

The oil was taken up in 10 ml. of benzene and 40 ml. of benzene was added. The supernatant intensely fluorescent liquid was poured onto a column containing 15 g. of aluminum oxide. The undissolved green precipitate was treated once more in the same fashion. Fractional elution of the column with a benzene-benzin mixture containing up to 50% benzene gave unchanged starting material. Further elution with benzene containing 10-20% of ether gave light pink crystalline material. The latter fractions were combined and sublimed at a bath temperature of 150-160° in a vacuum of 0.001 mm. The almost colorless sublimate, on recrystallization from benzene-benzin, gave well-shaped shining colorless rods subliming at 140° and melting, alone or mixed with synthetic 3,3-dibenzyl- $\psi$ -oxindole, at 201-202°.

**B. By Rearrangement of 2,2-Dibenzyl- $\psi$ -indoxyl with Sodium Isoamyl Oxide.**—A solution of 0.5 g. of 2,2-dibenzyl- $\psi$ -indoxyl in 10 ml. of isoamyl alcohol was added to the cooled solution of 0.5 g. of sodium in 15 ml. of isoamyl alcohol. The mixture, which assumed a distinct red color, was refluxed for 8 hours under nitrogen. The resulting dark red solution was concentrated as much as possible on the steam-bath at 15 mm. The residue was taken up in ether, the ether extract was washed with water, dilute acid, sodium bicarbonate solution and then water again. After drying over sodium sulfate, benzene was added and the whole evaporated to dryness in a stream of nitrogen. The residue, on recrystallization from alcohol, yielded 0.1 g. of starting material. The mother liquor on concentration gave 0.4 g.

of a red oil which was purified by chromatography similar to the procedure described above for the acid rearrangement. Starting material together with almost colorless non-fluorescent crystals was obtained by elution with benzene containing 4, 10 and 20% ether. Sublimation, followed by recrystallization from benzene-benzin yielded again colorless, shining rods, subliming at 140° and melting at 201-202°.

**C. By Benzoylation of Oxindole.**—A solution of 1.3 g. of oxindole in 10 ml. of absolute alcohol was added to a solution of 0.23 g. of sodium in the same solvent. To this mixture was added 1.2 g. of benzyl bromide. This solution, on refluxing for 2.5 hours, deposited sodium bromide, turned light-red, and became neutral to moist litmus paper at the end of the refluxing period. The reaction mixture was concentrated in vacuum and poured into water. The resulting oil was extracted with benzene, the extract was washed with water, filtered and concentrated. The dried, slightly red solution was filtered through 5 g. of aluminum oxide which removed most of the color. The filtrate and washings were concentrated almost to dryness. Addition of benzene and scratching brought about crystallization. Recrystallization from ethyl acetate yielded 0.82 g. of well-shaped colorless shining rods subliming at 140° and melting at 202-203°, identical with the material obtained by methods A and B.

*Anal.* Calcd. for  $C_{22}H_{19}NO$ : C, 84.45; H, 6.12; N, 4.45. Found: C, 83.98; H, 6.08; N, 4.24.

BETHESDA, MARYLAND

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

## Antitubercular Studies. I. N-Diphenylmethyl-4-alkylpyridines<sup>1,2</sup>

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The preparations and properties of a number of N-diphenylmethyl-4-alkylpyridines and N-(9-fluorenyl)-4-alkylpyridines are described. None of the fluorenyl compounds showed appreciable antituberculous activity, *in vitro*, and the activity of the N-diphenylmethyl-4-alkylpyridines was markedly affected by the nature of the 4-alkyl group.

The preparation of a number of N-diphenylmethyl-4-alkylpyridines and N-(9-fluorenyl)-4-alkylpyridines has been undertaken in order to study the correlation of antitubercular properties and the nature of the 4-alkylpyridine moiety. These compounds are structurally related to other physiologically active diphenylmethyl derivatives, such as N,N-diethylaminodiphenylmethane.<sup>3</sup> According to a theory advanced by Burger, Graef and Bailey,<sup>4</sup> the activity of the tuberculostatic drug, 4,4'-diaminodiphenyl sulfone,<sup>5</sup> may be increased by introduction of other lipid solubilizing groups in place of the sulfone linkage. This has been borne out to some degree by the work of Kirkwood and Phillips<sup>6</sup> and Markees and Burger.<sup>7</sup> It seemed of interest to study a group of compounds with the 4-alkylpyridine group attached to the methyl radical of diphenylmethane in order to determine the antituberculous activity of these derivatives. The similarity between the diphenyl-

methyl radical and the 9-fluorenyl radical made the inclusion of derivatives of the latter appear of interest.

The N-diphenylmethyl-4-alkylpyridines were prepared by the catalytic hydrogenation of the N-diphenylmethyl-4-alkylpyridinium bromides. This approach represents the same general method used by Kröhnke and Fasold<sup>8</sup> in the synthesis of certain N-phenacylpyridines. The 9-fluorenyl derivatives were prepared by the same procedures.

The initial condensation of the diphenylmethyl and 9-fluorenyl bromides with the 4-alkylpyridines was accompanied by the formation of colored products. The general nature of this type of material has been discussed in a paper by Pinck and Hilbert<sup>9</sup> and the colored products were discarded in the present investigation.

The condensation of diphenylmethyl bromide with 4-alkylpyridines gave the desired products. However, the yields were very low, 8-10%, and too, this method entailed the prior tedious hydrogenation of the 4-alkylpyridines. In contrast, the hydrogenation of the quaternary salts proceeded readily at high or low pressure in the presence of reduced platinum oxide catalyst or palladium-charcoal catalyst. The rates of hydrogenation with the latter catalyst were slower but gave the same products. Raney nickel catalyst also gave the tertiary amines, but the yields were much

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(2) This paper represents part of a thesis submitted to the Graduate School by W. J. Middleton in partial fulfillment of the requirements for the M.S. Degree.

(3) V. Caprara, *Farm. Sci. e. sec.*, **2**, 98 (1947); *C. A.*, **41**, 6989h (1947).

(4) A. Burger, E. Graef and M. Bailey, *THIS JOURNAL*, **68**, 1725 (1946).

(5) L. T. Coggeshall, J. Maier and C. A. Best, *J. Am. Med. Assoc.*, **117**, 1077 (1941).

(6) S. Kirkwood and P. H. Phillips, *ibid.*, **117**, 2405 (1941).

(7) S. Markees and A. Burger, *ibid.*, **70**, 3329 (1948).

(8) F. Kröhnke and K. Fasold, *Ber.*, **67**, 656 (1934).

(9) L. A. Pinck and G. E. Hilbert, *THIS JOURNAL*, **68**, 2011 (1946).

lower. The low yields with Raney nickel were due to cleavage of the pyridine ring as evidenced by the presence of ammonia at the conclusion of the reaction.

TABLE I<sup>a</sup>

Compd.	ANTITUBERCULAR ACTIVITY R-N		Activity, mg. %	Serum activity, 10 mg. %
	R	R'		
1	Diphenyl-	H	10.0	Growth
2	methyl	Methyl	0.156	Growth
3		1-Amyl	10.0	Growth
4		1-Octyl	0.156	Growth
5		1-Nonyl	2.5	Growth
6		5-Nonyl	10.0	Growth
7		1-(2-Methyl-octyl)	0.312	Growth
8		3-Propanol	10.0	Growth
9	9-Fluorenyl	H	5.0	No growth
10		Methyl	10.0	Growth
Control	4,4'-Diaminodiphenyl sulfone		1.25	No growth

<sup>a</sup> These tests were arranged for by Dr. Loren Long, Parke, Davis and Company, Detroit, Michigan.

group contains nine carbons, the arrangement of these carbons has a pronounced effect on the activity as noted by the fact that the 1-nonyl compound has the highest activity. This activity falls off as the point of attachment moves to the center of the carbon chain. These compounds, however, were inactive in the presence of serum. None of the 9-fluorenyl derivatives displayed appreciable activity, although number 9 prevented growth of the tubercle organism in the presence of serum.

### Experimental<sup>10</sup>

**N-Diphenylmethylpyridinium Bromides.**—These compounds were prepared in the general manner described below and the resulting salts listed and characterized in Table II. Variations in the heating period are noted in the Table.

**N-Diphenylmethylpyridinium Bromide.**—A solution of 24.7 g. (0.1 mole) of diphenylmethyl bromide and 7.9 g. (0.1 mole) of pyridine in 150 ml. of benzene was allowed to stand overnight at room temperature. The mixture was then refluxed for 18 hours and the pink solid which separated was removed by filtration. This solid weighed 10 g. When the filtrate was refluxed for a further 36-hour period, an additional 10 g. of pink solid was obtained. The combined precipitates were purified by recrystallization from hot alcohol and ether. This procedure gave 19.5 g., 60%, of the desired product which was now a white crystalline substance, m.p. 215–216°.

TABLE II

### N-DIPHENYLMETHYL-4-ALKYLPYRIDINIUM BROMIDES (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CH-N<sup>+</sup>—R-Br<sup>-</sup>

R	Yield, %	M.p., °C.	Reflux time, hr.	Formula	Analyses, %			
					Bromine		Nitrogen	
					Calcd.	Found	Calcd.	Found
Hydrogen <sup>a</sup>	60	215–216	48	C <sub>18</sub> H <sub>16</sub> BrN	24.5	24.5	4.29	43.8
Methyl	78	239–240	18	C <sub>19</sub> H <sub>18</sub> BrN	23.5	23.4	4.12	4.19
Ethyl	56	204–208	10	C <sub>20</sub> H <sub>20</sub> BrN	22.6	22.4	3.95	4.05
1-Amyl	73	95–98	8	C <sub>23</sub> H <sub>26</sub> BrN	20.2	20.0	3.54	3.62
1-Hexyl	78	123–125	7	C <sub>24</sub> H <sub>28</sub> BrN	19.5	19.6	3.41	3.52
1-Octyl	68	150–151	7	C <sub>26</sub> H <sub>32</sub> BrN	18.3	18.2	3.20	3.21
1-(2-Methyloctyl)	69	140–141	7	C <sub>27</sub> H <sub>34</sub> BrN	17.7	17.6	3.10	3.14
1-Nonyl	73	153–155	5	C <sub>27</sub> H <sub>34</sub> BrN	17.7	17.7	3.10	3.16
1-(5-Nonyl)	59	176–177	7	C <sub>27</sub> H <sub>34</sub> BrN	17.7	17.6	3.10	3.09

<sup>a</sup> This compound was first prepared by F. Kröhnke, *Ber.*, 71B, 2583 (1938).

TABLE III

### N-(9-FLUORENYL)-4-ALKYLPYRIDINIUM BROMIDES

R	Yield, %	M.p., °C.	Reflux time, hr.	Formula	Analyses, %			
					Bromine		Nitrogen	
					Calcd.	Found	Calcd.	Found
H <sup>a</sup>	80	209	6	C <sub>18</sub> H <sub>14</sub> BrN	24.7	24.7	4.32	4.38
Methyl	76	187–188	3	C <sub>19</sub> H <sub>16</sub> BrN	23.7	23.5	4.14	4.19
Ethyl	Not purified but was hydrogenated							
1-Hexyl	88	206–207	4	C <sub>24</sub> H <sub>26</sub> BrN	19.6	19.5	3.43	3.50
1-Octyl	82	108–110	5	C <sub>26</sub> H <sub>30</sub> BrN	18.4	18.2	3.21	3.35
1-Nonyl	76	114–115	4	C <sub>27</sub> H <sub>32</sub> BrN	17.8	17.7	3.11	3.23
1-(5-Nonyl)	44	192–193	5	C <sub>27</sub> H <sub>32</sub> BrN	17.8	17.7	3.11	3.21

<sup>a</sup> Pinck and Hilbert, *THIS JOURNAL*, 68, 2011 (1946).

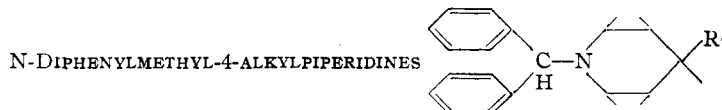
**Physiological Activity.**—It should be noted that despite the absence of substituent groups in the benzene rings, two of the compounds, numbers 2 and 4, exhibit activity at a dilution 10 times that of the standard. Although the activity of the compounds cannot be correlated with the number of carbons in the 4-alkyl group, when the 4-alkyl

The same general procedure was utilized for the preparation of **N-(9-fluorenyl)-4-alkylpyridinium bromides**. The data for these salts are listed in Table III.

**Hydrogenations.**—The catalytic hydrogenations of the diphenylmethylpyridinium bromides were carried out as described below and the data listed in Table IV.

(10) All melting points were made with a Fisher-Johns melting point apparatus and were not corrected.

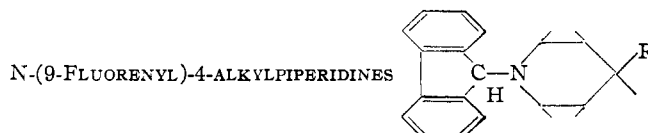
TABLE IV



R	Hydrobromides				Free bases						
	Yield, %	M.p., °C.	Formula	Analyses, %				M.p., °C.	Analyses, %		
				Bromine		Nitrogen			Nitrogen		
Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found				
H <sup>a</sup>	94	256-258	C <sub>18</sub> H <sub>22</sub> BrN	24.1	24.3	4.22	4.37	C <sub>18</sub> H <sub>21</sub> N	77.5	5.58	5.63
Methyl	87	230-231	C <sub>19</sub> H <sub>24</sub> BrN	23.1	23.0	4.04	4.00	C <sub>19</sub> H <sub>23</sub> N	96	5.28	5.33
Ethyl	83	157-158	C <sub>20</sub> H <sub>26</sub> BrN	22.2	22.4	3.89	3.99	C <sub>20</sub> H <sub>25</sub> N	62	5.02	4.99
1-Amyl	91	143-145	C <sub>23</sub> H <sub>32</sub> BrN	19.9	20.0	3.48	3.52	C <sub>23</sub> H <sub>31</sub> N	59.5	4.36	4.39
1-Hexyl	79	209-210	C <sub>24</sub> H <sub>34</sub> BrN	19.2	19.3	3.37	3.45	C <sub>24</sub> H <sub>33</sub> N	44	4.18	4.24
1-Octyl	66	213-215	C <sub>26</sub> H <sub>38</sub> BrN	18.0	17.9	3.17	3.21	C <sub>26</sub> H <sub>37</sub> N	61	3.86	3.91
1-(2-Methyl-octyl)	76	148	C <sub>27</sub> H <sub>40</sub> BrN	17.5	17.4	3.06	3.16				
1-Nonyl	94	147-149	C <sub>27</sub> H <sub>40</sub> BrN	17.5	17.4	3.06	3.11	C <sub>27</sub> H <sub>39</sub> N	77.5	3.71	3.68
1-(5-Nonyl)	76	155-157	C <sub>27</sub> H <sub>40</sub> BrN	17.5	17.3	3.60	3.14				

<sup>a</sup> Reported by N. Maxim and R. Mavrodineau, *Bull. soc. chim.*, [5] 3, 1084 (1936).

TABLE V



R	Hydrobromides				Free bases						
	Yield, %	M.p., °C.	Formula	Analyses, %				M.p., °C.	Analyses, %		
				Bromine		Nitrogen			Nitrogen		
Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found				
H	74	256-257	C <sub>18</sub> H <sub>20</sub> BrN	24.3	24.2	4.24	4.32	C <sub>18</sub> H <sub>19</sub> N	107	5.62	5.64
Methyl	86	244-246	C <sub>19</sub> H <sub>22</sub> BrN	23.3	23.2	4.06	4.15	C <sub>19</sub> H <sub>21</sub> N	73.5	5.32	5.29
Ethyl		168-170	C <sub>20</sub> H <sub>24</sub> BrN	22.4	22.6	3.91	3.96	C <sub>20</sub> H <sub>23</sub> N	64	5.05	4.99
1-Hexyl	81	172-173	C <sub>24</sub> H <sub>32</sub> BrN	19.3	19.3	3.38	3.49	C <sub>24</sub> H <sub>31</sub> N	74	4.20	4.25
1-Octyl	55	133-135	C <sub>26</sub> H <sub>36</sub> BrN	18.1	18.0	3.17	3.21	C <sub>26</sub> H <sub>35</sub> N	70	3.88	3.91
1-Nonyl	77	134-136	C <sub>27</sub> H <sub>38</sub> BrN	17.5	17.5	3.07	3.07	C <sub>26</sub> H <sub>34</sub> N	64	3.73	3.77
1-(5-Nonyl)	67	161-162	C <sub>27</sub> H <sub>38</sub> BrN	17.5	17.4	3.07	3.14	C <sub>27</sub> H <sub>37</sub> N	80	3.73	3.71

#### N-Diphenylmethyl-4-(1-nonyl)-piperidine Hydrobromide.

—A solution of 10 g. of N-diphenylmethyl-4-(1-nonyl)-pyridinium bromide in 100 ml. of absolute alcohol was hydrogenated at 50 p.s.i. of hydrogen in the presence of Adams catalyst. The hydrogenation required about one hour but this time could be cut to about 15 minutes by raising the pressure to 1000 p.s.i. There was no evidence of hydrogenation in the benzene rings at this higher pressure. When the hydrogenation was complete, the mixture was heated to dissolve the hydrogenated product and the catalyst removed by filtration. The product was recovered by cooling the filtrate overnight and the precipitate filtered. An additional amount of product could be obtained by addition of

ether to the filtrate. The product was recrystallized from ethanol, m.p. 147-149°.

The free base from the above hydrogen bromide salt was obtained by adding 2 g. of the salt to a 10% sodium bicarbonate solution. The free base separated as a white oil which solidified on standing in the cold-box for a few hours. The solid was recrystallized from ethanol to give very fine white needles, m.p. 77.7°. The data for the free bases are included in Table IV.

The N-(9-fluorenyl)-4-alkylpyridinium bromides were hydrogenated in the same manner as were the diphenylmethyl derivatives and the data listed in Table V.

DENTON, TEXAS

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