The results obtained by Richards and Thompson[13] on some substituted acetanilides in dioxane, suggest that similar carbonyl frequency shifts occur in this solvent. However, the work of these authors[13] shows that much bigger shifts occur with solid acetanilides and this is also apparent with solid acetophenones.[14] Substituted oxindoles[15] have carbonyl maxima that obey the equation $\nu - \nu_0 = 37.5\sigma$, ν_0 possessing the value 1725 cm.$^{-1}$ It is likely that the augmentation of the effect in the latter cases arises from the absence of free rotation about the Ph—N—C bonds in oxindoles, and in acetanilides and acetophenones in the solid state. As a result, the position of the carbonyl group is fixed, presumably in the plane of the benzene ring. The coplanarity assists the transmission of substituent effects. It is not clear why the shifts are small with substituted isatins.

Certain other features, present in the infrared spectra of substituted acetanilides in chloroform, now are briefly mentioned. All these compounds exhibit a single, very broad, band in the 3500–3200 cm.$^{-1}$ region, indicating that hydrogen bonding (presumably intermolecular) is very extensive in this solvent.[13] In most cases there was no evidence of any distinct maximum arising from an unassociated NH group, and, consequently, it was not possible to gain any information on the effect of substituents on the NH frequency. It is of interest to note, however, that Flett[3] has examined the NH_2 frequencies of substituted anilines in carbon tetrachloride. The symmetric and asymmetric stretching vibrations of the NH_2 group give rise to two maxima in the 3535–3400 cm.$^{-1}$ region. Substituents have a marked influence on the frequency maxima, the effect being more pronounced on the asymmetric mode. In each case, an approximately linear relationship exists between NH_2 frequency and σ value for those substituents possessing a σ value greater than -0.2.

The aromatic C—C stretching vibration is present in acetanilides close to 1610 cm.$^{-1}$, and this maximum undergoes splitting when *meta-* or weakly *ortho-para*-directing substituents are attached to the ring. Unassigned bands appear in the 1350–1300 cm.$^{-1}$ region, some of which may be related to the Ph—N stretching mode.

EXPERIMENTAL

The infrared spectra were determined in chloroform using a Perkin-Elmer 21 double-beam recording spectrometer with a rock-salt prism.

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(13) Richards and Thompson, *J. Chem. Soc.*, 1259 (1947).
(14) Soloway and Friess, *J. Am. Chem. Soc.*, **73**, 5000 (1951).
(15) Kellie, O'Sullivan, and Sadler, *J. Chem. Soc.* (in the press).

The Nuclear Magnetic Resonance Spectrum of Helvolic Acid

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A tentative structure was recently proposed for helvolic acid[2] in which all of the known groupings were accounted for with the exception of the location of one carbon atom. It is the purpose of this report to offer evidence for the position of this remaining atom.

The C-methyl analysis of helvolic acid gave a value of 3.62 C-methyls per mole.[2] This number is rather high to represent four, and can best be taken as indicative of five such methyls per molecule. The formula proposed earlier[2] would be predicted to give four C-methyls,[3] two from the acetoxyl groups, one from C_{18}, and one from the acetone resulting from cleavage of the side chain. The extra carbon atom would thus appear likely to be present as a methyl group.

Ordinarily extra carbon atoms in steroids are found as alkyl groups at C_{24}. The ultraviolet spectra of helvolic acid and its derivatives did not, however, appear consistent with a methyl group at this position. On the other hand, there was available some evidence which appeared to indicate that no hydrogen atom was present at C_{24}. There was no hydrogen out-of-the-plane bending band near 12 μ in the infrared spectrum, and there was no strong band in the 6μ region which could be attributed to the carbon-carbon double bond stretching absorption. The stretching absorption is ordinarily very intense for a double bond of the mesityl oxide type,[4] while it might be expected to be weak if a nearly symmetrical arrangement around the double bond existed, as it would if a C_{24} methyl were present. In view of the conflicting evidence, location of the extra carbon was not specified in the original formulation.

Recently nuclear magnetic resonance spectra have been used to locate the positions of double bonds in molecules by determining the number of hydrogens present on the double bonds,[5] and the success of this technique is dependent on the fact

(1) National Science Foundation Post Doctoral Fellow, 1955–1956. Present address: Chemistry Department, Wayne State University, Detroit, Michigan.
(2) Cram and Allinger, *J. Am. Chem. Soc.*, **78**, in press (1956).
(3) Eisenbraun, McElvain, and Aycock, *J. Am. Chem. Soc.*, **76**, 607 (1954).
(4) (a) Bellamy, *The Infrared-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, p. 37; (b) Djerassi, Bowers, and Khastgir, *J. Am. Chem. Soc.*, **78**, 1729 (1956).
(5) (a) Dauben and Hance, *J. Am. Chem. Soc.*, **77**, 2451 (1955); (b) Corey, Burke, and Remers, *J. Am. Chem. Soc.*, **77**, 4941 (1955); (c) Ettlinger and Kennedy, *Chemistry & Industry*, 166 (1956).

TABLE I
NORMALIZED BAND AREAS

Methyl Ester	δ →1.0	2.1	2.6	2.8	3.1	3.4	3.7	4.0
Helvolate	3	10	10	2	9	2	6	3
Tetrahydrohelvolate	3	8	10	2	0	15		12

that the magnitude of the magnetic field required for resonance differs for hydrogens on double bonds and for hydrogens on saturated carbon atoms. It is known from the work of Meyer, Saika, and Gutowsky[6] that the resonance field of a methyl group on a double bond is likewise displaced from that of a methyl group on a saturated carbon, and this latter fact is of use in the present case.

The nuclear magnetic resonance spectra of methyl helvolate and methyl tetrahydrohelvolate were determined in chloroform solution and are shown in Figure 1. In the spectrum of methyl helvolate

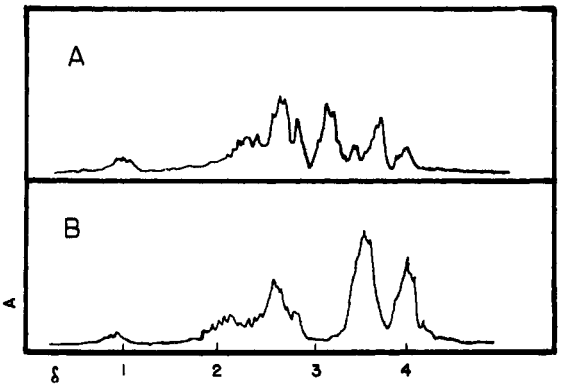
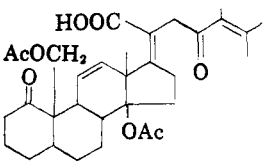


FIG. 1.—NUCLEAR MAGNETIC RESONANCE SPECTRA: Curve A, Methyl helvolate; Curve B, Methyl tetrahydrohelvolate.

there are visible eight distinct bands which are listed in Table I consecutively in order of increasing field strength. The corresponding absorption for methyl tetrahydrohelvolate is also listed.

The absorption due to the chloroform is off (to the left) the portions of the spectra shown. The hydrogens on the double bonds could not be detected with certainty. The high molecular weight of the compounds and the fact that these spectra had to be determined in a *ca.* 25% (saturated) solution, coupled with the fact that the absorptions of these two hydrogens probably occur at slightly different fields, reduced the intensities of these bands to the point where they could not be separated from the background noise. The band at δ equals 1.0 is clearly due to the methyl group of the methyl ester, as the spectrum of helvolic acid is identical with that of the ester in all respects except that this band is missing. It is clear that the band δ equals 4.0 is due to the methyl groups on saturated carbons, since it occurs at the highest field strength.[6] From the integrated normalized intensities it is clear that there is one such methyl (3 hydrogens) in methyl helvolate (C_{18}) and four such methyls in methyl tetrahydrohelvolate. The band at δ equals 3.1 can be assigned to methyl groups on double bonds. The location of the band in the spectrum is consistent with such an assignment,[6] and the area of the band indicates that there are three such groups in methyl helvolate and none in the tetrahydro ester. The two methyl groups at the end of the side chain are known to be situated on a carbon atom which is converted from unsaturated to saturated in the transformation of methyl helvolate to the tetrahydro derivative. It is now clear that a third methyl group is similarly situated and would thus have to be at C_{11}, C_{12}, or C_{24}. Either of the first two positions is *a priori* highly improbable for a naturally occurring compound. In addition, the infrared and ultraviolet spectra of the isolated double bond as well as the ultraviolet spectrum of its tetranitromethane complex all indicate that it is disubstituted.[2]

The extra carbon atom can now, on the basis of these data, be placed at C_{24}, and helvolic acid is hence represented by structure I. The ultraviolet



I

spectra of helvolic acid and its carbonyl derivatives remain somewhat anomalous, but in view of the homoconjugation[7] which may occur, and the possibility that the Δ^{17} double bond in some of the derivatives may have shifted to the cross-conjugated ($\Delta^{20(22)}$) position, some deviation from ideality is perhaps not unexpected.

The nuclear magnetic resonance spectrum of methyl dihydrohelvolate was also desired, and the compound had been previously prepared by a partial hydrogenation of methyl helvolate.[2] Repeated attempts to again obtain the dihydro compound in the same way, but using a different batch of catalyst, were unsuccessful. In each case a mix-

(6) Meyer, Saika, and Gutowsky, *J. Am. Chem. Soc.*, **75**, 4567 (1953).

(7) For examples of the effects of homoconjugation on ultraviolet spectra see (a) Braude, Jones, Sondheimer, and Toogood, *J. Chem. Soc.*, 607 (1949); (b) Winstein, Brown, Schreiber, and Schlesinger, *J. Am. Chem. Soc.*, **74**, 1140 (1952); (c) Hine, Brown, Zalkow, Gardner, and Hine, *J. Am. Chem. Soc.*, **77**, 594 (1955); (d) Bartlett and Lewis, *J. Am. Chem. Soc.*, **72**, 1005 (1950).

ture containing starting material and the tetrahydro derivative was obtained.

EXPERIMENTAL

Methyl helvolate, methyl tetrahydrohelvolate, and helvolic acid were available[8] from earlier work.[2] Attempts were made to prepare the dihydro ester by the method used earlier, but were unsuccessful. When the theoretical amount of hydrogen was added to methyl helvolate, a mixture was obtained which contained 30–35% starting material. Further hydrogenation led to mixtures from which no pure compound short of the tetrahydro derivative could be isolated.

The spectra were obtained on a Varian Associates High Resolution n-m-r spectrometer, V-4300B, using a spinning sample, O.D. 5 mm. The radio frequency was 40 mc., sweep width about 100 milligauss, sweep rate about 20 mg./sec. Toluene was used for the calibrations by the capillary tube method,[9] and the values of δ are in parts per million.

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(8) The author is indebted to Dr. D. J. Cram for making available samples of these compounds.

(9) Bothner-By and Glick, *J. Am. Chem. Soc.*, **78**, 1071 (1956).

A Facile New Synthesis of Poly-D,L-phenylalanine

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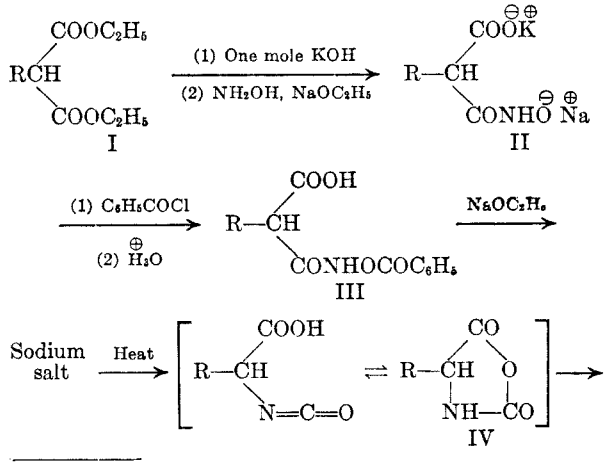
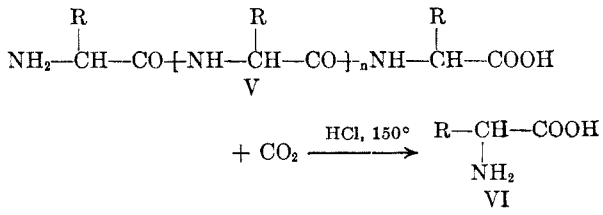
The transformation of malonic esters to either polypeptides or amino acids using the Lossen rearrangement has been described previously.[1] This degradation is aptly shown by this scheme:



(1) (a) C. D. Hurd and C. M. Buess, *J. Am. Chem. Soc.*, **73**, 2409 (1951); (b) C. D. Hurd and L. Bauer, *J. Am. Chem. Soc.*, **73**, 4387 (1951); (c) C. D. Hurd and L. Bauer, *J. Org. Chem.*, **18**, 1440 (1953).

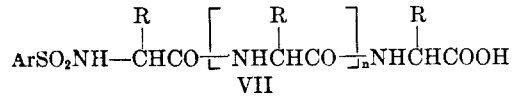


The recent introduction of sulfonyl halides[2,3] as reagents for the Lossen rearrangement shortens the degradation considerably. Thus, sodium benzohydroxamate is converted to benzo(phenylcarbamylhydroxamic) acid, $C_6H_5CONH—O—CONHC_6H_5$, in one step. Presumably, the intermediate arenesulfonic derivative, $C_6H_5CONH—O—SO_2Ar$, is unstable and rearranges spontaneously to phenyl isocyanate. The latter reacts with the original sodium benzohydroxamate to form the carbamic derivative of benzohydroxamic acid.

In an endeavor to shorten the polypeptide synthesis outlined above, the alkali salt of α-carboxy-β-phenylpropionohydroxamic acid (II, R = benzyl) was treated with benzenesulfonyl chloride. No visible reaction occurred until the mixture was heated to at least 50°. Then, a gummy solid commenced to precipitate and carbon dioxide was released. Similar reactions were observed in either water or benzene, although water was the preferred solvent.

The product of the reaction was treated with cold 10% aqueous sodium hydroxide solution. The insoluble portion (A) was filtered and the filtrate was acidified to yield another substantial fraction (B). Both (A) and (B) were insoluble in water and hydrochloric acid, but were readily soluble in ethanol. An attempt to fractionate either (A) or (B) by conventional means yielded a series of gums. No crystalline material was afforded by either fraction. Hydrolysis of both fractions independently gave D,L-phenylalanine (VI, R = benzyl) identified as the benzoyl derivative.

Polypeptides made by the conventional Lossen rearrangement[1] were completely insoluble in sodium hydroxide solution. To explain the solubility of fraction (B) in alkali, it was assumed that the polypeptide was of type (VII) (Ar = phenyl R = benzyl).



In VII, the two acid functions, the sulfonamide and carboxylic acid groups, might well explain this solubility. And, in fact, the infrared spectrum clearly showed the presence of bands due to the —COOH, Ar—SO_2—NH—, and —CONH— groups (*cf.* experimental section).

(2) C. D. Hurd and L. Bauer, *J. Am. Chem. Soc.*, **76**, 2791 (1954).

(3) M. A. Stolberg, R. C. Tweit, G. M. Steinberg, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 765 (1955).