

increases rapidly with increasing concentration, the maximum in the theoretically significant  $(i/G\eta)_{C=0}$  curve would be much sharper than that of the  $(i/G)_{C=0}$  curve of Fig. 3. According to theory,<sup>6,7</sup>  $(i/G\eta)_0$  should be proportional to concentration for molecules of fixed geometry. The fact that  $(i/G)_0$  is not a linear function for our polyelectrolytes is, therefore, experimental evidence that the average shape of the polyelectrolyte depends on the total concentration.

The curve of Fig. 3 approximates linearity with a high slope at zero concentration; we ascribe this to a rod-like configuration of the polyelectrolyte at low concentrations, corresponding to a very small rotatory diffusion constant; as concentration increases, association of counter ions to the polyion neutralizes increasingly more of its total charge, thus reducing intramolecular repulsion, and permitting the molecule to approach the statistical coil which has a larger diffusion constant.

A final test of the hypothesis that polyelectrolyte configuration is determined by electrostatic forces was made by measuring a solution containing 0.193 g. of polysalt and 0.95 g. of potassium bromide in 100 cc. The polyelectrolyte concentration is that corresponding to the maximum birefringence but a large excess (12 times stoichiometric equivalence) of counter ions is now present. We would expect this excess of counter ions to neutralize (electrostatically) the polyelectrolyte and then the resulting structure should shrink in volume to a rather compact spherical particle due to intramolecular attraction of the sort which stabilizes an ordinary ionic crystal. For table angles of 40, 60, 80, 100 and 120°, the following values of analyzer displacements necessary for equally bright half-fields were observed at a gradient of 20,000 sec.<sup>-1</sup>: +0.1°, -0.3°, 0.0°, -0.5°, -0.2°. No trace of streaming birefringence is visible; by way of comparison, the solution containing 0.207 g. polysalt/100 ml. gave a maximum analyzer displacement of 1.8° at a gradient of only 850 sec.<sup>-1</sup>. The birefringence data thus completely confirm the conclusions<sup>5</sup> which were deduced from the viscosities of solutions of these salts.

(6) C. Sadron, *J. chim. phys.*, **36**, 73 (1939).

(7) A. Peterlin and H. A. Stuart, *Z. Physik*, **112**, 1 (1939).

THEODOR KOCHER INSTITUT  
UNIVERSITÄT BERN  
BERN, SWITZERLAND

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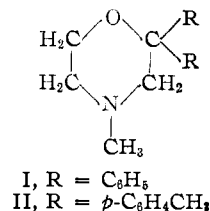
#### 4-Methyl-2,2-diarylmorpholines

BY T. A. GEISSMAN, MURRAY BASSIN AND ERNEST J. ZEILBERGER

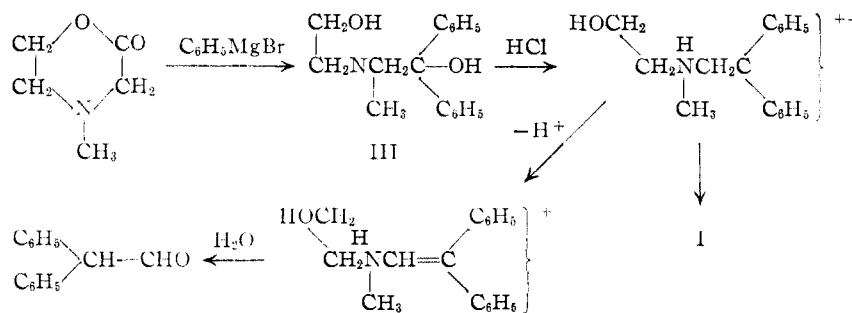
The recent description of the preparation of 4-methyl-2,2-diphenylmorpholine (I) by the reduction of 3-keto-4-methyl-2,2-diphenylmorpholine<sup>1</sup>

(1) A. L. Morrison, R. F. Long and M. Königstein, *J. Chem. Soc.*, 952 (1951).

prompts us to report our preparation of I, which may be considered as a cyclic form of the anti-histaminic  $\beta$ -dimethylaminoethyl benzhydryl ether ("Benadryl" base), and of the *p*-tolyl analog (II) by a procedure different from that used by the English workers.



The reaction of the lactone of N-methyl-N- $\beta$ -hydroxyethyl-glycine<sup>2</sup> with phenylmagnesium bromide and with *p*-tolylmagnesium bromide led in the first case to 1,1-diphenyl-2-(methyl- $\beta$ -hydroxyethylamino)-ethanol (III). The corresponding *p*-tolyl compound was isolated but not characterized, being converted directly into II. The carbinol III showed a surprising reluctance to cyclize to I: it could be distilled at 10 mm. without change, but upon boiling with 6 *N* hydrochloric acid it was converted slowly into the morpholine. The structures of the compounds were demonstrated by (a) the formation of diphenylacetaldehyde from III during the treatment with acid, and (b) the formation of benzophenone-4,4'-dicarboxylic acid from II on oxidation.



Compound I, when tested for its activity against aerosolized histamine in guinea pigs, was found to be devoid of activity up to a dose level of 20 mg./kg.<sup>3</sup>

#### Experimental

4-Methylmorpholone-2 was prepared as described by Kiprianov.<sup>2</sup>

1,1-Diphenyl-2-(methyl- $\beta$ -hydroxyethylamino)-ethanol (III).—To the Grignard reagent prepared from 118 g. of bromobenzene in ether was added slowly an ether solution of 35 g. of 4-methylmorpholone-2. After an hour refluxing the mixture was decomposed with iced sulfuric acid and the ether layer separated. The ether solution was washed with dilute sulfuric acid and the combined aqueous solutions were basified with dilute sodium hydroxide. The colorless crystalline product which separated was recrystallized from ether-petroleum ether and from ethanol. It formed colorless prisms (31 g.), m.p. 110–111°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>21</sub>O<sub>2</sub>N: C, 75.22; H, 7.82. Found: C, 75.32, 75.43; H, 7.87, 7.82.

(2) A. Kiprianov, *Ukrain. Khim. Zhur.*, **4**, Sci. pt., 231 (1929); *C. A.*, **24**, 1084 (1930).

(3) The authors are indebted to Dr. E. J. Fellows, Smith, Kline and French Laboratories, for the pharmacological tests.

The hydrochloride formed white prisms (from alcohol-ether), m.p. 157–158°. Calcd.: neut. equiv., 271. Found: neut. equiv., 267, 270.

The free base was distilled at 10 mm. It distilled cleanly and completely without change: the recrystallized distillate had m.p. and mixed m.p. 110–111°.

Attempts to prepare a crystalline *p*-nitrophenylurethan and *p*-nitrobenzoate were unsuccessful. The hydroxamic acid test on the acetylated material was positive.

**4-Methyl-2,2-diphenylmorpholine (I).**—A solution of 5.0 g. of the carbinol III in 100 ml. of 6 *N* hydrochloric acid was boiled under reflux for 4 hours. The solution was cooled and the small amount of acid-insoluble oily material taken up in ether.

The aqueous layer was made alkaline with sodium hydroxide. The colorless oil (4.7 g.) which separated crystallized on cooling; it was separated and purified by recrystallization from aqueous methanol. The morpholine formed colorless leaflets, m.p. 79.5–80° (reported<sup>1</sup> 79–80°).

*Anal.* Calcd. for C<sub>17</sub>H<sub>19</sub>ON: C, 80.58; H, 7.58. Found: C, 80.65; H, 7.84.

The methiodide formed colorless leaflets, m.p. 263–264° dec. (from methanol).

*Anal.* Calcd. for C<sub>18</sub>H<sub>22</sub>ONI: C, 54.67; H, 5.63. Found: C, 54.89; H, 5.96.

The picrate formed yellow needles, m.p. 234–236° dec.

*Anal.* Calcd. for C<sub>23</sub>H<sub>22</sub>O<sub>8</sub>N<sub>4</sub>: C, 57.27; H, 4.62. Found: C, 57.35; H, 4.99.

The acid-insoluble material removed by ether extraction of the original reaction mixture was recovered by removal of the ether. The oil which remained was treated with hydroxylamine hydrochloride and aqueous sodium hydroxide and the oxime which formed was recrystallized from alcohol. The colorless needles melted at 105–107° (reported<sup>4</sup> for diphenylacetaldoxime, m.p. 106°). The oxime was heated for 3 hours with acetic anhydride and the resulting nitrile hydrolyzed by further heating after the addition of 18 *N* sulfuric acid. The diphenylacetic acid which resulted was purified by recrystallization and melted at 144–145° (lit.<sup>5</sup> m.p. 145–146°).

**4-Methyl-2,2-di-*p*-tolylmorpholine (II).**—The crude carbinol resulting from the reaction between 4-methylmorpholine-2 and *p*-tolylmagnesium bromide was a waxy solid which was converted directly into the morpholine. A solution of 20 g. of this material in 400 ml. of 6 *N* hydrochloric acid was distilled until about 150 ml. of distillate had been collected. The residual solution was made alkaline with sodium hydroxide and extracted with ether. The red oil remaining after removal of the ether was distilled under reduced pressure, yielding 15 g. of a pale yellow distillate which crystallized upon standing. Recrystallization from aqueous methanol afforded colorless prisms, m.p. 76–77.5°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>22</sub>ON: C, 81.10; H, 8.25. Found: C, 81.25; H, 8.28.

The picrate formed bright yellow needles, m.p. 209–210° dec.

*Anal.* Calcd. for C<sub>25</sub>H<sub>26</sub>O<sub>8</sub>N<sub>4</sub>: C, 58.81; H, 5.13. Found: C, 58.70; H, 5.43.

The methiodide formed colorless leaflets (from methanol-ether), m.p. 251–252°.

*Anal.* Calcd. for C<sub>20</sub>H<sub>26</sub>ONI: C, 56.74; H, 6.19. Found: C, 56.46; H, 6.22.

(4) A. Klages and J. Kessler, *Ber.*, **39**, 1753 (1906).

(5) R. Symons and Th. Zincke, *Ann.*, **171**, 122 (1873).

DEPARTMENT OF CHEMISTRY  
UNIVERSITY OF CALIFORNIA  
LOS ANGELES 24, CALIFORNIA

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## Chromones. VI. The Synthesis of Khellol

BY T. A. GEISSMAN AND JAMES W. BOLGER

Of the three chromones occurring in the fruit of *Ammi visnaga*, khellin (I) and visnagin (II) have been synthesized.<sup>1</sup> Khellol (III), the gluco-

(1) For references to the literature, see T. A. Geissman and T. G. Hallsall, *THIS JOURNAL*, **73**, 1280 (1951).

side of which accompanies the two methylchromones in the plant, has now been prepared starting with visnaginone benzyloxyacetate (IV). Rearrangement of IV with the aid of sodium hydride in pyridine followed by treatment of the product with hydrochloric acid under conditions which brought about both ring closure of the intermediate (uncharacterized) diketone and debenzoylation of the benzyloxymethyl residue, afforded khellol. The identity of the synthetic material with the natural substance was established by direct comparison (m.p. and mixed m.p.), the preparation of the acid succinate<sup>2</sup> and by comparison of the absorption spectra of the natural and synthetic samples (Fig. 1).

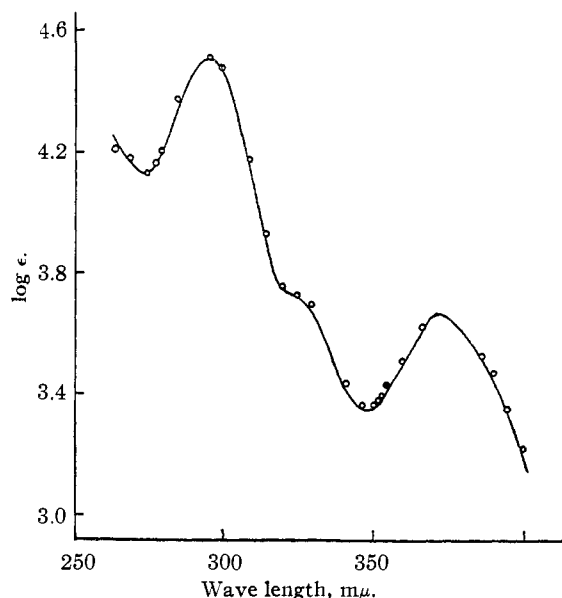
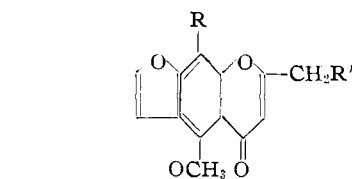
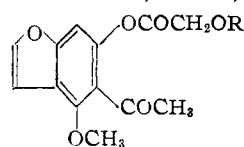


Fig. 1.—Ultraviolet absorption spectrum of khellol: solid line, natural, from khellol glucoside; circles, synthetic material; solvent, 95% ethanol.

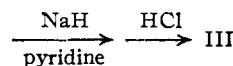
In preliminary experiments, the model compounds 2-benzyloxymethylchromone and 2-hydroxymethylchromone were prepared for the purpose of studying the conversion of the benzyl ether into the hydroxy compound. Cleavage with sulfuric or hydrochloric acid was found to proceed satisfactorily. Catalytic debenzoylation was ex-



I, R = OCH<sub>3</sub>, R' = H  
II, R = H, R' = H  
III, R = H, R' = OH



IV, R = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>  
V, R = COCH<sub>3</sub>



(2) T. A. Geissman, *ibid.*, **73**, 3355 (1951).