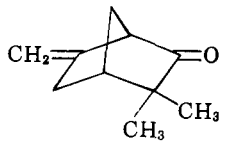
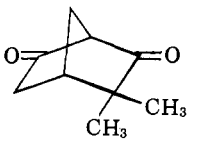
of X provided the β-diketone (XII); $\lambda_{max}^{CCl_4}$ 5.66, 5.74 μ; n.m.r. 3.22 δ (1 H, singlet), 1.26 δ (3 H, singlet), 1.03 δ (3 H, singlet) (the remaining protons appeared as a complicated series of multiple peaks from 2.1–3.0 δ indicating that the equivalent bridge protons has moved downfield as expected). Mild base treatment of XII provided the keto acid XIII; $\lambda_{max}^{CCl_4}$ 5.74 and 5.86 μ.

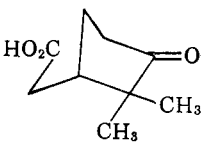
The acid rearrangement of IV also gave small amounts of the isomeric ketone XIV; $\lambda_{max}^{CCl_4}$ 3.27, 5.73 μ; $\lambda_{max}^{CH_3OH}$ 305 mμ (ε 282); n.m.r. 1.04 δ (3 H, singlet), 1.13 δ (3 H, singlet), 1.81 δ (3 H, doublet, J = 2.0 c.p.s.), 2.18 δ (2 H, narrow multiplet), 2.65 δ (1 H, triplet, J = 4.5 c.p.s.), 2.82 δ (1 H, doublet, J = 1.0 c.p.s.), and 6.15 δ (1 H, quartet, J = 2.0 c.p.s.). The structure of XIV was established by catalytic hydrogenation to XI.



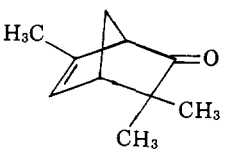
X



XII

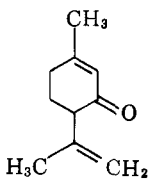


XIII

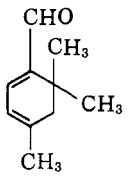


XIV

Pyrolysis of IV at 340° provided isopiperitenone[12] (XV) (2,4-dinitrophenylhydrazone, m.p. 155–156°) and piperitenone (II) as the major products. A minor pyrolysis product was the aldehyde XVI ($\lambda_{max}^{CH_3OH}$ 310 mμ (ε 9800); $\lambda_{max}^{CCl_4}$ 3.69, 5.95 μ; semicarbazone, m.p. 211–213°). The structure of XVI was established by comparison with an authentic sample[13] prepared from 3-methyl crotonaldehyde. Pyrolysis of IV at higher temperatures led to piperitenone and *m*-xylene



XV



XVI

formed by the demethylation and decarbonylation of XVI.

Acknowledgment.—The author is indebted to Professor G. Büchi for many stimulating discussions.

(12) Y. R. Naves, *Bull. Soc. Chim. France*, 1881 (1961).

(13) F. G. Fischer and K. Löwenberg, *Ann.*, **494**, 263 (1932); E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3334 (1955).

MEDICAL RESEARCH LABORATORIES
CHAS. PFIZER & CO., INC. J. J. BEEREBOOM
GROTON, CONNECTICUT

RECEIVED SEPTEMBER 3, 1963

The Interaction of Urea and Acetamide with Polyglycine[1]

Sir:

We have measured the association of urea and acetamide with polyglycine in water and dioxane, by observing the mobility of the amides on polyglycine columns, a technique which permits rapid comparison of the interaction under a variety of conditions. If it is assumed that the binding of the amides is through peptide hydrogen bonds, then the association is a measure of hydrogen bond formation and strength. Several differing estimates of peptide hydrogen bond strength have been reported,[2-4] the most recent being that of Klotz and Franzen,[2] who found that in water the bond is very weak. The data presented here confirm this conclusion.

Polyglycine was prepared by polymerization of the N-carboxyanhydride in pyridine.[5] Thermostated columns (0.6 × 20 to 30 cm.) were operated under 5 lb. pressure, with a flow rate of no more than 2 ml./hr. Samples (0.1 ml.) were applied to the column, and the effluent fractions were analyzed for urea or acetamide by acid hydrolysis followed by ninhydrin determination of the ammonia liberated. The volume at which unretarded material emerged was determined using solutes which would not interact with polyglycine (*i.e.*, sodium chloride, acetic acid, or acetone, when water was the solvent, and azulene or acetic acid for dioxane).

Simple chromatographic theory shows $R_f = 1/(1 + K_d)$, where R_f is the mobility, and K_d is the distribution coefficient of the solute between the liquid and solid phases.[6] Table I presents values of K_d for chromatography of urea and acetamide on polyglycine, in water and dioxane, at several temperatures. Neither

TABLE I
THE CHROMATOGRAPHY OF UREA AND ACETAMIDE ON POLYGLYCINE

Solute	Solvent	Temperature, °C.	Distribution coefficient	Monomer concn., M	Association constant
0.05 M urea or acetamide	H_2O	0 or 40	<0.035	5.2	<0.007
0.05 M acetamide	Dioxane	12	4.0	5.6	0.72
0.05 M acetamide	Dioxane	40	2.3	5.6	0.41

solute was measurably retarded in water, but acetamide was retarded in dioxane. The insolubility of urea in dioxane precluded measurement of its chromatographic behavior using this solvent. The distribution coefficient for acetamide in dioxane was at least 100 times that in water, in agreement with the data of Klotz and Franzen[2] for the dimerization of N-methylacetamide in these same solvents, *i.e.*, association constants 0.005 and 0.52, for water and dioxane, respectively, at 25°. An association constant for the formation of an acetamide–polyglycine complex can be calculated from the distribution coefficient by introducing the concentration of polymer peptide bonds, which was crudely approximated as the molar concentration of monomer in the column packing. The resulting values are shown in Table I. The agreement with the constants of Klotz and Franzen is remarkable, and almost certainly fortuitous. The probable unavailability of some peptide bonds of the solid polyglycine may have been compensated by more than one hydrogen bond formed per acetamide bound, or a more favorable entropy for binding to solid polyglycine, compared with the dimerization of two free molecules. It must be emphasized that the chromatographic

(1) This work was supported by Research Grant G-21030, from the National Science Foundation.

(2) I. M. Klotz and J. S. Franzen, *J. Am. Chem. Soc.*, **84**, 3461 (1962).

(3) J. A. Schellman, *Compt. rend. Trav. Lab. Carlsberg*, **29**, 223 (1955).

(4) S. J. Gill, J. Hutson, J. R. Clopton, and M. Downing, *J. Phys. Chem.*, **65**, 1432, (1961).

(5) Y. Go and H. Tani, *Bull. Chem. Soc. Japan*, **14**, 510 (1939).

(6) J. C. Giddings and R. A. Keller, in "Chromatography," E. Heftmann, Ed., Reinhold Publishing Corp., New York, N. Y., 1961.

experiments permit only *comparison* of the interaction under different conditions. However, this may be done simply and rapidly, and if independent data are available describing the interaction in one environment, then it may be quantitatively evaluated for others.

The enthalpy of the interaction between the amide and polyglycine can be calculated from the temperature dependence of K_α, and will be independent of the concentration of available peptide bonds. For acetamide in dioxane the value obtained was −3600 cal./mole. Klotz and Franzen found an enthalpy of −800 cal./mole for the dimerization of N-methylacetamide in dioxane. The more negative value obtained in the chromatographic experiments suggests that acetamide may bind to polyglycine with more than one peptide hydrogen bond. Since a maximum of three such bonds can be formed by each acetamide molecule, the value of the enthalpy may be as low as −1200 cal./mole of hydrogen bonds. An enthalpy could not be calculated for water, since binding was not observed at either 0 or 40° in this solvent.

These experiments will be extended to evaluate the characteristics of the association in other solvents.

DEPARTMENT OF CHEMISTRY
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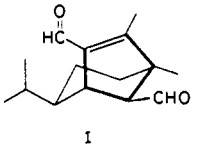
RECEIVED SEPTEMBER 19, 1963

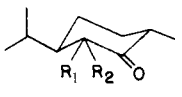
Total Synthesis of Helminthosporal

Sir:

Recently the constitution of helminthosporal, the important crop-destroying toxin of the fungus *Helminthosporium sativum*, has been demonstrated by an incisive chemical investigation.[1] Subsequent studies on this substance have also permitted the assignment of stereochemistry, exclusive of absolute configuration, as in I.[2] We report here the total synthesis of helminthosporal by a method which confirms the previous structural conclusions and which additionally allows the designation of absolute configuration.



I



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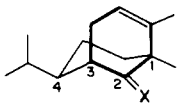

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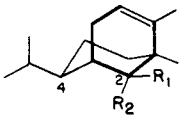

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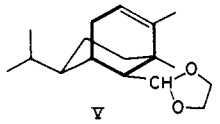

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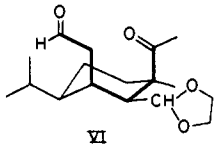
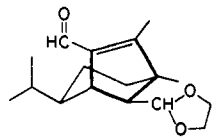
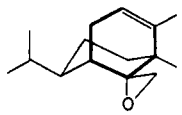


VI



VII



VIII

(1) P. de Mayo, E. Y. Spencer, and R. W. White, *J. Am. Chem. Soc.*, **84**, 494 (1962); P. de Mayo, E. Y. Spencer, and R. W. White, *Can. J. Chem.*, **39**, 1608 (1961).

(2) P. de Mayo, personal communication.

(−)-Carvomenthone[3,4] (II, $R_1 = R_2 = H$) was converted *via* the known α-hydroxymethylene derivative[5] to the diketo aldehyde II ($R_1 = CHO$, $R_2 = CH_2CH_2COCH_3$), using methyl vinyl ketone and triethylamine at room temperature (3 days, 71%).[6] This substance was deformylated by 2% ethanolic potassium carbonate at reflux (16 hr.) to give the diketone II ($R_1 = H$, $R_2 = CH_2CH_2COCH_3$,[7] 70% yield, infrared max. 5.82 μ, n.m.r. peaks[8] at 0.87–1.02 δ due to three methyl groups and at 2.05 δ due to C-acetyl. Treatment of this diketone with boron trifluoride in methylene chloride solution at 25° (16 hr.) afforded in 40% yield the bridged keto olefin III (X = O) and its C-4 epimer in a ratio of 4:1. These liquid epimers were purified by v.p.c. or *via* the crystalline semicarbazones. The major isomer has b.p. 66–68° (0.06 mm.), infrared absorption at 5.83 μ, n.m.r. peaks at 0.80–1.01 δ due to three methyl groups attached to saturated carbon, at 1.6 δ (doublet) due to one methyl attached to unsaturated carbon, and at 5.60 δ due to one olefinic proton; both isomers lack ultraviolet absorption characteristic of α,β-unsaturated ketones.[9]

The assignment of configuration at C-4 to III (X = O) and its 4-epimer rests partly on the fact that reduction with lithium aluminum hydride produces a mixture of secondary alcohols from the former (ratio 4:1) but only a single alcohol from the latter. That the predominating course of reduction of both III (X=O) and its C-4 epimer is (as it is expected to be) that which produces an hydroxyl with axial orientation of the cyclohexane ring (IV, $R_1 = H$, $R_2 = OH$, and the C-4 epimer) is indicated by n.m.r. data. The n.m.r. peak due to the —CH—O proton is at 3.54 δ for IV ($R_1 = H$, $R_2 = OH$) and at 3.48 δ for the C-4 epimer; the corresponding proton in the spectrum of the minor alcohol from III (X = O) (IV, $R_1 = OH$, $R_2 = H$) shows a peak at 3.10 δ.[10]

Reaction of the unsaturated ketone III (X = O) with methoxymethylene triphenylphosphorane in dimethyl sulfoxide[11] at 40° (12 hr.) gave a 90% yield of the Wittig product III ($X = CHOCH_3$) which was further transformed into the ethylene acetal V (together with minor amounts of the C-2 epimer) with ethylene glycol–benzene-*p*-toluenesulfonic acid at reflux (1 hr., 86% yield). Hydroxylation of V with osmium tetra-

(3) Prepared by hydrogenation of (+)-carvone; see E. S. Rothman and A. R. Day, *J. Am. Chem. Soc.*, **76**, 111 (1954).

(4) Formal total syntheses of both (−)- and (+)-carvomenthone are provided by the terpene literature. For example; a route for the (−) isomer appears in the series (a) W. H. Perkin, Jr., *J. Chem. Soc.*, **85**, 654 (1904); K. Alder and W. Vogt, *Ann.*, **564**, 109 (1949); (b) A. T. Fuller and J. Kenyon, *J. Chem. Soc.*, **125**, 2304 (1924); (c) K. Fujita and T. Matsuura, *J. Sci. Hiroshima Univ.*, **18A**, 455 (1955) [*Chem. Abstr.*, **50**, 10682 (1956)]; (d) M. G. Vavon, *Compt. rend.*, **153**, 70 (1911).

(5) V. Šorm, J. Černy, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **19**, 566 (1954).

(6) R. B. Turner, D. E. Nettleton, Jr., and R. Ferebee, *J. Am. Chem. Soc.*, **78**, 5923 (1956).

(7) Satisfactory analytical data were obtained for this and the other major intermediates in this synthesis. All the assigned structures are supported by spectral data though these are not extensively reported here.

(8) Expressed as parts per million shift (δ) downfield from tetramethylsilane.

(9) The formation of bridged-ring products such as III (X = O), as a side reaction in the Robinson annulation process, has been discussed recently by W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960); S. Julia, *Bull. Soc. Chim. France*, **21**, 780 (1954). In the present instance the conditions are such as to render the normal Robinson reaction mode almost insignificant. Further, the ratio of C-4 epimers of III (X = O) can also be altered markedly by varying reaction conditions.

(10) The carbinyl proton resonance in IV ($R_1 = OH$, $R_2 = H$) can be expected to occur at higher field than that in the epimeric IV ($R_1 = H$, $R_2 = OH$) by *ca.* 0.5 p.p.m. See, *e.g.*, A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962); R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(11) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).