

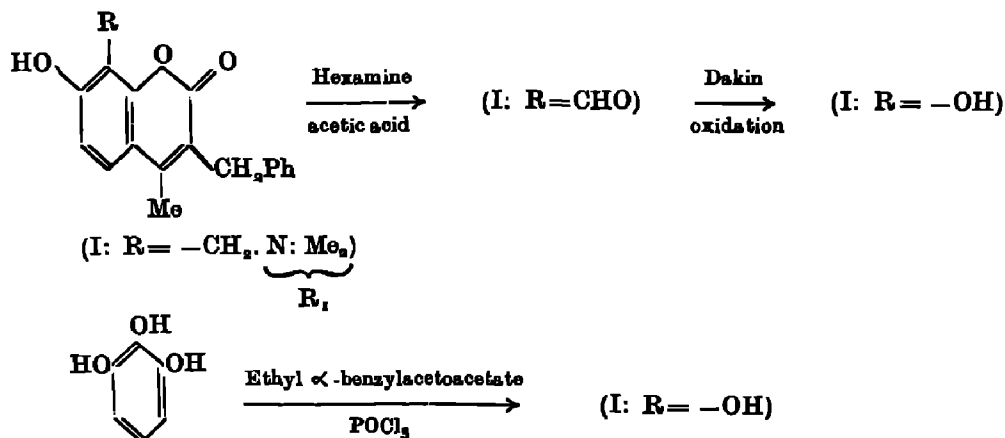
## Oxygen Heterocyclic Compounds as Possible Central Nervous System Stimulants. Part II. Mannich Bases from 7-Hydroxy-3-benzyl-4-methylcoumarin

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Synthesis of some Mannich bases has been effected from 7-hydroxy-3-benzyl-4-methylcoumarin and a few secondary amines with a view to studying their central nervous system-stimulating activity.

In extension of our previous work<sup>1</sup> the synthesis of a few Mannich bases from 7-hydroxy-3-benzyl-4-methylcoumarin has been undertaken. This coumarin is prepared from resorcinol and ethyl  $\alpha$ -benzylacetoacetate, using various condensing agents, such as sulphuric acid<sup>2</sup>, phosphorus pentoxide<sup>3</sup>, phosphoric acid, sodium acetate, sodium ethoxide<sup>4</sup>, and phosphorus oxychloride<sup>5</sup>. Polyphosphoric acid has been found to provide a better yield and a purer product. Mannich bases have been obtained by refluxing the solution of the coumarin and paraformaldehyde in absolute ethanol with different secondary amines and isolated as hydrochlorides (Table I).

The aminomethyl group in these bases is in 8-position, as confirmed by conversion of the dimethylaminomethyl derivative of 7-hydroxy-3-benzyl-4-methylcoumarin to an aldehyde derivative by boiling with hexamine and acetic acid. The oxidation of the aldehyde derivative, following the Dakin modification of the Baeyer-Villiger procedure<sup>6</sup>, furnishes a product, which is identical with 7,8-dihydroxy-3-benzyl-4-methylcoumarin, also obtained by condensing pyrogallol with ethyl  $\alpha$ -benzylacetoacetate<sup>5</sup>.



1. *Ind. J. Appl. Chem.*, 1963, **26**, 149.
2. Baker, *J. Chem. Soc.*, 1925, 2349.
3. Chakravarti, *this Journal*, 1931, **8**, 129.
4. *Idem, ibid.*, 1935, **12**, 536.
5. Neik *et al.*, *ibid.*, 1929, **6**, 801.
6. Hassel, "Organic Reactions", 1957, vol. 9, p. 73.

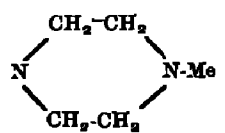
## EXPERIMENTAL

**7-Hydroxy-3-benzyl-4-methylcoumarin.**—A mixture of resorcinol (12 g.), ethyl  $\alpha$ -benzyl-acetoacetate (20 g.) and polyphosphoric acid (180 g.) was heated on a steam bath for  $\frac{1}{2}$  hr. and then poured on crushed ice. The solid (22 g.) separating was filtered and crystallised from ethanol, m.p. 224°. (Found: C, 76.50; H, 5.34. Calc. for  $C_{17}H_{14}O_3$ : C, 76.69; H, 5.26%).

**7-Hydroxy-3-benzyl-4-methyl-8-dimethylaminomethylcoumarin Hydrochloride.**—A mixture of the preceding coumarin (2.6 g.) in absolute ethanol (100 ml), paraformaldehyde (0.6 g.), and dimethylamine (3 ml) was refluxed on a steam bath for about 10 hr. After cooling, the mixture was acidified with EtOH-HCl, concentrated, and cooled. The hydrochloride separating was crystallised from ethanol, m.p. 226°. Mannich base hydrochlorides from other secondary amines were prepared in the same way (Table I).

TABLE I

*N-Substituted 7-hydroxy-3-benzyl-4-methyl-8-aminomethylcoumarin hydrochlorides.*

No.	*R <sub>1</sub> .	**M.P.	Yield.	Formula.	%Nitrogen.		%Chlorine.	
					Found.	Reqd.	Found.	Reqd.
1	NMe <sub>2</sub>	226°	50%	C <sub>20</sub> H <sub>22</sub> O <sub>3</sub> NCl	3.75	3.89	9.85	9.87
2	NEt <sub>2</sub>	110°	55	C <sub>22</sub> H <sub>26</sub> O <sub>3</sub> NCl	3.52	3.60	9.13	9.16
3	N- <i>n</i> -Pr <sub>2</sub>	208°	45	C <sub>24</sub> H <sub>30</sub> O <sub>3</sub> NCl	3.30	3.36	8.50	8.54
4	N- <i>n</i> -Bu <sub>2</sub>	210°	40	C <sub>26</sub> H <sub>34</sub> O <sub>3</sub> NCl	3.10	3.15	8.10	8.00
5	N- <i>iso</i> -Bu <sub>2</sub>	218°	42	„	3.20	3.15	8.11	8.00
6	N-(Isoamyl) <sub>2</sub>	275°	30	C <sub>28</sub> H <sub>38</sub> O <sub>3</sub> NCl	3.00	2.98	7.50	7.52
7	N(C <sub>3</sub> H <sub>7</sub> OH) <sub>2</sub>	150°	60	C <sub>28</sub> H <sub>36</sub> O <sub>5</sub> NCl	3.28	3.33	8.42	8.46
8	N(C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> ) <sub>2</sub>	185°	65	C <sub>32</sub> H <sub>30</sub> O <sub>3</sub> NCl	2.69	2.73	6.93	6.94
9	N(C <sub>3</sub> H <sub>10</sub> )	230°	62	C <sub>23</sub> H <sub>26</sub> O <sub>3</sub> NCl	3.42	3.50	8.80	8.88
10	N(C <sub>4</sub> H <sub>9</sub> O)	168°	70	C <sub>22</sub> H <sub>24</sub> O <sub>4</sub> NCl	3.40	3.48	8.85	8.84
11	N(C <sub>4</sub> H <sub>9</sub> )	130°	54	C <sub>22</sub> H <sub>24</sub> O <sub>3</sub> NCl	3.59	3.63	9.17	9.20
12		240°	35	C <sub>23</sub> H <sub>27</sub> O <sub>3</sub> N <sub>2</sub> Cl	6.70	6.75	8.58	8.56

\*Vide structure (I).

**8-Formyl-7-hydroxy-3-benzyl-4-methylcoumarin.**—To a solution of the preceding aminomethylcoumarin (5 g.) in hot acetic acid (100 ml) hexamine (10 g.) was added and the reaction mixture was gently refluxed for 8 hr. HCl (conc., 50 ml) was then added and the reaction mixture further refluxed for 2 hr., cooled, and extracted with ether. The product, obtained on removal of the ether, was crystallised from ethanol, m.p. 250°, yield 1 g. (Found: C, 73.30; H, 4.70.  $C_{18}H_{14}O$  requires C, 73.47; H, 4.76%). 2,4 DNP m.p. 295° (decomp.).

\*\*All melting points are uncorrected.

**7,8-Dihydroxy-3-benzyl-4-methylcoumarin.**—To the above formylcoumarin (1 g.) in 2% NaOH solution (20 ml) at 0° was added 6% H<sub>2</sub>O<sub>2</sub> (6 ml) with stirring during  $\frac{1}{2}$  hr. Stirring was continued for further 1 hr. and then acidified. The product separating was crystallised from ethanol, m.p. 193°. Mixed m.p. with an authentic sample of 7, 8-dihydroxy-3-benzyl-4-methylcoumarin, prepared according to Naik *et al.*<sup>3</sup>, was not depressed. (Found: C, 72.20; H, 4.7. Calc. for C<sub>17</sub>H<sub>14</sub>O<sub>4</sub>: C, 72.34; H, 4.96%).

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