hours at room temperature. After eighteen hours, the solution was diluted to eight liters with ice and water and allowed to stand one hour. The white precipitate was collected on the filter, washed with water and with mixed hexanes, and dried at 50° for three hours. The yield was 72 g., m. p. 94°. From the filtrate, by the addition of 100 g. of hydrated sodium acetate, there was obtained an additional 12.5 g. having a melting point of 91–93°.

Anal. (first crop) Calculated for $C_{13}H_{10}BrNO$: C, 56.5; H, 3.63; Br, 28.94; N, 5.07. Found: C, 55.4; H, 3.66; Br, 28.9; N, 4.98.

4-(α-Bromophenacyl)-pyridine Hydrobromide.—In a similar experiment this compound was obtained in 99% yield. The hydrobromide crystallized directly from the acetic acid reaction mixture. A better product was obtained by the rapid addition of bromine before the precipitation occurred. It was recrystallized from glacial acetic acid and melted at 223–224° (dec.). This product is stable if kept in a tightly stoppered bottle but decomposes rapidly and turns brown on exposure to moist air or water.

Anal. Calcd. for $C_{13}H_{10}BrNO \cdot HBr$: C, 43.71; H, 3.11; Br, 44.75; N, 3.92. Found: C, 43.3; H, 3.1; Br, 44.6; N, 4.14.

See also Table I, section F, for other α-bromophenacylheterocycles.

G. α-Aminophenacylheterocycles (VII). General Procedure.—The α-bromoketone (or its hydrobromide) was treated with the secondary amine in dry benzene (or ether), usually at room temperature. In reactions using 4-(α-bromophenacyl)-pyridine hydrobromide, best results were obtained below 10°. An excess of the secondary amine was used to neutralize the acid produced in the reaction. The course of the reaction was followed by the recovery of the secondary amine hydrobromide formed; it was usually complete in three to twenty-four hours, depending on the temperature employed in the reaction. After removal of the secondary amine hydrobromide, the benzene solution was extracted with dilute hydrochloric acid several times, and the acid extracts were neutralized with ammonia. The crude bases were soft and slow to crystallize. In some cases, they were recrystallized from a suitable solvent such as alcohol or hexane; in others, it was more convenient to convert the crude base to the hydrochloride salt which was then readily purified by recrystallization from alcohol–ether mixtures.

In the 2-quinoline series, stable α-halogen derivatives were not isolated. 2-Phenacylquinoline[4] and 2-(4-chlorophenacyl)-quinoline were brominated in ether solution, and the mixture was treated with piperidine directly. The products were then worked up as described above.

Properties of the amino ketones which were synthesized are described in Table I, Section G. Specific examples are given below.

2-[α-(1-Piperidyl)-phenacyl]-pyridine.—A mixture of 10 g. of 2-(α-bromophenacyl)-pyridine and 8 g. of piperidine in 50 ml. of benzene was heated under reflux for three hours. Piperidine hydrobromide precipitated and was removed by filtration (6.1 g., quantitative). The benzene solution was extracted with dilute hydrochloric acid, washed with water, and the aqueous extracts were neutralized with ammonia. The oil, which precipitated, solidified on standing. This was purified further by reprecipitation from dilute hydrochloric acid followed by recrystallization from mixed hexanes which gave 2.7 g. of product, m. p. 66–67.5°.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.12; H, 7.19; N, 10.00. Found: C, 76.5; H, 7.0; N, 10.1.

In a similar experiment in which the condensation was carried out at room temperature for twenty hours the crude base was converted to the **hydrochloride,** which was purified by recrystallization from alcohol–ether and alcohol–isopropyl acetate mixtures; m. p. 200–220°.

Anal. Calcd. for $C_{18}H_{20}ClN_2O \cdot HCl$: C, 68.2; H, 6.68; Cl, 10.9; N, 8.82. Found: C, 68.1; H, 6.6; Cl, 9.5, 9.77; N, 8.91.

2-[α-(1-Piperidyl)-phenacyl]-quinoline Hydrochloride.—Fifty grams of 2-phenacylquinoline[4] was suspended in 1500 ml. of absolute ether, and 20 g. of calcium carbonate powder was added. Then, at 25°, 32 g. of bromine in 500 ml. of absolute ether was added rapidly. After three hours, 50 ml. of piperidine was added; the mixture was allowed to stand overnight at room temperature. The insoluble material was removed by filtration; the ether solution was then extracted with dilute hydrochloric acid and from these extracts, on neutralization, an oily product was obtained. This was converted to the hydrochloride and purified further by recrystallization from alcohol–ether mixtures. The yield was 22 g. of product; m. p. 223–223.5°.

Anal. Calcd. for $C_{22}H_{23}ClN_2O$: Cl, 9.66; N, 7.64. Found: Cl, 9.77; N, 7.76.

Acknowledgments.—We are indebted to Dr. Robert A. Lehman, of the New York University School of Medicine, for the pharmacological testing. We are also indebted to Mr. Frank W. Bagienski for technical assistance in the preparation of certain of the compounds reported in this paper.

Summary

As new analgesics, a series of ten α-aminophenacylpyridines and -quinolines has been prepared by treatment of the α-bromophenacyl heterocycles with a secondary amine. The effect on analgetic potency of changes in the molecule has been investigated, such as varying the amine, the heterocycle, and substituents on the benzene ring. Among the most active analgesics are 4-[α-(1-piperidyl)-phenacyl]-pyridine dihydrochloride and 2-[α-(1-piperidyl)-4-chlorophenacyl]-pyridine hydrochloride. Preliminary pharmacological data in animals indicate an order of activity approximately equal to that of codeine.

As variations in the molecule were investigated, a number of new styryl-, α(or β-)-bromostyryl-, α,β-dibromophenethyl-, phenethynyl-, phenacyl- and α-bromophenacylpyridines and -quinolines were prepared. N-Perbromides were obtained in the bromination of some of the styrylpyridines and -quinolines, which rearranged on heating to the α(or β)-bromostyrylpyridine or -quinoline hydrobromides.

BOUND BROOK, NEW JERSEY RECEIVED MAY 5, 1948