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

Antitubercular Studies. II. 4-Alkyl-1-phenacylpyridinium Halides and Reduction Products[1]

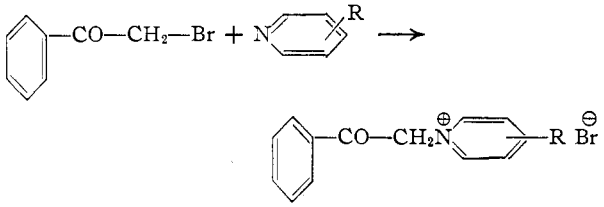
BY PRICE TRUITT, BURL BRYANT, WILLIAM E. GOODE AND BENNIE ARNWINE

Preparation of a number of compounds which contain the 1-(4-alkylpiperidyl) moiety are described. The hydrogenations of 1-phenacylpyridinium halides with an alkyl group in the 2- or 4-position of the pyridinium ring are described. Some of the resultant compounds exhibit significant antitubercular activity. Other physiological properties are also noted.

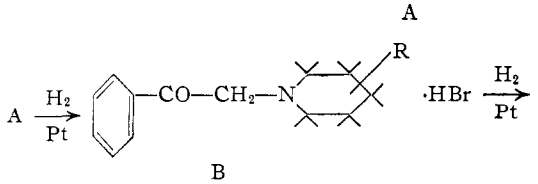
In 1930, Blicke and Blake[2] reported that the hydrochlorides of 1-(2-hydroxy-2-phenylethyl)-piperidine and the corresponding benzoates have anesthetic properties. These workers also indicated that 1-phenacylpiperidine hydrochloride possesses similar activity. Kröhnke[3] observed that certain 1-substituted pyridinium compounds possess both pressor and ergot-like activities. Thus, an investigation of various derivations of 1-phenacylpyridinium salts was undertaken at this Laboratory because of the structural similarity of these compounds to certain well-known pressor amines, the above-mentioned substances, and the 1-diphenylmethyl-4-alkylpiperidines reported in the previous paper.[4]

Kröhnke[3] found that low-temperature, low-pressure hydrogenation of 1-phenacylpyridinium bromide reduced the pyridine ring but not the ketone group. Riegel and Wittcoff,[5] however, were able to reduce preferentially the carbonyl group by low temperature, high pressure (80 atmospheres) catalytic hydrogenation. However, when the benzene ring was substituted, this preferential hydrogenation was often impossible to accomplish. Blicke and Blake[2] were able to reduce 1-phenacylpiperidine to the corresponding carbonol by catalytic hydrogenation with 4 atmospheres of hydrogen pressure and at room temperature.

Thus the following procedure seemed feasible for the preparation of the desired 4-alkyl-1-phenacylpiperidines and 1-(2-hydroxyl-2-phenylethyl)-2-alkyl or 1-(2-hydroxy-2-phenylethyl)-4-alkylpiperidines.



A



B

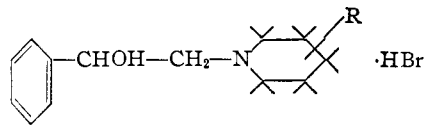
(1) This work was aided by grants from the Graduate School of North Texas State College and from Parke, Davis and Company, Detroit, Michigan.

(2) F. F. Blicke and E. S. Blake, THIS JOURNAL, **52**, 235 (1930).

(3) F. Kröhnke (with K. Faslod), *Ber.*, **67**, 656 (1934).

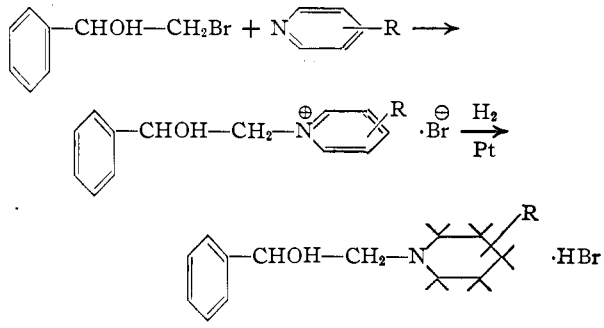
(4) Price Truitt and W. J. Middleton, THIS JOURNAL, **73**, 5669 (1951).

(5) Byron Riegel and Harold Wittcoff, *ibid.*, **68**, 1805 (1946).



C

Except when the R-group was hydrogen, methyl or an ethyl group it was impossible in our hands to secure the phenacylpiperidines (B). If the hydrogenation was stopped when only one, three or four moles of hydrogen had been absorbed, the same product (C) was obtained, along with unreacted starting material. The yield was, of course, much lower when smaller amounts of hydrogen were absorbed. In order to ascertain the structure of the hydrogenation products, alternate syntheses for the preparation of the completely reduced compounds were utilized.



C-1

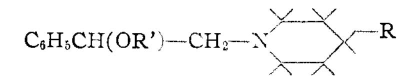
To further confirm that compounds (C and C-1) obtained by the two procedures, were identical the acetyl derivatives of these alcohols were prepared. The acetyl derivatives were identical for the compounds from both synthetic procedures when the R radical in the 4-position is larger than an ethyl group. However, hydrogenation of all the pyridinium compounds was not successful. The 2-(1-amyl)-1-phenacylpyridinium bromide and 2-(1-hexyl)-1-phenacylpyridinium bromide absorbed hydrogen but no crystalline product could be isolated. The preparation of derivatives of these hydrogenated materials met with failure.

The piperidine compounds reported in this paper exhibited a slight pressor activity. The antituberculous activities of the 4-alkyl-1-(2-hydroxy-2-phenylethyl)-piperidines were closely related to the nature of the 4-alkyl group as is shown in the following Table I. The 1-phenylacylpyridinium salts did not exhibit appreciable antituberculous activity.

The methyl-1-phenacylpiperidines and 4-ethyl-1-phenacylpiperidine showed little activity in the above test.

TABLE I

ANTITUBERCULOUS ACTIVITY



R	R'	Activity mg., %	Plasma activity at 10 mg., %
1-Hexyl	H	5.0	No growth
1-Octyl	H	5.0	No growth
1-Nonyl	H	1.25	No growth
5-Nonyl	H	1.25	No growth
5-Nonyl	Acetyl	10.00	No growth
4,4'-Diamino-diphenyl sulfone		2.5	No growth

Experimental[7]

The alkylpyridines used in the present work were of commercial grade and were redistilled before use.

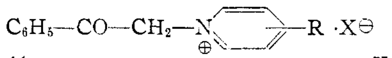
2-Methyl-1-(phenacyl)-pyridinium Bromide.[3]—Twenty grams (0.1 mole) of phenacyl bromide was dissolved in 150 ml. of anhydrous ether and 10 g. (0.1 mole) of 2-methylpyridine added. The mixture was allowed to stand one week, then filtered. Recrystallization from alcohol gave 26 g. of product.

The data for this and the other similar compounds which were prepared in the same manner are recorded in Table II.

4-(1-Hexyl)-1-(2-hydroxy-2-phenylethyl)-pyridinium Bromide.—A solution of equimolar quantities of styrene bromohydrin and 4-(1-hexyl)-pyridine in absolute alcohol were refluxed for 14 hours. The product melted at 144–147° without recrystallization.

TABLE II

SUBSTITUTED 1-PHENACYLPYRIDINIUM SALTS

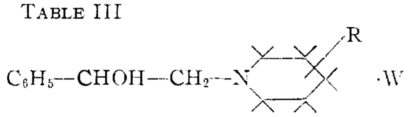


	R	X	M.p., °C.	Yield, %	Formula	Halogen, % Calcd.	Halogen, % Found
1	2-Methyl	Br	208–213	88	Ref. 3		
2	3-Methyl	Br	192–193	88	$C_{14}H_{14}BrNO$	27.34	27.21
3	4-Methyl	Br	226–230	83	$C_{14}H_{14}BrNO$	27.34	27.23
4	4-Ethyl	Cl	225–227	64	$C_{15}H_{16}ClNO$	13.6	13.7
5	2-(1-Amyl)	Br	125–128	36	$C_{18}H_{22}BrNO$	22.92	22.86
6	4-(1-Amyl)	Cl	179–180.5	72	$C_{18}H_{22}ClNO$	11.67	11.62
7	2-(1-Hexyl)	Br	136	6	$C_{19}H_{24}BrNO$	22.00	21.94
8	4-(1-Hexyl)	Cl	181–182	61	$C_{19}H_{24}ClNO$	11.18	11.31
9	4-(1-Octyl)	Cl	188–190	61	$C_{21}H_{28}ClNO$	10.28	10.41[a]
10	4-(1-Nonyl)	Cl	187–190	66	$C_{22}H_{30}ClNO$	9.85	10.00[b]
11	4-(2-Octylmethyl)	Cl	145–147	58	$C_{22}H_{30}ClNO$	9.85	9.84[c]
12	4-(5-Nonyl)	Cl	162–167	41	$C_{22}H_{30}ClNO$	9.85	9.73

[a] Calcd.: N, 4.04. Found: N, 3.99. [b] Calcd.: N, 3.89. Found: N, 3.72. [c] Calcd.: N, 3.89. Found: N, 4.00.

TABLE III

SUBSTITUTED PIPERIDINES[a]



	R	W	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	2-Methyl[b]	HCl	145–150	85	$C_{14}H_{20}ClNO$	66.25	66.23	7.95	7.90		
2	3-Methyl[b]	HBr	175–177	63	$C_{14}H_{20}BrNO$	56.39	56.41	6.71	6.54		
3	4-Methyl[b]	HBr	177–178	80	$C_{14}H_{20}BrNO$	56.39	56.47	6.71	6.84		
4	4-Methyl[b]	..	87–88	86	$C_{14}H_{19}NO$	77.38	77.56	8.81	8.66		
5	4-Ethyl[b]	..	76.5	68	$C_{15}H_{21}NO$	77.87	77.85	9.15	9.27	6.06	6.10
6	4-(1-Amyl)	..	59–61	35	$C_{18}H_{29}NO$	78.49	78.43	10.61	10.64	5.09	5.15
7	4-(1-Hexyl)[c]	HCl	214–217	40	$C_{19}H_{32}ClNO$	(Chlorine		10.88	10.99)	4.30	4.27
8	4-(1-Octyl)[c]	..	72.5	83	$C_{21}H_{35}NO$	79.44	79.61	11.11	11.23	4.42	4.37
9	4-(1-Nonyl)[c,d]	..	76.5	72	$C_{22}H_{37}NO$	79.70	79.83	11.25	11.38	4.23	4.33
10	4-(5-Nonyl)	..	66	82	$C_{22}H_{37}NO$	79.70	79.88	11.25	11.41	4.23	4.40
11	4-(5-Nonyl)	HCl	174–179	90	$C_{22}H_{38}ClNO$	(Chlorine		9.65	9.81)	4.23	4.25
12	4-(2-Octyl methyl)[c,d]	..	64[e]	73	$C_{22}H_{37}NO$	79.70	79.76	11.25	11.29	4.23	4.43

[a] Prepared by low pressure hydrogenation of the corresponding phenacylpyridinium halides in aqueous or alcoholic solution with Adams catalyst. [b] The corresponding ketone was obtained instead of the secondary alcohol. [c] Also prepared by hydrogenation of the 4-(alkyl)-1-(2-hydroxy-2-phenylethyl)-pyridinium bromide. [d] The 4-(alkyl)-1-(2-hydroxy-2-phenylethyl)-pyridinium bromide was prepared from styrene bromohydrin and 4-(1-alkyl)-pyridine and hydrogenated without characterization. [e] The base from procedure (d) melted at 66° and a mixed melt showed no depression in the value.

4-(1-Hexyl)-1-(2-hydroxy-2-phenylethyl)-piperidine hydrochloride was found to be only 0.6% as active as Chloromycetin[6] against *Salmonella sonne*. The remaining compounds of this group demonstrated less activity in this test.

4-(1-Octyl)-1-(2-hydroxy-2-phenylethyl)-piperidine hydrochloride was amebicidal (*in vitro*) at 1:5000 dilution and inactive at 1:50,000 dilution. The corresponding hexyl derivative was equally active.

(6) Parke Davis and Company Trade Mark.

Anal. Calcd. for $C_{19}H_{26}BrNO$: Br, 21.94; N, 3.84. Found: Br, 22.13; N, 3.92.

4-(1-Octyl)-1-(2-hydroxy-2-phenylethyl)-pyridinium Bromide.—A solution of 6 g. (0.03 mole) of styrene bromohydrin and 8.2 g. (0.04 mole) of 4-(1-octyl)-pyridine in 50 ml. of absolute ethanol was refluxed for 12 hours. Concentration of the solution, followed by addition of ether gave ten grams of white crystals. The crystals began to soften at 133° and were completely melted at 149°. This material was reduced without further purification and yielded the corresponding piperidine (see Table III, compound number 8).

(7) All melting points were made with a Fisher-Johns melting point apparatus and are uncorrected.

2-[4-(1-Hexyl)-1-(2-acetoxy-2-phenylethyl)]-piperidine Hydrochloride.—Two samples of this compound were prepared by the acetylation of compound III-7. Each sample of compound III-7 was by a different method. Each salt melted at 169–171° (dec.) and a mixture of the two melted at 168–170° (dec.).

Anal. Calcd. for $C_{21}H_{34}ClNO_2$: Cl, 9.64; N, 3.81. Found: Cl, 9.76; N, 4.02.

2-[4-(1-Octyl)-1-(2-acetoxy-2-phenylethyl)]-piperidine Hydrochloride.—Two samples of compound III-8 (prepared by two different procedures) were esterified by refluxing with acetic anhydride. The reddish oils which resulted could not be crystallized; however, the respective hydrochlorides were obtained and found to be identical, m.p. 152–157°. A mixture of the two melted at 152–156°. A separate analysis for each gave almost identical per cent. composition.

Anal. Calcd. for $C_{28}H_{38}ClNO_2$: Cl, 8.95; N, 3.54. Found: Cl, 9.12; N, 3.54.

2-[4-(1-Nonyl)-1-(2-acetoxy-2-phenylethyl)]-piperidine Hydrochloride.—The above ester was prepared by refluxing the alcohol (III-9) with acetic anhydride. The hydrochloride of the ester was isolated and purified, m.p. 150–156°.

Anal. Calcd. for $C_{24}H_{40}ClNO_2$: Cl, 8.65; N, 3.42. Found: Cl, 8.69; N, 3.32.

2-[4-(5-Nonyl)-1-(2-acetoxy phenylethyl)]-piperidine Hydrochloride.—The acetate was prepared from the parent alcohol (III-10) and isolated as the hydrochloride, m.p. 150–157°.

Anal. Calcd. for $C_{24}H_{40}ClNO_2$: Cl, 8.65; N, 3.42. Found: Cl, 8.83; N, 3.44.

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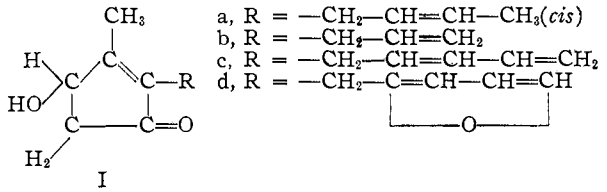
Furethrin

BY MASANAO MATSUI, F. B. LAFORGE, N. GREEN AND MILTON S. SCHECHTER

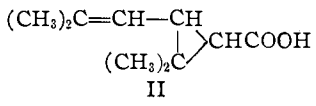
The preparation of furethrin, a mixture of stereoisomeric insecticidal esters of the type of pyrethrin I but with a 2-furfuryl side chain, is described. The procedures follow those employed in the synthesis of allethrin, a commercially available mixture of synthetic esters of the pyrethrin type, with furfurylacetone as a starting material.

The development of a general method for the synthesis of cyclopentenolones[1] of the type of cinerolone (formula Ia) has led to the preparation of a number of cyclopentenolones of formula I having various substituents for R.[1-3] Acylation of these synthetic cyclopentenolones with the acid



a, R = $-CH_2-CH=CH-CH_3$(*cis*)
b, R = $-CH_2-CH=CH_2$
c, R = $-CH_2-CH=CH-CH=CH_2$
d, R = $-CH_2-C=CH-CH=CH$ (with O)

I



II

chloride of natural *d-trans*-chrysanthemum monocarboxylic acid or with the mixture of acid chlorides of synthetic *dl-cis*- and *dl-trans*-chrysanthemum monocarboxylic acids[4] (formula II) furnished insecticidally active esters[1-3] of the pyrethrin or cinerin type. The mixture of esters known as allethrin, produced by acylating 2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one (allethrolone) (formula Ib) with a mixture of *dl-cis*- and *dl-trans*-chrysanthemum monocarboxylic acid chlorides, was selected as being the simplest and least expensive of these esters to manufacture. It is now being produced commercially. The presence of unsaturation in the radical R seems to be advantageous for high knock-down and kill of house flies, pyrethrin I, the ester of *d-trans*-chrysanthemum monocarboxylic acid with *d*-pyrethrolone (formula Ic), being one of the most toxic to insects. The cyclopentenolone of formula Id resembles pyrethrolone with respect to the number of carbon atoms and the relative positions of the side chain double bonds. We have synthesized this cyclopentenolone, which we propose to name "furethrolone," by the following steps (Fu = 2-furyl)

$$CH_3COCH{=}CHFu \xrightarrow[\text{catalytic}]{[H]} \underset{\text{III}}{CH_3COCH_2CH_2Fu} \xrightarrow[NaH \text{ or } NaOC_2H_5]{(C_2H_5)_2CO_3} \underset{\text{IV}}{C_2H_5OOCCH_2COCH_2CH_2Fu} \xrightarrow{\text{aq. KOH}} \underset{\text{V}}{KOOCCH_2COCH_2CH_2Fu} \xrightarrow{CH_3COCHO} \underset{\text{VI}}{CH_3COCHOHCH_2COCH_2CH_2Fu} \xrightarrow{\text{aq. NaOH}} \text{Id}$$

The starting material is furfuralacetone, which can be hydrogenated to furfurylacetone. The subsequent steps are the same as those described for the synthesis of cyclopentenolones.[1]

The acylation of furethrolone with the mixture of acid chlorides of *dl-cis*- and *dl-trans*-chrysanthemum monocarboxylic acids furnished a mixture of isomeric esters for which the name "furethrin" is proposed. Its production might be more economical than that of allethrin, owing to the low cost and ready availability of furfuralacetone.

In tests on house flies furethrin proved to be about equal to pyrethrins in toxicity.[5]

(1) M. S. Schechter, N. Green and F. B. LaForge, THIS JOURNAL, **71**, 1517, 3165 (1949).

(2) M. S. Schechter, N. Green and F. B. LaForge, Abstracts, 118th Meeting American Chemical Society, p. 34N, September, 1950.

(3) L. Crombie and S. H. Harper, *Nature*, **164**, 534 (1949); *J. Chem. Soc.*, 1152 (1950); L. Crombie, A. J. B. Edgar, S. H. Harper, M. W. Lowe and D. Thompson, *ibid.*, 3552 (1950); Y. Katsuda, Y. Inouye, A. Nishimura, K. Kitagawa, T. Shinohara and M. Ohno, *Botyu Kagaku*, **16**, 115 (1951).

(4) I. G. M. Campbell and S. H. Harper, *J. Chem. Soc.*, 283 (1945); S. H. Harper, H. W. B. Reed and R. A. Thompson, *J. Sci. Food Agr.*, **2**, 94 (1951); R. Schett, *Beitrag zur Kenntnis der Pyrethrine, Dissertation*, Zurich (1947).

(5) Preliminary data by W. A. Gersdorff and N. Mitlin and by J. Fales, Bureau of Entomology and Plant Quarantine.