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Note

Synthesis of Diethylaminoethyl Esters of *p*-Carboxyphenylphenylcarbinols

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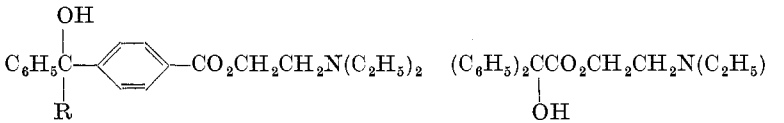
The 2-diethylaminoethyl esters of *p*-carboxyphenylphenylcarbinol (I; R = H) and *p*-carboxyphenyldiphenylcarbinol (I; R = C_6H_5), which are vinylogues of diethylaminoethyl benzilate (II), have been synthesized for testing as possible antispasmodics.



(I)

(II)

The preparation involved treating the corresponding acids[1,2] with 2-diethylaminoethyl chloride and isolating the esters as the hydrochlorides.

Extension of the reaction to esters of alkyl-*p*-carboxyphenylphenylcarbinol was not successful. Methyl-*p*-carboxyphenylphenylcarbinol, which was prepared by the oxidation of methyl-*p*-tolylphenylcarbinol[3] with potassium permanganate, gave upon treatment with 2-diethylaminoethyl chloride an oil which would not crystallize.

A synthesis of the ethyl analogue (I; R = C_2H_5) by this method failed because of the instability of the ethylphenyl-*p*-tolylcarbinol. The only product isolated from the addition of ethylmagnesium iodide to phenyl-*p*-tolyl ketone was 1-phenyl-1-*p*-tolyl-1-propene. Direct addition of ethylmagnesium iodide to

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2-diethylaminoethyl *p*-benzoylbenzoate[4] followed by treatment with gaseous hydrogen chloride gave a poor yield of a crystalline solid which analysed approximately for the ethyl analogue. This procedure, however, could not be repeated successfully.

The diethylaminoethyl esters of *p*-carboxyphenylphenylcarbinol (I; R = H), *p*-carboxyphenyldiphenylcarbinol (I; R = C_6H_5), and *p*-benzoylbenzoic acid, were tested for 'atropine-like' action at a level 100 times an effective dose of atropine sulphate using the mouse mydrasis test.[5] The compounds exhibited no anticholinergic action at this level and are considered to be inactive. They were also screened for their ability to potentiate the sleeping time produced by hexobarbital in mice and were found to be inactive.

Experimental*

Diphenyl-p-*carboxyphenylcarbinol, diethylaminoethyl ester* (*I*; *R* = C_6H_5) *hydrochloride.* Diphenyl-*p*-carboxyphenylcarbinol[2] (6·3 g) and 2-chloroethyldiethylamine (2·9 g) were refluxed in anhydrous *iso*propyl alcohol for 12 h. Upon cooling the hydrochloride of the ester separated and was re-crystallized from *iso*propyl alcohol; yield, 2·3 g; m.p. 147–148°.

Anal. Calcd. for $C_{26}H_{30}ClNO_3$: C, 70·96; H, 6·88. Found: C, 71·09; H, 7·04.

Phenyl-p-*carboxyphenylcarbinol, diethylaminoethyl ester* (*I*; *R* = *H*). Phenyl-*p*-carboxyphenylcarbinol[1] (10 g) and 2-chloroethyldiethylamine (5·9 g) were refluxed in anhydrous *iso*propyl alcohol (125 ml) for 6 h. The resulting oil could not be induced to crystallize. The free amine obtained by treatment with 10 per cent sodium carbonate solution was re-crystallized from (30–40°) petroleum ether and melted at 54–56°; yield, 8·15 g.

Anal. Calcd. for $C_{20}H_{25}NO_3$: C, 73·36; H, 7·70; N, 4·28. Found: C, 73·33; H, 7·67; N, 4·30.

Diethylaminoethyl p-*benzoylbenzoate.* This ester, which was obtained only as the hydrochloride by Sandahl and Christiansen,[4] was found to distil at 190–192° (0·08 mm) without decomposition.

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73·82; H, 7·12. Found: C, 73·82; H, 7·20.

* Melting points are corrected and boiling points are uncorrected.

Reaction of ethylmagnesium iodide with diethylaminoethyl p-*benzoylbenzoate.* A solution of diethylaminoethyl *p*-benzoylbenzoate (10 g) in ether (100 ml) was treated with a solution of ethylmagnesium iodide (5·5 g) in ether (100 ml). The resulting solution was made basic with 3 N sodium hydroxide and the ether layer was dried over calcium chloride. Addition of dry hydrogen chloride to the ether solution gave an oil which was taken up in *iso*propyl alcohol. A white crystalline compound appeared after two months at 5°; m.p. 128–129°; yield, 0·6 g.

Anal. Calcd. for $C_{22}H_{30}ClNO_3$: C, 67·41; H, 7·71. Found: C, 66·71; H, 7·53.

p-*Carboxyphenylphenylcarbinol.* A mixture of *p*-benzoylbenzoic acid (10 g), sodium hydroxide (10 g), and zinc dust (10 g) in water (500 ml) was stirred at room temperature for 5 h and at 100° for 1 h and then filtered. Acidification of the filtrate gave a white crystalline mass which was re-crystallized from ethanol; m.p. 164–165°; yield, 10 g. Zincke,[1] who prepared this compound using zinc and hydrochloric acid, reports a similar melting point.

Methylphenyl-p-*carboxyphenylcarbinol.* Methylphenyl-*p*-tolylcarbinol[3] (15 g) was refluxed with potassium permanganate (31·6 g) and sodium hydroxide (52·8 g) in water (800 ml) for 3 h and poured into 500 ml of ice water. Decolorization with a saturated solution of sodium bisulphite followed by acidification with dilute hydrochloric acid gave methylphenyl-*p*-carboxyphenylcarbinol (10 g). After one re-crystallization from ethanol the acid melted at 133–134·5°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74·37; H, 5·82. Found: C, 74·48; H, 5·87.

Reaction of phenyl-p-*tolyl ketone with ethylmagnesium iodide.* A solution of ethylmagnesium iodide (9·2 g) in anhydrous ether (150 ml) was added to a solution of phenyl-*p*-tolyl ketone (10 g) in ether (100 ml) and the resulting mixture was refluxed for 2 h. Decomposition with ammonium chloride followed by removal of the ether gave an oil which reacted with bromine in carbon tetrachloride. This liquid distilled at 126·5–127·5° (0·3 mm) and analysed for 1-phenyl-1-*p*-tolyl-1-propene; yield, 8 g.

Anal. Calcd. for $C_{16}H_{16}$: C, 92·35; H, 7·69. Found: C, 92·09; H, 7·86.

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