1-(3′,4′-Dimethoxyphenyl)-isopropylamine.—B.p. 163–165° (18 mm.),[14] yield 83%, n^{25}_D 1.5328.

The amides of Table I, their intermediate acids, the isoquinolines of Table II and their salts, Table III, were prepared according to the methods described in the previous papers in this series.

6,7-Dimethoxy-1-(4′-ethoxy-3′-methoxybenzyl)-3-methylisoquinoline Phosphate.—A sample of this compound prepared in the usual manner utilizing an excess of phosphoric acid yielded a salt of m.p. 197–199° which analyzed unexpectedly high for phosphorus. The following more closely controlled conditions were found to be typical of a number of preparations:

Twenty grams (0.0545 mole) of 6,7-dimethoxy-1-(4′-ethoxy-3′-methoxybenzyl)-3-methylisoquinoline was dissolved in 200 ml. of hot 95% ethanol. Six and three-tenths grams (0.0545 mole) of 85% phosphoric acid was added rapidly with stirring. The salt precipitated readily. The crystalline suspension was chilled, filtered and rinsed with ethanol to yield 18.8 g. of the salt, m.p. 197–199°, unchanged on recrystallization from dilute alcohol. Calculated on the basis of phosphoric acid, this yield represented 98.7% of the theory in view of the analysis.

Anal. Dried at 100° for 3 hours *in vacuo* over phosphorus pentoxide. Calcd. for $C_{22}H_{25}NO_4\cdot{}^1/_2H_3PO_4\cdot{}^1/_2H_2O$: C, 50.48; H, 5.87; N, 2.68; P, 8.88. Found: C, 50.75; H, 5.91; N, 3.03; P, 8.88.

Concentration of the original mother liquor yielded a second crop of material weighing 5.8 g. It had a melting point of 121–122° which was not depressed when mixed with a sample of the original base. This therefore represented 86% of the unreacted base.

When the above procedure was repeated except that 10 g. (0.087 mole, or 1.6 moles of acid per mole of base) of phosphoric acid was employed, a salt identical with the above was obtained in 96.5% yield.

Acknowledgment.—The authors are indebted to Mr. W. L. Brown and his associates for the analyses and to Drs. H. M. Lee and R. E. Shipley for the pharmacological evaluation of these compounds.

INDIANAPOLIS, INDIANA

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[14] C. Mannich and W. Jacobsohn, *Ber.*, **43**, 189 (1910).

[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY][1]

The Alkaline Isomerization of Humulone

BY J. F. CARSON

RECEIVED MARCH 18, 1952

The isomerization of humulone (an antibiotic and flavoring component of hops) in alkaline methanol yields complex mixtures from which three crystalline isomers of humulone have been isolated in small yield. On the basis of evidence of chemical reactions and of absorption spectra, two of the compounds are best represented by structure II and the third by structure III. The three compounds are not bitter and are bacteriostatically inactive to several test organisms. In addition to the crystalline components, an oil is isolated consisting of at least two non-crystallizing components and a crystalline fraction. The two oily fractions are bacteriostatically inactive and intensely bitter. These structures have not been elucidated but they appear to be closely related to the crystalline isomers on the basis of chemical reactions and absorption spectra.

In connection with the investigation of antibiotic materials from hops related to humulone and lupulone, the alkaline rearrangement of humulone I[2] has been studied.

Verzele and Govaert[3] reported that refluxing a solution of humulone in absolute methanol containing sodium hydroxide yielded an oil which was named isohumulone. The material was considered interesting not only as a possible intermediate in the transformation of humulone (I) to humulinic acid (IV) or V,[4] but also as an important flavoring component or bitter principle of beer contributed by the humulone of hops.[5] Verzele and Govaert[3] proposed the structure II for the oil with the double bond of the chain attached to C_4 in the α,β-position rather than β,γ to the carbonyl group as shown. The product was characterized only by the equivalent weight, and the structure II was based on the evidence of equivalent weight, 362, the absorption of two moles of hydrogen catalytically to yield a tetrahydro derivative and degradation by aqueous alkali to yield humulinic acid and isobutyraldehyde.

Investigations in this Laboratory have shown that for rearrangement to occur in methanol, there must be an excess of alkali beyond that needed for the neutralization of the humulone. No reaction occurs when a methanolic solution of the sodium salt of humulone is refluxed for six hours. However, solutions of the sodium or potassium salt of humulone in methanol containing sodium hydroxide, potassium hydroxide, or sodium methylate in concentrations of 0.02–0.075 *N* when refluxed three to six hours yield oils in practically quantitative yields having equivalent weights from 370–380. That the humulone has been completely transformed is shown by the failure to yield an insoluble lead salt or *o*-phenylenediamine complex. From the oil, white crystalline material can be obtained in yields of 15–18%. Fractional crystallization from methanol separates the crude crystalline fraction into a less soluble levorotatory isomer and a more soluble dextrorotatory isomer. Fluorescent chromatography of the mother liquor yields a very

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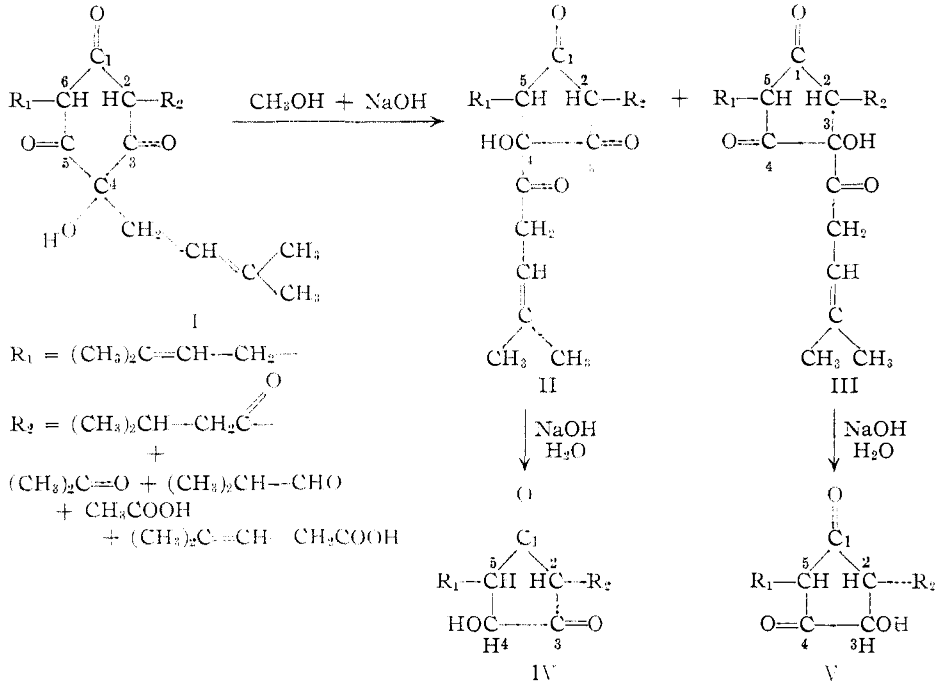
[1] Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

[2] The structures for humulone and its degradation products are here written in the keto form rather than the enolic form. There is little reason to select the C_3-carbonyl of humulone as the enol, as is customary, in preference to the C_1-carbonyl, since either enol can form a hydrogen bridge with the keto group of R_2 to give a six-member ring. Cyclic 1,3-diones also form H-bonded dimers as well as intramolecular ones from infrared evidence (R. J. Rasmussen, D. D. Tunnicliff and R. R. Brattain, THIS JOURNAL, **71**, 1068 (1949)).

[3] M. Verzele and F. Govaert, Int. Congress for Fermentation Industries, Lectures and Communications, Ghent, 297–301 (1947).

[4] Although the expression IV is ordinarily written for humulinic acid, the proof of structure of the compound (H. Wieland, *Ber.*, **58**, 102 (1925) and H. Wieland and E. Martz, *ibid.*, **59**, 2352 (1926)) did not eliminate the possibility of structure V. Both possible structures are here included as IV and V.

[5] W. Windisch, P. Kohlbach and R. Schleicher (*Woch. Brau.*, **44**, 453, 473, 485, 497 (1927)) observed that boiling aqueous solutions of humulone yielded resinous substances of greater bittering power than the original humulone.



small quantity of a third crystalline isomer which is optically inactive. The properties of the three compounds and of the starting material, humulone, are recorded in Table I. The compounds are here designated dextrorotatory, levorotatory and inactive isohumulone.

TABLE I

ANALYSES OF ISOHUMULONE ISOMERS

Compound	M.p., °C.	$[\alpha]^{25}D$	Equiv. wt.	Analyses, %[c] Found C	H
Dextro isohumulone	133–134	+113°[a]	367	69.6	8.40
Levo isohumulone	134–135	−60.6[a]	367	69.6	8.38
Inactive isohumulone	145–146	0[a]	372	69.6	8.43
Humulone	55	−212[b]	362		

[a] In ethyl acetate. [b] In methanol. [c] Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34.

The compounds differ from humulone in that they do not form insoluble lead salts or crystalline *o*-phenylenediamine complexes. Like humulone, no crystalline derivatives could be prepared utilizing the carbonyl, enolic or tertiary hydroxyl functions. Attempts to prepare methyl ethers with diazomethane, acetates, phenylurethans, oximes, semicarbazones or 2,4-dinitrophenylhydrazones have yielded only oils or resins. The crystalline isomers give a red color with ferric chloride. They are not bitter in alcoholic or aqueous solution, in contrast to the oily isohumulone mother liquor which is intensely bitter.

That the compounds are isomeric with each other and with humulone is shown by equivalent weights and carbon–hydrogen analyses. Potentiometric titration of the three crystalline isohumulones in 80% methanol with aqueous alkali gives pK_a values ($pH_{1/2}$ neutralization) of 3.3–3.5. Humulinic acid under the same conditions has the pK_a 3.45 and humulone, 5.5. The fact that the three isomers are approximately equally acidic and about one hundred times as strong as humulone is in agreement with the idea that the isomers and humulinic acid have a similar cyclopentanedione ring structure. More convincing is the evidence of ultraviolet absorption spectra. In alkaline methanol, the three isomers and humulinic acid all have a maximum at approximately 253 mμ and an inflection at 260–270 mμ (Fig. 1). Humulone in alkaline methanol has a principal maximum at 330 mμ and a second peak at 360 mμ.[6]

Alkaline degradation of the three isomers, in each case, yields optically inactive humulinic acid and a mixture of acetone and isobutyraldehyde. The dextro- and levorotatory isohumulones differ from humulone on catalytic hydrogenation. While humulone on reduction with platinum oxide or palladium-on-carbon yields a tetrahydroxybenzene derivative accompanied by the loss of isopentane, the optically active isohumulones yield the corresponding dihydro derivatives, still optically active. Crystalline tetrahydro compounds could not be isolated. Alkaline degradation of the dihydrolevorotatory and dihydrodextrorotatory isohumulones yields, in each case, dihydrohumulinic acid and a mixture of acetone and isobutyraldehyde showing that the double bond in R_1 attached to C_5 of II or III was reduced.

The isolation of acetone and isobutyraldehyde from the alkaline degradation of the isohumulones or of their dihydro derivatives is of no value in assigning a position for the double bond in the side chain attached to C_4 of II or C_3 of III. A similar situation existed in the alkaline degradation of humulone.[7] A structural isomerism resulting from a shift of the double bond from the β,γ- to the α,β-position in this side chain with the further possi-

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(6) T. W. Campbell and G. M. Coppinger, THIS JOURNAL, **73**, 1848 (1951).

(7) J. F. Carson, *ibid.*, **73**, 4652 (1951); A. H. Cook and G. Harris *J. Chem. Soc.*, 1873 (1950).

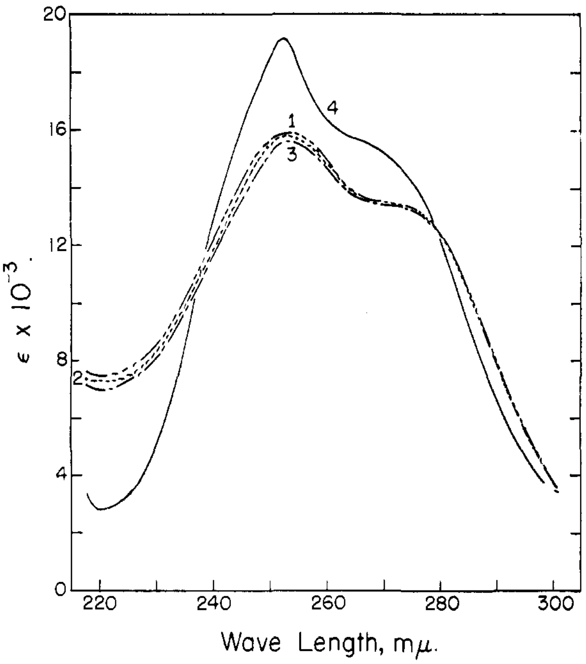

Fig. 1.—Ultraviolet absorption spectra in alkaline methanol (concn. 50 μg./ml.): 1, – – – – – – – – –, dextrorotatory isohumulone; 2, - - - - - - - - - - - - -, levorotatory isohumulone; 3, — — — — —, inactive isohumulone; 4, ———, humulinic acid.

bility of *cis–trans* isomerism in the latter position is conceivable under the alkaline conditions of rearrangement. This was ruled out in the case of the three crystalline isomers by ozonization. Acetone and no isobutyraldehyde was produced in each case.

In the rearrangement of humulone (I), if the bond between C_3 and C_4 is broken, II may result and if the bond between C_4 and C_5 is broken, III could be formed. The two isomers, II and III, might further yield, on aqueous alkaline degradation, IV and V, respectively, assuming no rearrangement. When humulone rearranges to II, the carbon atom C_4 of I loses its asymmetry to become a keto group in II, but C_5 of humulone becomes the asymmetric C_4 of II. If the rearrangement proceeds by a concerted process with one configuration preferred at C_4, an optically active product would be expected. C_5 of II, since it is now adjacent to only one keto group instead of two carbonyl groups as in humulone, may function as an asymmetric atom and therefore four optically active isomers may be formed corresponding to structure II. On the other hand, in structure III, C_3 is asymmetric but both C_2 and C_5 are adjacent to two keto groups and should racemize too readily to expect isolable optical isomers. On this basis, while four optical isomers or two D,L-pairs are possible with structure II, only two optical isomers or one racemate would be expected from III. Since alkaline degradation of each of the isomers yields the same identical humulinic acid IV or V as is formed from humulone itself, it was first thought that the three isomers should be represented by II and humulinic acid by IV. The dextro- and levorotatory isomers would then be diastereomers resulting from the asymmetry of C_4 and C_5 of II and the inactive compound would be a racemate of one of the isomers. However, this is not the case, as is shown by absorption spectra in the ultraviolet and particularly in the infrared.

The ultraviolet absorption spectra of the three compounds in alkaline methanol (Fig. 1) are almost superimposable. In acidified methanol, however, the compounds show significant differences (Fig. 2) and the spectrum of each compound is reversible between acid and alkali. A racemate in solution would be expected to have a spectrum identical with its own D- or L-form if association effects were eliminated. Ultraviolet absorption spectra therefore suggest strongly that the inactive compound is not a racemate of either the dextro- or levorotatory isomer. The infrared spectra are even more convincing. Figure 3 shows the infrared spectra of carbon tetrachloride solutions of the three compounds over the range of 2.5–12 microns. Small but significant differences appear. To eliminate the possible effect of molecular association, in which case the spectrum of a racemate could differ from that of its D- or L-form, infrared spectra were obtained at high and low concentrations for the hydroxyl stretching frequency region, 3300–3600 cm.$^{-1}$. Examination of the spectra (Fig. 4) shows that although on dilution the curves show changes in certain regions, the curve for the inactive compound does not approach either of the other curves. Since the lower curves of Fig. 4 were obtained at a molar concentration (0.00033) at which similar studies on alcohols indicate that negligible association occurs,[8] the differences persisting on a 200-fold dilution demonstrate that the inactive compound is not a racemate of either of the other two compounds.

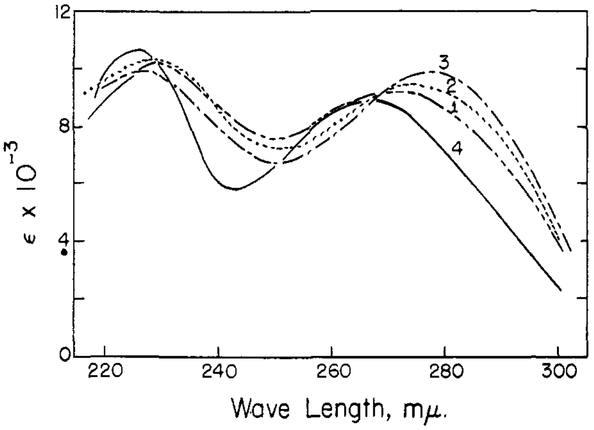

Fig. 2.—Ultraviolet absorption spectra in acidified methanol (concn. 50 μg./ml.): 1, —. . . – – – – – —, dextrorotatory isohumulone; 2,- - - - - - - - - - - - - - - - -, levorotatory isohumulone; 3, —·—·—·—, inactive isohumulone; 4, —–-—, humulinic acid.

The best explanation for the structures of the three compounds compatible with the chemical reactions and with the absorption spectra is that the three compounds cannot all be represented by one structure, II or III, but both structures must

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[8] F. A. Smith and E. C. Creitz, *J. Research Natl. Bur. Standards*, **46**, 145 (1951).

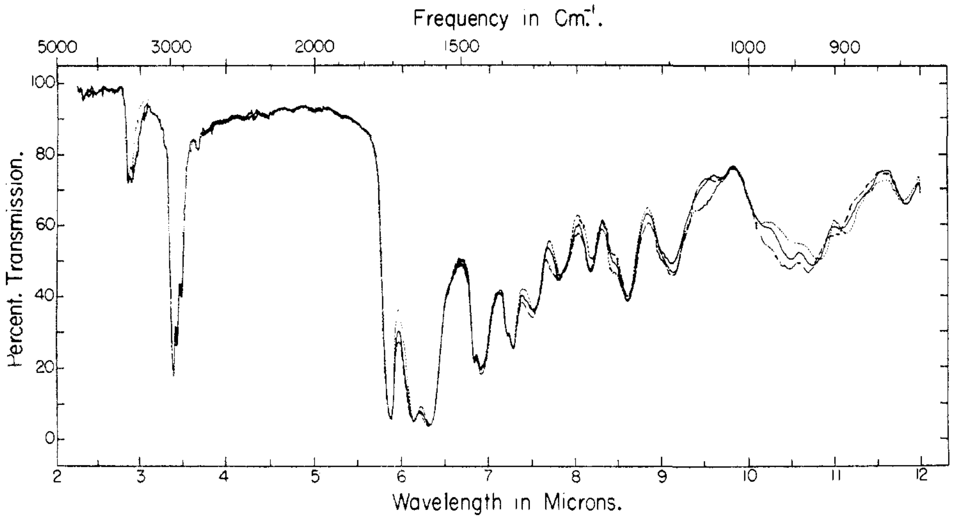

Fig. 3.—Infrared spectra of the isomers in carbon tetrachloride, sodium chloride prisms, concn. 24.6 mg./ml., path length 0.463 mm.: levorotatory isohumulone, ———; dextrorotatory isohumulone, - - - - - - - - - - - -; inactive, — — — —.

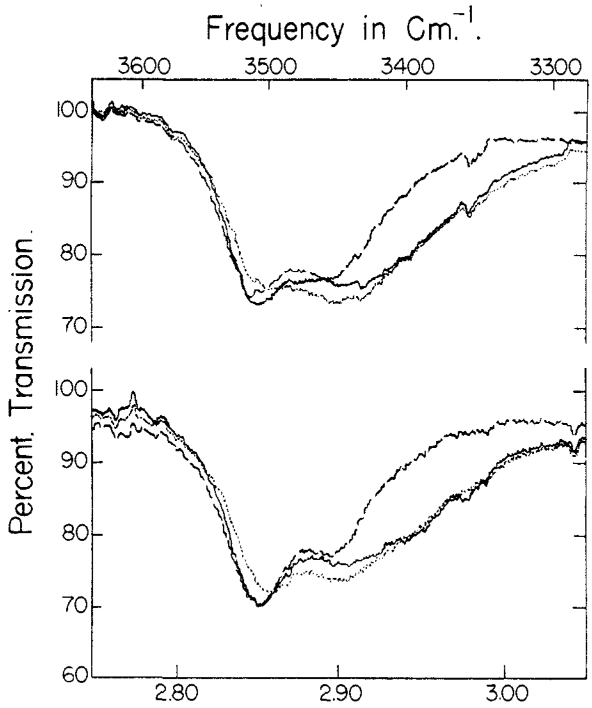

Fig. 4.—Infrared absorption spectra of the three isomers in the range 3300–3600 cm.$^{-1}$ in carbon tetrachloride solution with calcium fluoride prisms: upper curves, concentration 24.5 mg./ml.; path length 0.463 mm.; lower curves, concentration 0.123 mg./ml.; path length, 95.3 mm. levorotatory isohumulone, - - - - - - - - - - -; dextrorotatory isohumulone, — — —; inactive isohumulone, ———.

be considered. Assuming that structure II has two stable asymmetric carbon atoms and structure III one asymmetric atom, it follows that two of the compounds will correspond to structure II and the third to structure III. Evidence is not available to decide which of the isomers should be assigned a particular structure. To reconcile the fact that all three compounds give the same humulinic acid on alkaline degradation, a rearrangement must be assumed to occur in which both II and III will give predominately one compound, either IV or V. The actual yields of pure humulinic acid isolated were in the range of 46–65%. No other crystalline component could be isolated from the mother liquors.

Chromatography of the oil, after removal of the crystalline isomers, on silicic acid–zinc sulfide yields two additional optically active fractions as non-crystallizing oils. They have equivalent weights of 363–375 and have absorption maxima in the ultraviolet in alkaline methanol at 253 mμ and extinction coefficients very close to the values of the crystalline isomers. These two oily fractions on alkaline degradation yield humulinic acid in 50–60% yields and acetone and isobutyraldehyde. Each of the two fractions on ozonization yields acetone and small yields of isobutyraldehyde indicating the possible presence of compounds similar to II or III with the double bond in the α,β- instead of the β,γ-position.

A crystalline optically inactive fraction was obtained, in small yield, analyzing closely for $C_{15}H_{20}O_4$, with the equivalent weight 269. The compound was yellow and differed in absorption spectra in the ultraviolet from all other fractions obtained. In alkaline methanol, it had maxima at 265 and 304 mμ and in acidified methanol, maxima at 254 and 278 mμ. The structure of this compound has not been investigated.

Humulinic acid, the three crystalline isohumulone isomers and crude isohumulone oil were all bacteriostatically inactive at 0.1% for *E. coli*, *M. conglomeratus*, *M. pyogenes* var. *aureus*, *Sarcina lutea* and *M. tuberculosis* var. *hominis* by an agar streak method.[9]

Acknowledgment.—The author gratefully acknowledges the assistance of F. T. Jones for microscopic identifications, G. M. Coppinger and G. Bailey for absorption spectra, L. M. White and G. E. Secor for carbon–hydrogen analysis, and Fred Stitt and Lloyd Ingraham for helpful discussions.

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(9) I am indebted to Dr. L. M. Sacks of this Laboratory for these measurements.

Experimental

Isomerization of Humulone.—Humulone, 162 g. (0.446 mole), was dissolved in a liter of methanol, neutralized with potassium hydroxide to a phenolphthalein end-point and additional methanol and potassium hydroxide, 9.2 g., added to give 2 liters of solution, 0.07 *N* in potassium hydroxide. The solution was refluxed for three hours, cooled to 20°, acidified with 20 ml. of 5 *N* hydrochloric acid, and concentrated *in vacuo* $< 25°$ to 400 cc. The concentrate was treated with 600 cc. of normal hydrochloric acid and the resinous suspension extracted three times with 400-cc. portions of ether. The combined ether extracts, after washing with distilled water and drying over sodium sulfate, were concentrated *in vacuo* to a thick amber oil which was thinned with 400 cc. of petroleum ether (30–60°) and stored at 0° for several days. The thick crystalline mush was filtered to yield 24.8 g. (15%) of yellow crystalline product. Recrystallization from 600 cc. of petroleum ether (60–70°) at −28° yielded 23.5 g. of white fluffy crystals. The product at this stage usually has a wide melting point range 118–125°, a small dextrorotation, $[\alpha]^{25}\mathrm{D}$ +8 to +15° in methanol, and equivalent weights of 370–380.

The mother liquor, after removal of the first crop of crystals was seeded with pure dextrorotatory isohumulone and stored for one week at −28°. A second crop of crystals, 3.7 g., was obtained giving a total yield of crystalline product, 18%. The second crop of crystals consisted principally of the dextrorotatory isomer. Recrystallization once from petroleum ether (60–70°) and twice from methanol at −27° yielded 2.2 g., $[\alpha]^{26}\mathrm{D}$ +112° (methanol), m.p. 133–134° and equiv. wt. 367.

The Isolation of Levorotatory and Dextrorotatory Isohumulones.—Pure levorotatory isohumulone was separated from the dextro isomer by fractional crystallization from methanol. The crude isohumulone, 23.5 g., after ten recrystallizations from methanol yielded 2.2 g. of impure levorotatory isomer $[\alpha]^{25}\mathrm{D}$ −48.5° (methanol). Five additional recrystallizations from methanol yielded the pure levorotatory isomer, 1.14 g., $[\alpha]^{25}\mathrm{D}$ −60.6° (methanol) unchanged on further recrystallization. The mother liquor from these recrystallizations was concentrated *in vacuo* to 400 cc., cooled to −27°, and a fraction, 10 g., was collected. The mother liquor from this was concentrated to 100 cc., diluted with 50 cc. of water, and a third crystalline crop, 7 g., was collected. Five recrystallizations of the last fraction from methanol yielded 2 g. of pure dextrorotatory isomer. By repeating the process with the middle fraction, additional levorotatory isomer can be obtained as the less soluble portion with the dextro isomer concentrating in the mother liquor. Time is saved with no apparent loss in yield if the recrystallization of the levorotatory isomer is performed as rapidly as possible by cooling the methanol solutions in a cold chest at −27° for one to two hours before filtration. The dextrorotatory isomer crystallizes more slowly. Attempts to separate the two isomers by chromatography on silicic acid–fluorescent zinc sulfide have not been successful.

The Isolation of Inactive Isohumulone.—The inactive isohumulone accumulates in the last mother liquor remaining from the recrystallization of the dextro isomer. The resinous yellow crystals, 4.5 g., obtained from the mother liquor from the dextro isomer, were dissolved in a mixture of 50 ml. of benzene and 150 ml. of petroleum ether (60–70°) and absorbed on a column of silicic acid + fluorescent zinc sulfide (2.5%) 52 × 205 mm. and developed with petroleum ether (60–70°)–ether (15:1 by volume). Under ultraviolet light, a sharp fast moving dark zone and a slow moving faint diffuse shadowy zone were observed. The fast band yielded resinous crystals from which 1.2 g. of pure dextrorotatory isomer was obtained by recrystallization from methanol. The slow moving zone yielded 3 g. of resinous material. Extraction of the resin with 100 cc. of boiling petroleum ether (60–70°), filtration and concentration of the filtrate to 35 cc. yielded 1.07 g. of white prisms. Five recrystallizations from petroleum ether yielded 580 mg. of the pure inactive isomer, m.p. 145–146°, $[\alpha]^{26}\mathrm{D}$ 0° (ethyl acetate or chloroform).

Chromatography of Isohumulone Oil.—After removal of the crystalline isohumulone, the oily mother liquor had the equiv. wt. 375, and $[\alpha]\mathrm{D}$ +35° (ethyl acetate). A sample of the oil, 10.3 g., in 100 cc. of petroleum ether was absorbed on two columns of silicic acid–zinc sulfide ($2^1/_2$%) 48 × 200 mm. Four bands were observed under ultraviolet light when the column was developed with petroleum ether (60–70°)–ether (15:1). A non-mobile band, accounting for 20% of the total, yielded a sticky resin not further investigated. The slowest moving band, designated as B, the next faster as C, and the fastest as D, were isolated as yellow oils and accounted, respectively, for 35, 30 and 7% of the total. B fraction had $[\alpha]\mathrm{D}$ +17.7° (ethyl acetate), equiv. wt. 375, and ultraviolet spectrum in alkaline methanol, $\lambda_{\max}$ 253 mμ; $E_{1\%}$ 435. The C fraction had $[\alpha]\mathrm{D}$ +50.3° (ethyl acetate). *Anal.* Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 68.5; H, 8.74; ultraviolet spectrum in alkaline methanol, $\lambda_{\max}$ 253 mμ; $E_{1\%}$ 461. Repeated chromatography of these two fractions failed to change the specific rotations or to yield crystalline material. Hydrogenation of the two fractions in the presence of palladium-on-carbon also failed to yield crystalline products. The D fraction after standing at −27° for several days yielded 150 mg. of yellow crystals, m.p. 130–133°. Three recrystallizations from petroleum ether (60–70°) gave 90 mg. of yellow crystals, m.p. 133–133.6°, optically inactive. *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; equiv. wt., 264.3. Found: C, 68.4; H, 7.80; equiv. wt., 269. This compound had the ultraviolet absorption spectrum, in alkaline methanol, $\lambda_{\max}$ 265 mμ, $E_{1\%}$ 600; $\lambda_{\max}$ 304 mμ, $E_{1\%}$ 590, in acidified methanol; $\lambda_{\max}$ 254 mμ, $E_{1\%}$ 825; $\lambda_{\max}$ 278 mμ, $E_{1\%}$ 725.

Hydrogenation of Dextro- and Levorotatory Isohumulones.—Dextrorotatory isohumulone, 0.5 g. (0.00138 mole) in 45 ml. of methanol and 185 mg. of palladium-on-carbon[10] was shaken for ten minutes with hydrogen at 26° and 760 mm. The net absorption of hydrogen, 38.5 cc. (S.T.P.), corresponded to 1.25 g. moles/mole of compound. Addition of water to the reduction solution yielded 360 mg. (72%), m.p. 140–143°. Several recrystallizations from aqueous methanol yielded the pure dihydro dextrorotatory isohumulone, m.p. 147–148°; $[\alpha]^{26}\mathrm{D}$ 72.4 ± 1.0° (ethyl acetate). *Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.1; H, 9.03.

Levorotatory isohumulone, when hydrogenated under the same conditions yielded the dihydro levorotatory isohumulone, recrystallized from aqueous methanol, m.p. 162–165°; $[\alpha]^{26}\mathrm{D}$ −76.9 ± 1.0° (ethyl acetate). *Anal.* Found: C, 69.3; H, 8.93.

Alkaline Degradations of the Crystalline Isohumulone Isomers.—In a typical experiment, 540 mg. of levorotatory isohumulone in a solution of 15 ml. of absolute ethanol and 50 ml. of *N* potassium hydroxide was refluxed for two hours and then concentrated by distillation to one-third its original volume. The distillate was collected in a receiver containing 1.0 g. of 2,4-dinitrophenylhydrazine in 50 ml. of 3 *N* hydrochloric acid. The alkaline concentrate on acidification with hydrochloric acid yielded 357 mg. of crystalline product. Several recrystallizations from petroleum ether (60–70°) yielded 183 mg. (46%) of humulinic acid, m.p. 93–94°, identified by mixed melting point with humulinic acid prepared from humulone, microscopic examination of the optical properties and by the preparation of the oxime, m.p. 145–146° (dec.).

The distillate was extracted four times with 50-ml. portions of benzene, the benzene extract dried over sodium sulfate and concentrated to 50 ml. The solution of dinitrophenylhydrazones was diluted with 100 ml. of petroleum ether (60–70°) and adsorbed on a column of silicic acid 48 × 210 mm. Development with petroleum ether–ether (6:1) yielded two bands. The fast moving band yielded 180 mg. (48 mole %) of isobutyraldehyde 2,4-dinitrophenylhydrazone, m.p. 184–186°, identified by mixed melting point with authentic material. The slower band yielded 40 mg. (11 mole %) of acetone 2,4-dinitrophenylhydrazone, m.p. 125–126°, identified by microscopic examination of fusion behavior. The dextrorotatory and inactive isohumulones and also the two oily fractions obtained by chromatography yielded humulinic acid, acetone and isobutyraldehyde.

Alkaline Degradation of the Dihydro Derivatives of Dextro- and Levorotatory-isohumulones.—In a typical experiment, 74 mg. of dihydrolevoisohumulone in 15 ml. of ethanol and 20 ml. of *N* potassium hydroxide was refluxed three hours and concentrated by distillation to half its volume. The distillate was collected as before in a suspension of dinitrophenylhydrazine in hydrochloric acid. The alkaline

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[10] Baker and Co., Inc., Newark, N. J. Palladium on activated charcoal powder.

concentrate, after acidification with hydrochloric acid, was extracted with ether from which semi-crystalline material was obtained. Two crystallizations from hexane yielded dihydrohumulinic acid, m.p. 124.8–125.4°, identical with the hydrogenation product of humulinic acid, by mixed melting point. The distillate when treated as before and then chromatographed on silicic acid yielded two bands identified as acetone and isobutyraldehyde dinitrophenylhydrazones. Similar results were obtained with the dihydro dextrorotatory isohumulone.

Ozonization of Isohumulone Fractions.—In a typical experiment, ozonized oxygen was bubbled through a solution of 337 mg. (0.928 millimole) of levorotatory isohumulone in 30 ml. of acetic acid at 19–20° for 30 minutes. The ozonide was decomposed by addition of 100 cc. of water and 5 g. of zinc dust. The suspension was filtered and the filtrate distilled to approximately one-third its original volume. The distillate was collected in a flask containing 1 g. of 2,4-dinitrophenylhydrazine in 40 ml. of 3 *N* hydrochloric acid. The dinitrophenylhydrazones were extracted into benzene (250 ml.), which was then concentrated to 100 ml. and diluted with 200 ml. of petroleum ether. Adsorption on a silicic acid column 48 × 200 mm. followed by development with petroleum ether (60–70°)–ether (6:1) yielded a slow intense band and a fast faint band. The slow band yielded 210 mg. (93 mole %) of acetone dinitrophenylhydrazone identified by melting point 125–126°, mixed melting point and optical properties. The fast moving band yielded 12 mg. of the dinitrophenylhydrazone of methyl *n*-propyl ketone.[11] No evidence for isobutyraldehyde could be obtained. Comparable results were obtained in the ozonization of the dextrorotatory and inactive isomers. When the oily fractions B and C obtained by chromatography of isohumulone oil were ozonized, in addition to acetone dinitrophenylhydrazone, small yields of isobutyraldehyde 2,4-dinitrophenylhydrazone (9–14 mole %) were isolated and identified by mixed melting points and examination of optical properties.

Absorption Spectra.—Ultraviolet absorption spectra were determined with a Cary recording spectrophotometer and infrared spectra were obtained with a Beckman IR-3 recording spectrophotometer.

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[11] Humulone, lupulone and humulinic acid have been found to yield traces of this compound on ozonization, J. F. Carson, THIS JOURNAL, 73, 4652 (1951).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF ILLINOIS]

The Electrolytic Reduction of Bicyclic α-Aminoketones. A New Method for the Synthesis of Medium Rings[1] Containing Nitrogen[2,3]

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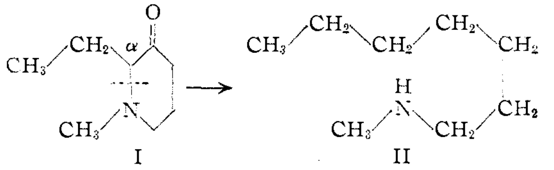
A new method has been discovered for the synthesis of medium-size ring compounds containing a nitrogen atom, namely, the electrolytic reduction of bicyclic α-aminoketones at a lead cathode in 30% sulfuric acid at 60°. Certain nine- and ten-membered-ring aminoalcohols have been obtained in good yields by this method. Specifically, the electrolytic reduction of 1-ketoquinolizidine led to the monocyclic product, 5-hydroxyazacyclodecane. The presence of a secondary amine function in the product was established by N-methylation with formaldehyde-formic acid, and the size of the ring present in the product was determined by its conversion to azacyclodecane through the successive operations of dehydration and catalytic reduction. The similar electrolytic reduction of 1-ketoöctahydropyrrocoline produced 4-hydroxyazacyclononane and 8-keto-octahydropyrrocoline gave the isomeric 5-hydroxyazacyclononane. Indication of the monocyclic nature of the products was obtained from the fact that both could be methylated readily by means of formaldehyde–formic acid.

Previous work in these laboratories has shown that the reduction of 1-methyl-2-ethyl-3-piperidone (I) at a lead cathode in 30% sulfuric acid at 60° yields, as the main product, N-methylheptylamine (II).[4] On the basis of this discovery, it was anticipated that the electrolytic reduction, under the same conditions, of *bicyclic* α-aminoketones (III, XI, XV) should yield medium-size rings containing a nitrogen atom. In the past, the main factor limiting the preparation of cycles having nine or ten members has been the difficulty of closure of rings of this size. The selection of bicyclic compounds (5,6 or 6,6 rings) as precursors would circumvent this difficulty since the medium ring (9 or 10) is already existent in the external boundary of the bicyclic system. The facile scission of the C_α–N bond of α-aminoketones under electrolytic reduction conditions[4] offers a unique method for bringing about a valence-bridge cleavage which converts a bicyclic to a monocyclic compound.



I II

The electrolytic reduction of 1-ketoquinolizidine (III) at a lead cathode in a catholyte of 30% sulfuric acid at 60° gave a mixture of two products. The lower boiling fraction, obtained in 4.5% yield, was shown to be 1-azabicyclo[5.3.0]decane (IV),[5] by direct comparison of the picrate with an authentic sample.[6] The higher boiling material, obtained in 59% yield, showed a strong infrared absorption band at 3345 cm.$^{-1}$, indicating the presence of an hydroxyl (and/or NH) group. Microanalysis of the base and its picrate indicated a molecular formula, $C_9H_{19}NO$, consistent with a monocyclic aminoalcohol structure. The production of an open-chain aminoalcohol by the electrolytic reduction of 1-butyl-3-pyrrolidone[4] suggested, by analogy, that the $C_9H_{19}NO$ compound was 5-hydroxyazacyclodecane (V). In order to

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[1] We are using the classification of H. C. Brown and V. Prelog (see ref. 21 in H. C. Brown, Roslyn S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951)) of medium rings as those containing 8 to 12 members.

[2] This work was supported in part by a grant from E. I. du Pont de Nemours and Company, Inc.

[3] Presented at the 121st National Meeting of the American Chemical Society, Buffalo, N. Y., March 24, 1952.

[4] N. J. Leonard, S. Swann, Jr., and H. L. Dryden, Jr., THIS JOURNAL, **74**, 2871 (1952).

[5] V. Prelog and K. Seiwerth, *Ber.*, **72**, 1638 (1939), proved that this compound was the product of the Clemmensen reduction of 1-ketoquinolizidine.

[6] N. J. Leonard and W. C. Wildman, THIS JOURNAL, **71**, 3100 (1949).