Experimental Part

1,3-Dimethylphloroglucinol was prepared from trinitro-*m*-xylene.[5]

Acylation of 1,3-dimethylphloroglucinol was carried out after the method employed by Karrer.[6] Dimethylphloroacetophenone, m.p. 221–222°. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.4; H, 6.18. Found: C, 60.9; H, 6.19. Dimethylphlorobutyrophenone, m.p. 140°. *Anal.* Calcd. for $C_{12}H_{16}O_4$: C, 64.4; H, 7.20. Found: C, 64.2; H, 7.29.

Air Oxidation of Dimethylacylphloroglucinol.—One mole of phlorophenone was dissolved in twenty times its weight of methanol, and a solution of one mole of lead acetate in an equal volume of methanol was added. This solution on agitation in an atmosphere of oxygen absorbed one mole of oxygen rapidly with evolution of heat and production of a yellow precipitate. After one hour, the precipitate was filtered off, washed with methanol, and decomposed by shaking with excess aqueous 6 *N* sulfuric acid and ether. The ether layer was separated, dried and evaporated. The residue was recrystallized once from aqueous methanol. The two compounds prepared were nicely crystalline light yellow solids, obtained in 30–50% yields, based on the acyldimethylphloroglucinol. Butyro-3,5-dimethyl-2,3-dihydroxy-4,6-diketocyclohexene-1, m.p. 104.5–105.0. *Anal.* Calcd. for $C_{12}H_{16}O_4$: C, 56.7; H, 5.70. Found: C, 56.7; H, 5.81. Aceto-3,5-dimethyl-2,3-dihydroxy-4,6-diketocyclohexene-1, m.p. 150.5–151.5. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 60.0; H, 6.67. Found: C, 60.0; H, 6.74.

Absorption Spectra.—The spectra of the two synthetic analogs are shown in Fig. 1, compared with the spectrum of humulon itself.

Acknowledgments.—We wish to thank Dr. John Carson for a sample of humulon and Miss Geraldine Secor and Mrs. Mary Kilpatrick for the carbon–hydrogen analyses reported here.

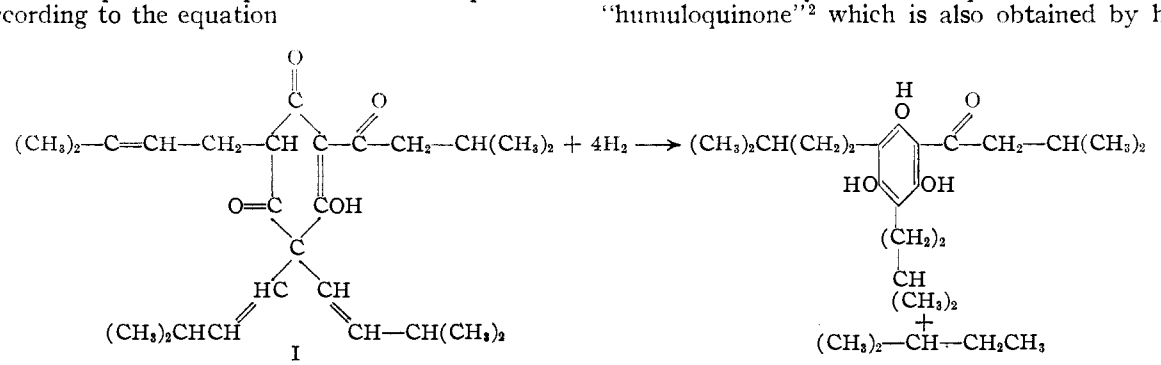
WESTERN REGIONAL RESEARCH LABORATORY[7]
ALBANY, CALIF. RECEIVED SEPTEMBER 12, 1950

(5) H. Weidel and F. Wenzel, *Monatsh.*, **19**, 249 (1898).
(6) P. Karrer, *Helv. Chim. Acta*, **2**, 473 (1917).
(7) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

The Hydrogenation of Lupulone and Humulone

BY J. F. CARSON

In connection with investigations of the antibiotic properties of hop constituents, the hydrogenation of lupulone and humulone has been studied. Wöllmer[1] found that hydrogenation of lupulone (I) in the presence of palladium chloride proceeds according to the equation



I

Wieland[2] observed that humulone, in which one gem isopentenyl group of I is replaced by a tertiary hydroxyl group, under the same conditions absorbed 3 moles of hydrogen and split out isopentane to yield a disubstituted 1,2,3,5-tetrahydroxybenzene derivative.

We have found that hydrogenation of lupulone in methanol in the presence of palladium-on-charcoal or of platinum oxide yields a crystalline compound, hexahydrolupulone. Ultraviolet absorption spectra of the reduced compound show that no significant amounts of phloroglucinol derivatives are formed and that hydrogenolysis does not occur under these conditions.

Hexahydrolupulone has the same characteristic ring structure as lupulone and differs structurally only in that the three exocyclic olefinic double bonds are saturated as is shown by the following evidence: 3.0–3.3 moles of hydrogen are absorbed in reduction in contrast to 3.8–4.0 observed when palladium chloride is the catalyst. The ultraviolet absorption spectrum in alkaline methanol (max. ϵ_{molar} = 20,400 at 3555 Å.) is almost identical with that of lupulone.[3] Potentiometric titration in 80% methanol to *p*H 9.0 gives the neutralization equivalent 419 (calcd., 420.6). Titration of lupulone under the same conditions gives the neut. equivalent 409 (calcd. 414). Both lupulone and the hexahydro derivative have practically superimposable titration curves in 80% methanol with the pk_a (*p*H $^1/_2$ neut.) = 5.8–5.85. Carbon–hydrogen analyses agree closely with hexahydrolupulone.

The difference in the catalysts, palladium chloride and palladium-on-carbon, cannot be explained merely by the presence of hydrochloric acid produced by reduction of the former, since addition of hydrochloric acid to palladium-on-carbon prior to reduction did not alter the course of the reduction. Tetrahydrohumulone, on the other hand, could not be prepared by hydrogenation of humulone in the presence of platinum oxide or palladium-on-carbon. The reduction was always accompanied by appreciable hydrogenolysis of the isopentenyl group and complex mixtures were obtained. Absorption spectra of the hydrogenated solutions showed no evidence of the characteristic absorption of humulone or of tetrahydrohumulone. On exposure to air, the reduced solutions yielded small quantities of the red "humuloquinone"[2] which is also obtained by hydrogenating humulone in the presence of palladium chloride followed by air oxidation.

(1) W. Wöllmer, *Ber.*, **58**, 675 (1925).
(2) H. Wieland, *ibid.*, **58**, 110 (1925).
(3) J. C. Lewis, *et al.*, Antibacterial Agents from Hops, mimeographed circular of information (A.I.C.-231), Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture, April, 1949.

Hexahydrolupulone is more stable to air than lupulone. Samples of the latter resinify after a few days exposure to the atmosphere at 20–25°, while the hexahydro derivative is stable for several months under these conditions. It is less soluble in organic solvents than lupulone and the sodium salt has a lower solubility in water than the salt of lupulone. Hexahydrolupulone was found to be 6–8 times as active as lupulone on bacteriostatic *in vitro* tube assay to *Streptococcus faecalis* and to *Staphylococcus aureus*.[4] The compound is inactive in the presence of serum. It is equally as active as lupulone against *Mycobacterium tuberculosis* (H37Rv)[5] but is inactive to mouse tuberculosis.[6]

Experimental

Lupulone and humulone were isolated from hops by the procedure of Lewis, *et al.*[3,7]

Hydrogenation of Lupulone.—Lupulone (m.p. 93–94°) 822 mg. and 250 mg. of palladium-on-charcoal[8] in 40 ml. of methanol were shaken with hydrogen at atmospheric pressure and 26° for 30 minutes when the absorption of hydrogen became very slow (141.6 cc. (S.T.P.) equivalent to 3.2 moles per mole of lupulone). In a second experiment, 818 mg. of lupulone and 25 mg. of platinum oxide (Adams catalyst) in 40 ml. of methanol were shaken with hydrogen for 45 minutes when reduction was complete. The absorption of hydrogen, 133.5 cc. (S.T.P.) was equivalent to 3.0 moles per mole of lupulone.

On a larger scale 11 g. of lupulone and 3 g. of palladium-on-carbon in 250 ml. of methanol were shaken in a Parr hydrogenation apparatus at 25 lb./sq. in. and 25° for 90 minutes. Removal of catalyst and concentration of the solution *in vacuo* to 50 ml. followed by the addition of 10 ml. of water yielded 8.7 g. (78% yield) of crystalline material, m.p. 134–137°. Recrystallization from hexane and then from methanol at −10° gave hexahydrolupulone, m.p. 140–141°. *Anal.* Calcd. for $C_{26}H_{44}O_4$: C, 74.24; H, 10.54. Found[9]: C, 73.9; H, 10.4.

When aqueous palladium chloride was used, the results of Wöllmer[1] were completely confirmed. The crude reduction product had an absorption spectrum very similar to that of 3,5-dimethylphloroacetophenone[10] and oxidation with air in the presence of lead acetate in methanol yielded tetrahydrohumulone, m.p. 82–83°.

The Hydrogenation of Humulone.—Humulone (1.048 g.) and 600 mg. of palladium-on-carbon in 35 ml. of methanol were shaken with hydrogen for 1 hour when absorption became very slow (hydrogen uptake = 153 cc. (S.T.P.) equivalent to 2.4 moles of hydrogen per mole of humulone). The reduced solution, initially green, rapidly turned red on exposure to air and on concentration *in vacuo* yielded humuloquinone,[2] m.p. 60–61°, in 5% yield. Platinum oxide gave similar results. The use of smaller quantities of catalyst or termination of the reduction before hydrogen absorption was complete failed to yield tetrahydrohumulone as judged by the absorption spectra of the solutions.

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(4) I am indebted to L. E. Sacks of this Laboratory for these measurements.

(5) These tests were performed by Y. C. Chin and H. H. Anderson of the University of California Medical School, San Francisco, Calif.

(6) Personal communication from F. G. Jones, Eli Lilly Co., Indianapolis, Indiana.

(7) J. C. Lewis, *et al.*, *J. Clin. Invest.*, (Pt. 1), **28**, 916 (1949).

(8) 5% palladium-on-activated charcoal powder, Baker & Co., Newark, N. J. Mention of this product does not imply that it is endorsed or recommended by the Department of Agriculture over others of a similar nature not mentioned.

(9) I am indebted to Miss G. E. Secor for carbon–hydrogen analyses.

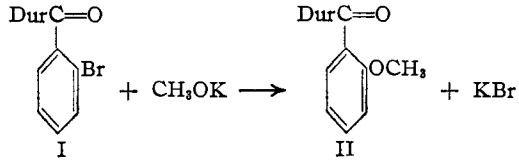
(10) T. W. Campbell and G. M. Coppinger, to be published. Absorption spectra were determined by G. M. Coppinger of this Laboratory.

Methanolysis of Carbonyl-Activated Aryl Bromides

BY REYNOLD C. FUSON AND WILLIAM C. HAMMANN[1]

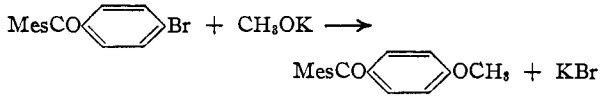
In a search for a convenient method of preparing *o*-methoxybenzoyldurene (II) we were led to attempt alkali-catalyzed methanolysis of the corresponding bromo compound (I). Alcoholysis of aromatic halogen compounds, usually difficult to effect, is known to proceed readily when a nitro group is in an ortho or para position.[2] However, when a keto group is in an ortho or para position, alcoholysis has not been realized, presumably because of involvement of the carbonyl group.[3] It was to be expected that the behavior of ortho and para bromo derivatives of highly hindered ketones would resemble that of the corresponding bromo nitro compound since the ketone group would be protected from attack.

Experiments with *o*-bromobenzoyldurene and with *m*- and *p*-bromobenzoylmesitylene have shown this surmise to be accurate. The *o*-bromo ketone, when heated with a 4.7 *N* potassium methoxide solution for one hour, suffered quantitative displacement of the halogen and gave the corresponding methoxy ketone (II) in a 95% yield.



I II

Under similar conditions *p*-bromobenzoylmesitylene gave *p*-methoxybenzoylmesitylene in a yield of 94%.



m-Bromobenzoylmesitylene reacted sluggishly and in a different manner. A 48-hour period of heating with a 6.0 *N* solution of potassium methoxide sufficed to remove 78% of the bromine, the product being benzoylmesitylene. By contrast, *o*-bromobenzophenone reacted with a 5.3 *N* potassium methoxide solution to yield a mixture containing benzophenone and probably benzohydrol. At the reflux temperature a vigorous reaction took place, and at the end of a 30-minute period of heating, 97% of the bromine had been displaced.

It is known that 4-chloro- and 4-bromobenzophenone react slowly with 3.6 molal ethanolic potassium hydroxide without loss of halogen to yield the corresponding benzohydrol, while 2,4,6-tribromobenzophenone yields 4-bromobenzohydrol.[3]

Thus it appears that the facility with which methanolysis of *o*- and *p*-bromo hindered benzophenones occurs in the presence of potassium methoxide does not extend to the corresponding meta derivatives or to unhindered bromobenzophenones.

(1) Rohm and Haas Fellow, 1950–1951.

(2) See L. C. Raiford and J. C. Colbert, THIS JOURNAL, **48**, 2652 (1926).

(3) M. P. J. Montagne, *Rec. trav. chim.*, **27**, 327 (1908).