7-Carbomethoxy-3,4-dihydro-2(1H)-quinoxalones. ("Dihydroquinoxalones") VII.—A solution of 0.5 millimole of the N-(4-carbomethoxy-2-nitrophenyl)-amino acid and 55 mg. (0.65 millimole) of sodium bicarbonate in 3 ml. of water was placed in a micro hydrogenator with 20 mg. of platinum oxide. The theoretical amount of hydrogen was absorbed in 30 to 60 minutes. (The hydrogenation mixture turns dark brown during the hydrogenation and becomes colorless, or very nearly so, at the end of the hydrogenation.) The catalyst was removed by filtration, using care to avoid unnecessary exposure of the solution to air. The sodium salts were neutralized with 0.65 ml. of 1.00 *N* hydrochloric acid. The 7-carbomethoxy-3,4-dihydro-2(1H)-quinoxalone precipitated immediately, sometimes as an oil, and the mixture was cooled. If the product had precipitated as an oil, it crystallized at once. The product was collected by filtration, washed with water, and dried *in vacuo*, yield 80–95%. It was recrystallized (recovery 50–85%), usually from methanol (see Table I); if necessary it was decolorized by treatment of the methanol solution with charcoal. The properties of these compounds are summarized in Table I.

The 7-carbomethoxy-3,4-dihydro-2(1H)-quinoxalones (VII) exhibit absorption maxima at 320 mμ, log ε 4.20 and 258 mμ, log ε 4.28, and a minimum at 278 mμ, log ε 3.53 (95% ethanol).

(Catalytic reduction of N-2,4-dinitrophenylglycine using the same procedure gave a purplish-black solid, insoluble in ethanol and ether and very soluble in water. Crystallization from water gave a low yield of black crystals which did not melt below 290°.)

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTH TEXAS STATE COLLEGE]

Antitubercular Studies. IV. Derivatives of 1-(4-Nitrophenacyl)-4-alkypyridium Bromides

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The synthesis and properties of various compounds containing the 1-(4-alkylpyridinium) and 1-(4-alkylpiperidyl) moieties are described. This group of substances are primarily 4-nitrophenacyl and 4-aminophenacyl derivatives. Although none of the compounds reported in this paper exhibit antitubercular activity, a number of them do have interesting antifungal and amebacidal properties.

Previous work in this Laboratory[1,2] indicated that certain compounds containing the 1-(4-alkylpiperidyl) grouping possess some antitubercular activity. This activity was highest with 1-(diphenylmethyl)-4-alkylpiperidines,[1] but these materials were inactive in the presence of serum. The 4-alkyl-1-(2-hydroxyl-2-phenylethyl)-piperidines[2] were active at 10 mg. % in the presence of serum. Thus, it seemed of interest to prepare other structurally related compounds in order to test their physiological properties as growth inhibitors.

The general methods used for these preparations were similar to those reported by Truitt, Hall and and Arnwine[3] for the preparation of 4-hexyl-1-(4-nitrophenacyl)-pyridinium bromide and the corresponding reduction products. References to other pertinent work are also given in this article and in reference (2).

Physiological Activity[4]

None of the compounds of this series appear to have antitubercular activity. *In vitro* tests with other organism were also negative, except that compound no. 16 exhibited moderate activity against *Strep. hemolyticus*.

Compounds no. 5, 10, 16, 17 and 20 were tested for amebacidal activity. Compound no. 10 was least active. Compounds no. 5 and no. 16 were amebacidal at 1:5,000 dilution and amebastatic at 1:50,000 dilution. Compounds no. 17 and no. 20 were amebacidal at 1:50,000 dilution. However, these more active compounds were not promising *in vivo* in rats at 0.5% concentration in the diet.

1-(4-Aminophenacyl)-4-(octyl)-pyridinium bromide (no. 17) gave complete inhibition of the following fungi: *Candida albicans*, 125 mg./ml.; *Trichophyton interdigitale*, 31.25 mg./ml.; *Nocardia asteroides*, 250 ml./ml.; and *Histoplasma capulatum*, 31.25 mg./ml. Compound no. 22 gave complete inhibition of the same fungi, as follows: *Candida albicans*, 125 mg./ml.; *Trichophyton interdigitale*, 31.25 mg./ml.; *Nocardia asteroides*, 62.5 mg./ml.; and *Histoplasma capsulatum*, 15.6 mg./ml.

Experimental

Procedure I. 1-(4-Nitrophenacyl)-4-alkylpyridinium Bromide.—To a solution of 0.10 mole of 4-nitrophenacyl bromide in 100 ml. of acetone was added 0.103 mole of 4-alkylpyridine. A reaction began almost immediately and the formation of an oil or crystals was noted. The reaction mixture was allowed to stand overnight; at the end of this time the oil (if present) had changed to a light yellow crystalline solid.

The crystals were filtered, washed with ether and recrystallized from the appropriate solvent.

The data for this group of quaternary salts are included in Table I.

Procedure II. 1-(4-Acetylaminophenacyl)-4-alkylpyridinium Bromide.—A mixture of 0.0195 mole of 4-acetylaminophenacyl bromide, 200 ml. of toluene and 0.0195 mole of 4-alkylpyridine was refluxed for 30 minutes. The reaction mixture was allowed to cool and 200 ml. of ether was added. The crystalline solid was removed and recrystallized.

These compounds are listed with pertinent information in Table I.

Procedure III. 1-(4-Aminophenacyl)-4-alkylpiperidines and Hydrobromides.—A solution of 0.015 mole of 1-(4-nitrophenacyl)-4-alkylpyridinium bromide in 100 ml. of ethyl alcohol was hydrogenated at room temperature under 50 p.s.i. hydrogen pressure and with 0.1 g. of platinum oxide. About one hour was required for the theoretical amount (0.09 mole) of hydrogen to be absorbed.

The product, which had precipitated, was removed by

(1) Price Truitt and W. J. Middleton, THIS JOURNAL, **73**, 5669 (1951).

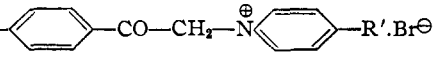
(2) Price Truitt, B. Bryant, W. E. Goode and B. C. Arnwine, *ibid.*, **74**, 2179 (1952).

(3) Price Truitt, R. E. Hall and B. C. Arnwine, *ibid.*, **74**, 4552 (1952).

(4) The testings were arranged for by Dr. Loren Long of Parke Davis and Company.

TABLE I

1-(4-SUBSTITUTED-PHENACYL)-4-ALKYLPYRIDINIUM BROMIDE



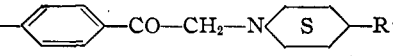
Solvent for recrystallization: A, abs. ethanol; B, acetone; C, ether; D, hexane; E, ethyl acetate; F, 50% ethanol

	R	R¹	Solvent	Yield, %[a]	Procedure	M.p., °C.	Empirical formula	Analyses, % Calcd. Br	Calcd. N	Found Br	Found N
2	$-NO_2$	Methyl	A–C	86	I	214–215	$C_{14}H_{13}BrN_2O_3$	23.7	8.31	23.8	8.47
3	NO_2	Ethyl[b]	A	63	I	200–201	$C_{15}H_{15}BrN_2O_3$	22.8	7.98	22.7	7.79
4	NO_2	1-Amyl	A	64	I	128–130	$C_{18}H_{21}BrN_2O_3$	20.3	7.16	20.4	7.17
5	NO_2	1-Hexyl[d]	B	57	I	144–146	$C_{19}H_{23}BrN_2O_3$	19.7	6.91	19.7	7.07
6	NO_2	1-Octyl	B–C	80	I	156–158	$C_{21}H_{27}BrN_2O_3$	18.4	6.45	18.5	6.57
7	NO_2	5-Nonyl	B–D	69	I	173–175	$C_{22}H_{29}BrN_2O_3$	17.8	6.25	18.0	6.16
8	NO_2	2-Octylmethyl	A–D	50	I	174–175	$C_{22}H_{29}BrN_2O_3$	17.8	6.25	18.1	6.16
9	NO_2	6-Methoxy[c]	A	33	I	255–258	$C_{18}H_{15}BrN_2O_4$	19.8	6.95	19.8	7.18
10	NO_2	6-Methyl[c]	A–C	82	I	220–222	$C_{18}H_{15}BrN_2O_3$	20.7	7.24	20.5	7.43
11	NO_2	7-Methyl[c]	A–C	60	I	218–220	$C_{18}H_{15}BrN_2O_3$	20.7	7.24	20.6	7.41
12	CH_3CONH-	Ethyl	A	85	II	251–255 (dec.)	$C_{17}H_{19}BrN_2O_2$	22.0	7.31	22.0	7.38
13	CH_3CONH-	1-Hexyl[d]	A	60	II	230–234 (dec.)	$C_{21}H_{27}BrN_2O_2$	19.1	6.66	19.3	6.79
14	CH_3CONH-	1-Octyl	A–E	68	II	246–249 (dec.)	$C_{23}H_{31}BrN_2O_2$	17.9	6.26	17.8	5.95
15	CH_3CONH-	2-Octylmethyl	A	60	II	215–218	$C_{24}H_{33}BrN_2O_2$	17.7	6.07	17.9	6.12
16	$-NH_2$	1-Hexyl[d]	A	52	IV	180–181	$C_{19}H_{25}BrN_2O$	21.3	7.42	21.2	7.49
17	$-NH_2$	1-Octyl	F	65	IV	190 (dec.)	$C_{21}H_{29}BrN_2O$	19.7	6.92	19.7	6.90

[a] All yields are reported on purified products. [b] The compound was first isolated as a hydrate which melted at 110–115° and then resolidified. It remelted at 200–201°. The hydrate showed a loss in weight equal to 94% of the equivalent of a monohydrate when heated at 110° for two days. [c] Pyridine nucleus replaced by the quinoline ring. [d] See reference 3.

TABLE II

1-(4-SUBSTITUTED-PHENACYL)-4-ALKYLPIPERIDINES



	R	R¹	Solvent[a]	Yield, %	Method no.	M.p., °C.	Empirical formula	Analyses, % Calcd. Br	Calcd. N	Found Br	Found N
18	$-NH_3Br$	Ethyl	A	46	III	255 dec.	$C_{15}H_{23}BrN_2O$	24.5	8.56	24.6	8.20
19	$-NH_3Br$	1-Amyl	F	54	III	250 dec.	$C_{18}H_{29}BrN_2O$	21.7	7.59	22.0	7.43
20	$-NH_3Br$	1-Hexyl[3]	F	50	III	265 dec.	$C_{19}H_{31}BrN_2O$	20.9	7.32	21.1	7.48
21	$-NH_3Br$	1-Octyl	F	57	III	240 dec.	$C_{21}H_{35}BrN_2O$	19.5	6.81	19.4	6.65
22	$-NH_3Br$	5-Nonyl	F	65	III	250 dec.	$C_{22}H_{37}BrN_2O$	18.8	6.59	18.8	6.35
23	$-NH_3Br$	2-Octylmethyl	F	23	III	245 dec.	$C_{22}H_{37}BrN_2O$	18.8	6.59	18.9	6.45
24	$-NH_2$	Ethyl	F	39	III	105–106	$C_{15}H_{22}N_2O$		11.38		11.39
25	CH_3CONH	2-Octylmethyl	F	85	III	150–152	$C_{24}H_{37}N_2O_2$		7.14		7.40

[a] See Table II for solvent designations.

filtration and recrystallized or it was converted to the free base by the addition of 5% sodium hydroxide or ammonium hydroxide solution. Refer to Table II.

Procedure IV. 1-(4-Aminophenacyl)-4-(1-hexyl)-pyridinium Bromide.—A mixture of 5 g. of 1-(4-acetylaminophenacyl)-4-alkylpyridinium bromide and 100 ml. of 20% hydrobromic acid was heated on a steam-bath until solution was complete. The acid was carefully neutralized with ammonium hydroxide and the solid collected and recrystallized. See Table I.

DENTON, TEXAS