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[1] 79–80°).

Anal. Calcd. for $C_{17}H_{19}ON$: 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 $C_{18}H_{22}ONI$: 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 $C_{23}H_{22}O_8N_4$: 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[4] 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.[5] m.p. 145–146°).

4-Methyl-2,2-di-*p*-tolylmorpholine (II).—The crude carbinol resulting from the reaction between 4-methylmorpholone-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 $C_{19}H_{22}ON$: 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 $C_{25}H_{26}O_8N_4$: 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 $C_{20}H_{26}ONI$: 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).

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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.[1] Khellol (III), the glucoside of which accompanies the two methylchromones int he 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 debenzylation 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[2] and by comparison of the absorption spectra of the natural and synthetic samples (Fig. 1).

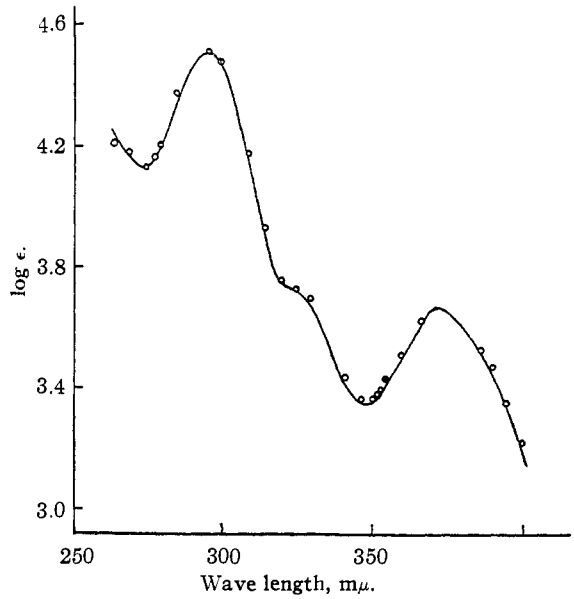
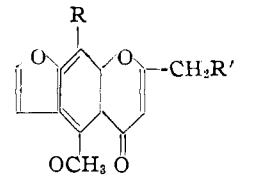
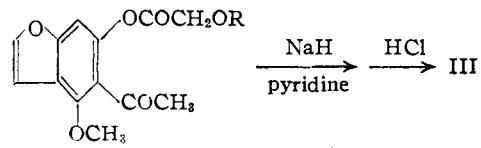


Fig. 1.—Ultraviolet absorption spectrum of khellol: solid line, natural, from khellol glucoside; circles, synthetic material; solvent, 95% ethanol.

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 debenzylation was ex-



I, R = OCH_3, R′ = H
II, R = H, R′ = H
III, R = H, R′ = OH



IV, R = $CH_2C_6H_5$
V, R = $COCH_3$

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

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

amined briefly and found to give a mixture of substances, probably as the result of hydrogenation of the other potentially reducible structural elements of the molecule.

The use of the acetoxyacetate (V) of visnaginone was also found to afford a means of introducing the chromone ring containing the 2-hydroxymethyl substituent, and khellol was prepared by this method as well.

Since the synthesis of visnaginone from phloroglucinol has been accomplished,[3] the present work constitutes a total synthesis of khellol.

Experimental

Visnaginone Benzyloxyacetate (IV).—A mixture of 3.0 g. of vignaginone, 3.23 g. of benzyloxyacetyl chloride[4] and 14 ml. of pyridine was allowed to stand at room temperature for 18 hours and poured into iced dilute hydrochloric acid. The oily product was taken up in ether, the solution treated with Norite and evaporated. The oily residue crystallized when rubbed with methanol. After several recrystallizations from methanol the ester formed colorless crystals with m.p. 80–81°.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.45; H, 5.26.

Visnaginone Acetoxyacetate (V).—To a cold (0°) solution of 2.15 g. of visnaginone in 10 ml. of pyridine was added 5.0 g. of acetoxyacetyl chloride.[5] The mixture was kept at 0° for two hours and poured into iced dilute hydrochloric acid. The dark, viscous crude product was extracted several times with Skellysolve C (b.p. 85–100°), from which was obtained 150 ml. of colorless crystals, m.p. 88–90°.

Anal. Calcd. for $C_{15}H_{14}O_7$: C, 58.82; H, 4.61. Found: C, 58.90; H, 4.84.

Khellol (from IV).—A mixture of 4.0 g. of visnaginone benzyloxyacetate (IV), 0.27 g. of sodium hydride and 15 ml. of anhydrous pyridine was refluxed until the sodium hydride had dissolved (15 min.). The reaction mixture was cooled and poured into iced hydrochloric acid (15 ml.); a yellow oil separated. The aqueous solution was decanted and the oil taken up in ether and washed with dilute hydrochloric acid. Removal of the ether left a yellow oil which was heated for one hour with concentrated hydrochloric acid on the steam-bath. The resulting aqueous solution was filtered (sintered glass), diluted and cooled. Repetition of the acid treatment of the unreacted oil yielded additional material. The cooled aqueous solution deposited a pink crystalline material which was recrystallized several times from boiling water. Continuous ether extraction of the acidic mother liquors afforded an additional amount of khellol, the total being 0.41 g. The recrystallized material melted at 176–178°, and a mixture of this with khellol (m.p. 176–178°) prepared from khellol glucoside melted at 176–179° (lit.[6] 178–179°).

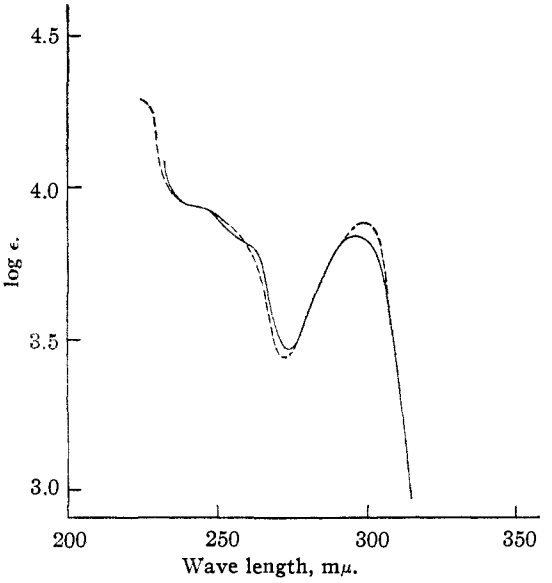


Fig. 2.—Ultraviolet absorption spectrum of 2-methylchromone (solid line); and 2-hydroxymethylchromone (dotted line); solvent 95% ethanol.

Anal. Calcd. for $C_{18}H_{10}O_5$: C, 63.41; H, 4.09. Found: C, 63.18; H, 4.18.

The absorption spectra of the natural and synthetic materials are shown in Fig. 1.

Khellol Acid Succinate.—A mixture of 100 mg. of synthetic khellol, 100 ml. of succinic anhydride and 3 ml. of pyridine was allowed to stand overnight. The mixture was poured onto iced dilute hydrochloric acid and the solid product collected and recrystallized from dilute acetic acid. The colorless crystals melted at 195–197°; mixed with a sample (m.p. 195–197°) prepared from natural khellol,[2] m.p. 195–197°.

Anal. Calcd. for $C_{17}H_{14}O_8$: C, 58.96; H, 4.07. Found: C, 58.79; H, 4.28.

***o*-(Benzyloxyacetoxy)-acetophenone.**—A solution of 20.0 g. of benzyloxyacetic acid in 14.5 ml. of thionyl chloride was refluxed for two hours. The excess thionyl chloride was removed (at 10 mm. and 60°) and to the residual acid chloride was added 13.5 g. of *o*-hydroxyacetophenone and 40 ml. of pyridine. The resulting solution was allowed to stand for 16 hours, and poured onto ice. The oily product was taken up in ether and the ether solution washed with water, dried, treated with Norite and evaporated. The oily residue crystallized on cooling and after recrystallization from methanol-petroleum ether (b.p. 60–70°) formed colorless crystals, m.p. 38–39.5° (17.0 g.).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.10; H, 5.22. Found: C, 71.27; H, 5.60.

2-(Benzyloxymethyl)-chromone.—A solution of 6 g. of *o*-(benzyloxyacetoxy)-acetophenone in 90 ml. of dioxane was heated with 0.5 g. of sodium hydride. The mixture was warmed to 70° to start the reaction, then allowed to stand without further heating until all the sodium hydride had dissolved (20 min.), leaving a clear solution. Ice and dilute hydrochloric acid were added and the bulk of the solvents removed *in vacuo* at about room temperature. The oily residue was taken up in ether and the washed and Norite-treated ether solution shaken mechanically with 150 ml. of a saturated aqueous solution of copper acetate. The copper complex (3 g.) was collected and washed with ether.

A mixture of 5 g. of the copper complex, 50 ml. of 1 *N* hydrochloric acid and 100 ml. of ether was shaken until the copper complex was decomposed. The ether solution, after washing, decolorization with Norite, and drying, was evaporated, leaving a nearly colorless oil, presumably *o*-hydroxybenzoyl-(benzyloxyacetyl)-methane. The crude diketone was dissolved in a mixture of 5 ml. of methanol and 5 ml. of concentrated hydrochloric acid. A solid, presumably the oxonium salt of the chromone (see below), separated, and after ten minutes was collected on a filter and washed with ether. Upon washing with water the crystalline salt decomposed, forming an oil which quickly crystallized. The crystalline material was dissolved in ether, and the solution was decolorized with Norite and evaporated to dryness, leaving 1.8 g. of a white, crystalline solid. This was recrystallized from aqueous methanol to yield the colorless chromone, m.p. 64–65°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.53; H, 5.31.

2-(Hydroxymethyl)-chromone.—A mixture of 0.2 g. of 2-(benzyloxymethyl)-chromone and 5 ml. of concentrated sulfuric acid was warmed on the steam-bath for 20 minutes and poured into 20 ml. of water. Extraction of the resulting solution with ether (four 20-ml. portions) and evaporation of the ether afforded 90 mg. of a crystalline solid which after recrystallization from methanol-petroleum ether (b.p. 20–40°) melted at 165–166.5° (with slight decomposition).

(3) T. A. Geissman and E. H. Hinreiner, THIS JOURNAL, **73**, 782 (1951).

(4) H. O. L. Fischer and B. Gohlke, *Helv. Chim. Acta*, **16**, 1130 (1933).

(5) R. Anschütz and W. Bertram, *Ber.*, **36**, 466 (1903).

(6) E. Späth and W. Gruber, *ibid.*, **74B**, 1549 (1941).

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.16; H, 4.58. Found: C, 67.82; H, 4.68.

The absorption spectra of the chromone and of 2-methylchromone are shown in Fig. 2.

The benzyl group of the benzyloxymethyl chromone could also be removed by treatment with hot, concentrated hydrochloric acid. An attempt to bring about the debenzylation by catalytic hydrogenation over 10% Pd–charcoal was unsuccessful: the uptake of hydrogen showed no distinct change after one mole had been absorbed, and no definite product was isolated when the experiment was interrupted at that point.

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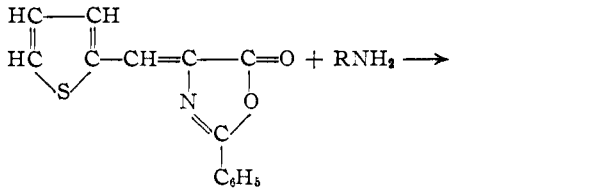
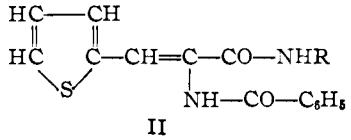
Aminolysis and Alcoholysis of a Thiophene Azlactone

BY ROBERT J. GIBBS,[1] SERGE N. TIMASHEFF AND F. F. NORD

When studying the interaction[2] of egg albumin with 2-phenyl-4-(2-thenal)-5-oxazolone (I) recently synthesized[3,4] from 2-thenaldehyde, it was observed that the azlactone reacts readily with the amino groups of the protein. It was therefore decided to investigate the behavior of the azlactone in the presence of a variety of compounds containing a primary amino group, inasmuch as this is by far the predominant group of this type in the protein. Under the experimental conditions employed, the expected[5] reaction is



I



II

Applying an earlier method,[6] it was possible to react I stoichiometrically with *n*-octylamine in ethanol to obtain the *n*-octylamide of α-benzamido-β-2-thienylacrylic acid (II, R = C_8H_{17}) in quantitative yield.[2] Similarly, 1-phenyl-2-aminopropane, 1-(2-thienyl)-2-aminopropane and 2-aminothiazole produced the expected amides, also in excellent yield. However, cytosine was found to be unreactive.

Aniline was treated in two ways, with ethanol and excess aniline, respectively, as solvents. The yellow crystalline substance obtained, however, was found to be merely the unreacted azlactone with some aniline physically adsorbed to it. This finding is of special interest, in view of the fact that aniline easily reacts with similar benzene analogs of the thiophene azlactone,[6] using the same two methods as above.

With 2-aminopyridine, and its 3- and 6-methyl analogs, reaction products were obtained which did not analyze properly for the respective amides. Further investigation showed that all three pyridines gave the same product, *i.e.*, the ethyl ester of the acrylic acid. This compound has been previously prepared[7] by treating the azlactone with ethanol in the presence of sodium ethoxide. The chemical identity of the three pyridine reaction products with the ethyl ester was demonstrated in three ways: (1) the analyses for carbon, hydrogen and nitrogen were within the range of the ethyl ester; (2) the melting points were the same as reported[7] for the ethyl ester, and mixed melting points of the products with one another, and with an authentic sample of the ester, gave no change in melting point; (3) ultraviolet spectra of the three products were sensibly identical, and fitted that of the ester (see Table I).

TABLE I

ABSORPTION MAXIMA AND MOLECULAR EXTINCTION COEFFICIENTS OF THE OXAZOLONE AND ITS DERIVATIVES

Compound	Maxima mμ	ε × 10⁻³
2-Phenyl-4-(2-thenal)-5-oxazolone[a]	269–270	15.1
	394	36.6
α-Benzamido-β-2-thienylacrylic acid	227	13.8
	306–307	14.9
B-t-acrylic acid methyl ester	Below 233	..
	315	18.8
B-t-acrylic acid ethyl ester[b]	Below 233	..
	315	18.8
B-t-acrylic acid ethyl ester[c]	229	13.9
	314	19.2
B-t-acrylic acid ethyl ester[d]	228–229	14.1
	314	19.4
B-t-acrylic acid ethyl ester[e]	228–229	14.1
	314	19.4
B-t-acrylic acid thiazolyl amide	223	16.4
	329–330	25.7
B-t-acrylic acid phenylisopropyl amide	230	15.3
	309	17.3
B-t-acrylic acid thienylisopropyl amide	230	18.0
	309–310	14.7
B-t-acrylic acid octyl amide	230	15.0
	309	19.2

[a] Ref. 3c. [b] Prepared using sodium ethoxide. [c] Prepared using 2-aminopyridine. [d] Prepared using 2-amino-3-methylpyridine. [e] Prepared using 2-amino-6-methylpyridine. B-t refers to α-benzamido-β-2-thienyl.

In the present case, it is obvious that the pyridineamines, being strong bases, act catalytically on the alcoholysis of the azlactone, so much so that the ester is formed in preference to the expected amide. However, an investigation of the available literature has disclosed no other case where alcoholysis of an azlactone occurred in preference to aminolysis. In fact, alcohols are often used as solvents for the latter reaction.[5]

(1) Predoctoral fellow of the Atomic Energy Commission.

(2) S. N. Timasheff and F. F. Nord, *Arch. Biochem. Biophys.*, **31**, 320 (1951).

(3) (a) G. Barger and A. P. T. Easton, *J. Chem. Soc.*, 2102 (1938); (b) B. F. Crowe and F. F. Nord, *Nature*, **163**, 876 (1949); (c) B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 81 (1950).

(4) S. N. Timasheff and F. F. Nord, THIS JOURNAL, **73**, 2390 (1951).

(5) H. E. Carter, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946. p. 198.

(6) C. Gränacher and G. Gulbas, *Helv. Chim. Acta*, **10**, 819 (1927).

(7) B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 1177 (1950).