hydroxy-4-androsten-17α-yl)propanoic acid lactone the 6-methyl in IV is in the equatorial (α) configuration, see Table II.

The structure of IV indicates that the predominant reaction of I and V with ethanethiolic acid takes place *via* a trans-diaxial addition to the 6,7 double bond. Although III should be more stable than its isomer II, the product of kinetic control, preliminary efforts to obtain a larger proportion of III by altering the conditions of the addition or by equilibration of II were fruitless.[13] It may be that under conditions necessary to effect equilibration, the addition is reversed and the ethanethiolic acid is lost by side reactions.

The aldosterone blocking potency[14] of IV is the same as that of II (spironolactone) given subcutaneous to adrenalectomized rats. Interestingly the inversion of the 7-acetylthio group lowers both the oral and parenteral activity; thus III has less than 10% of the activity of II.

Experimental[15]

3-(3-Oxo-7β-acetylthio-17β-hydroxy-4-androsten-17α-yl)-propanoic Acid Lactone (III).—A solution of 5.02 g. of 3-(3-oxo-17β-hydroxy-4,6-androstadien-17α-yl)propanoic acid lactone[2] in 5.0 ml. of ethanethiolic acid was heated on a steam bath for 1 hr. The residue, a light yellow gum, was crystallized from 50 ml. of methanol to afford 4.30 g. of material melting at 130–133°, with resolidification and final melting at 203–206°, $[\alpha]_D$ −37°. The infrared spectrum of this material was identical with that of an authentic sample of 3-(3-oxo-7α-acetylthio-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone.[2]

When the mother liquors from the above crystallization were concentrated to 25 ml. and the solution cooled to 0°, an additional crop of 0.95 g. of material, m.p. 135–137°, with partial resolidification and final melting at 180°, separated. Three crystallizations of this material from methanol afforded 0.204 g. of a substance (III) which melted at 227–230°; $[\alpha]_D$ +88°; $\lambda_{max}^{CH_3OH}$ 238 mμ, ε 19,100. The infrared spectrum (3% in $CHCl_3$) shows bands at 5.63, 5.91, 6.16, 6.81, 7.00, 7.20, 7.34, 7.49, 7.81, 8.1–8.4, 8.89, 9.29, 9.61, 9.82, 10.51, 10.93, and 11.50 μ.

Anal. Calcd. for $C_{24}H_{32}O_4S$: C, 69.20; H, 7.74. Found: C, 68.98, 69.20; H, 7.52, 7.56.

3-(3-Oxo-7α-acetylthio-17β-hydroxy-6α-methyl-4-androsten-17α-yl)propanoic Acid Lactone (IV).—3-(3-Oxo-17β-hydroxy-6-methyl-4,6-androstadien-17α-yl)propanoic acid lactone,[1] 224 mg., was dissolved in 0.5 ml. of ethanethiolic acid. The solution was heated for 2 hr. on the steam bath. Most of the excess thiolic acid was removed under vacuum and the residue was crystallized from ether to yield 144 mg. of IV, m.p. 237–240° (dec.), $\lambda_{max}^{CH_3OH}$ 237.5 mμ, ε 19,400.

Anal. Calcd. for $C_{25}H_{34}O_4S$: C, 69.73; H, 7.96. Found: C, 69.47; H, 8.14.

Acknowledgment.—We wish to thank Mr. T. A. Wittstruck for the determination and preliminary interpretation of some of the n.m.r. spectra.

(12) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., New York, 1960, p. 63.

(13) Unpublished work by Mr. R. T. Nicholson.

(14) C. M. Kagawa, *Endocrinology*, **67**, 125 (1960). We are most grateful to Dr. Kagawa and Mr. Robert Jacobs for these results.

(15) Rotations run in chloroform at 24 ± 2°.

Synthesis of Diacrylylmethane[1]

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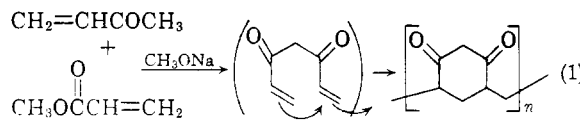
Received March 5, 1962

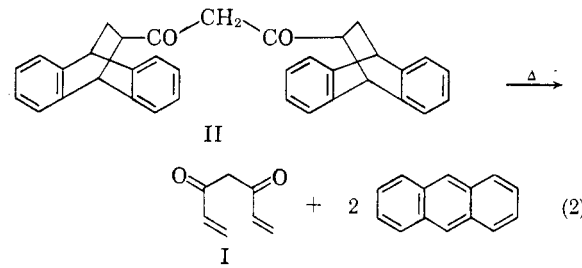
Polydiacrylylmethane prepared by allowing methyl vinyl ketone and methyl acrylate to react in the presence of sodium methoxide,[3] on the basis of microanalytical and infrared data,[4] is not a homopolymer but is apparently a copolymer of diacrylylmethane and methyl vinyl ketone. The expected reaction was



(1)

In order to prepare pure polydiacrylylmethane, which was needed as an intermediate for other studies, it was first necessary to obtain pure diacrylylmethane. This paper reports a successful route to the preparation of this monomer. Unsuccessful reactions are also recorded.

The pyrolytic reverse Diels-Alder reaction of 1,3-di(9,10-dihydro-9,10-ethanoanthracenyl-11)-1,3-propandione,[5] II, in the presence of *p*-terphenyl as an inert, high-boiling diluent produced diacrylylmethane in 47–56% yield. In the absence of *p*-terphenyl the yield averaged about 30%.



(2)

The use of the reverse Diels-Alder reaction to produce chemically unstable compounds is not uncommon. The most recent example is the synthesis, by Field,[6] of 1,3-dioxole,  , by pyrolysis of the corresponding anthracene derivative. Another very interesting example is the preparation of cyclopentadienone, also by pyrolysis of the

(1) This work was supported under contract AF 33(616)7908 with the Nonmetallic Materials Laboratory of Wright Air Development Division, Wright-Patterson Air Force Base, Ohio. This paper may be reproduced for any purpose of the United States Government.

(2) Present address: Department of Chemistry, University of Oklahoma, Norman, Oklahoma.

(3) J. F. Jones, *J. Polymer Sci.*, **33**, 7 (1958).

(4) T. Otsu, J. E. Mulvaney, and C. S. Marvel, *ibid.*, **46**, 546 (1960).

(5) J. J. Bloomfield, *J. Org. Chem.*, **27**, 2742 (1962).

(6) N. D. Field, *J. Am. Chem. Soc.*, **83**, 3504 (1961).

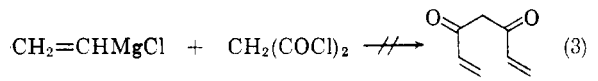
anthracene derivative.[7] The present case appears to be the first in which two double bonds have been protected simultaneously.

Diacrylylmethane is a pale yellow liquid with an intense, acrid odor and lachrymatory properties. It polymerizes very slowly at −23°, in the absence of polymerization inhibitors. It appears to be very stable at −80°. At room temperature, however, it slowly (over one to two days) polymerizes to a hard, insoluble, bright yellow resin. In dimethylformamide at −60° it was polymerized by sodium cyanide to an insoluble yellow powder. The analytical results on this polymer are not satisfactory and it will be fully characterized in a later communication.

The infrared spectrum of the pure monomer shows strong bands at 1650 and 1580 cm.$^{-1}$, which are indicative of the α,β-unsaturated β-diketone structure as are bands at 988(s), 960(s), and 884-(m) cm.$^{-1}$.[8] The ultraviolet spectrum in 95% ethanol has $\lambda\lambda_{max}$ 327 mμ, ϵ 1.5 × 10^4 and 222 mμ, ϵ 7.7 × 10^3. The ultraviolet spectrum of the green copper chelate in absolute ethanol has $\lambda\lambda_{max}$ 333 mμ, ϵ 2.8 × 10^4 and 249 mμ, ϵ 2.7 × 10^4, with a shoulder at 372–376 mμ, ϵ 1.7 × 10^4. The visible spectrum of the chelate has λ_{max} 650–660 mμ, ϵ 50.

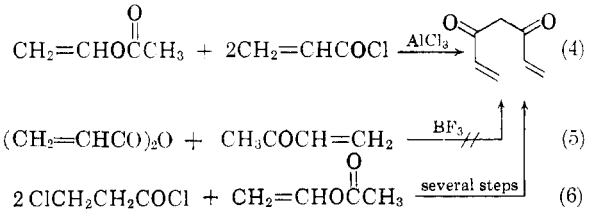
The integrated n.m.r. spectrum[9] indicates that diacrylylmethane is completely enolic. The band at −5.4 τ for the hydroxylic proton, which has also been observed in 2,4-pentanedione,[10] has an integral value corresponding to one proton. The doublet at 3.72 τ with an integral value corresponding to four protons is assigned to the terminal vinyl hydrogens. The unsymmetrical quartet centered at 4.3 τ with an integral value corresponding to three protons is assigned to the three nonterminal vinylic hydrogens in the enol. The entire quartet is between 4.22 τ and 4.42 τ.

There are many possible routes, on paper, to the preparation of diacrylylmethane. Of the two described above, one leads to polymer, equation 1; the other is the only successful route that was found to the monomer itself. The reaction of vinylmagnesium chloride with malonyl chloride, equation 3, was found to produce a polymer which had no properties of polydiacrylylmethane.[11] At an earlier stage of this work it was felt that diacrylylmethane might be synthesized by acid-catalyzed reactions,



(3)

equations 4–6. These three reactions also failed to produce the monomer; the major products were red, brown, or black polymers.



(4)

(5)

(6)

Experimental[12]

Diacrylylmethane (I).—The pyrolysis reactions were carried out at 20–30 mm. under prepurified nitrogen in an apparatus which consisted of a 100-ml. flask with a 24/40 neck connected at a 45° upward angle to an 18-in. unpacked "Vycor" tube, 20 mm. in diameter. The exit of this tube was attached by a ball and socket joint to the outside wall of a trap cooled at −80°. Pyrolysis was accomplished by gently heating the flask containing 2.4 g. (0.005 mole) to 9.6 g. (0.02 mole) of II with a free flame until the solid melted. The melt was then vigorously heated and the tube was kept hot (125–150°). Diacrylylmethane distilled into the cold trap. Yields ranging from 16 to 38% were obtained in this way. The presence of *t*-butylhydroquinone as a polymerization inhibitor did not improve the yield. Better yields were obtained with larger batches. In two experiments 4.8 g. of II and 10 g. of *p*-terphenyl and 9.6 g. of II and 20 g. of *p*-terphenyl were pyrolyzed, with *t*-butylhydroquinone (0.1 g.) added, to give yields of 46.8 and 56.2%, respectively. The *p*-terphenyl lowered the melting point of the mixture which was then refluxed vigorously. Condensate in the tube was also kept at the boiling point. Longer heating periods gave slightly higher yields. After the cold trap was warmed to room temperature it was connected to a second trap, cooled at −15°, and fitted so that the inner tube led directly to a tared vial. Then, trap to trap distillation at 0.05 mm. and room temperature permitted recovery of diacrylylmethane. Two such distillations gave the analytical sample, n^{28}D 1.5675.

Anal. Calcd. for $C_7H_8O_2$: C, 67.72; H, 6.49. Found: C, 67.55; H, 6.73; and C, 67.41; H, 6.51.

The infrared spectrum (neat) has bands at 3160(w), 3080(w), 1650(s), 1580(s), 1450(m), 1405(m), 1365(w), 1320(w), 1295(m), 1260(m), 1200(w), 1145(m), 1060(m), 1025(w), 988(s), 960(s), 884(s), 825(s), and 755(w) cm.$^{-1}$.

The copper chelate was readily formed by adding a methanol solution of diacrylylmethane to a warm 10% solution of copper acetate monohydrate. The chelate crystallized from methanol in green needles with an unusual melting point behavior. If the sample were placed in the bath at 175° or above, the compound decomposed after a few seconds with a slight puff of smoke. If the sample were placed in the bath at a temperature less than 175°, it merely darkened but did not melt, even at 360°.

Anal. Calcd. for $C_{14}H_{14}CuO_4$: C, 54.28; H, 4.55. Found: C, 54.17; H, 4.59.

The infrared spectrum (KBr disk) of the chelate has

(7) C. H. DuPuy and C. E. Lyons, *J. Am. Chem. Soc.*, **82**, 631 (1960).

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, 1958.

(9) Determined on the pure compound containing only a small amount of tetramethylsilane for reference purposes. The spectrum was obtained on a Varian A-60 spectrometer through the courtesy of Prof. G. S. Hammond and Mr. R. C. Neuman, Jr., at the California Institute of Technology.

(10) The work of several workers is cited by L. M. Jackman, "Applications of Nuclear Magnetic Resonance spectroscopy in Organic Chemistry," Pergamon Press, New York, 1959, p. 71.

(11) Unpublished observations of T. Otsu and C. S. Marvel.

(12) Melting points were taken with total immersion, calibrated thermometers. Boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord. Ultraviolet spectra were recorded on a Cary Model 11 spectrophotometer. Analyses were by Micro-Tech Laboratories, Skokie, Illinois.

bands at 3550(s), 1650(s), 1550(vs), 1465(s), 1400(w), 1300(w), 1220(w), 1178(m), 1080(m), 984(s), 950(s), 895(w), 820(s), 785(w), and 730(w) cm.$^{-1}$.

β-Chloropropionyl Chloride, Vinyl Acetate, and Aluminum Chloride. Method 6.—This reaction was run using 2 moles of β-chloropropionyl chloride.[13] In addition to a large amount of a chloroform-soluble, ether-insoluble red polymer there was obtained 3.3 g. of an orange liquid, b.p. 48°/0.25 mm., n^{25}D 1.4948. This material gave a positive enol test with ferric chloride and had two poorly resolved bands in its infrared spectrum between 1600 and 1700 cm.$^{-1}$ that might be indicative of the β-diketone structure.[3] Because of the low yield no further work was done on this reaction.

Acknowledgment.—The author is indebted to Professor C. S. Marvel for a postdoctoral research associateship and for his support and encouragement and to Dr. P. D. Gardner for helpful and stimulating conversations.

(13) A. Sieglitz and O. Horn. *Ber.*, **84**, 607 (1951).

Synthesis of Two Optically Active N-Acetyl Dipeptides by the *p*-Nitrophenyl Ester Method

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Received March 7, 1962

The desire recently arose in this laboratory to utilize the *p*-nitrophenyl ester of N-acetyl-S-benzyl-L-cysteine for the preparation of a protected nonapeptide which in turn was to be used for the synthesis of an acetyl derivative of lysine-vasopressin. The *p*-nitrophenyl ester of the N-carbobenzoxy derivative of S-benzyl-L-cysteine has been used in the synthesis of several peptides without any apparent racemization of the cysteine residue being encountered.[1-4] It was not known, however, whether the *p*-nitrophenyl ester of the N-acetyl derivative could be used similarly. The question of racemization was particularly important since optically active N-acetyl amino acids undergo conversion to their racemic form during peptide synthesis by most of the usual methods.[5,6] It was necessary, therefore, before the desired nonapeptide could be synthesized, to study the ability of *p*-nitrophenyl N-acetyl-S-benzyl-L-cysteinate to form a peptide bond without the configuration of the cysteine simultaneously being changed. The present report describes the preparation of this active ester and its use in the synthesis of two optically active N-acetyl dipeptides.

p-Nitrophenyl esters have been prepared routinely in this laboratory from the protected amino acid and *p*-nitrophenol with the aid of dicyclohexylcarbodiimide.[2,7,8] When the synthesis of *p*-nitrophenyl N-acetyl-S-benzyl-L-cysteinate from N-acetyl-S-benzyl-L-cysteine was attempted by this procedure, only the racemic product could be isolated. Likewise, the mixed anhydride method[9] yielded the optically inactive *p*-nitrophenyl ester. The desired optically active *p*-nitrophenyl ester could be obtained, however, by allowing *p*-nitrophenyl S-benzyl-L-cysteinate hydrobromide[10] to stand overnight in a solution of acetic anhydride in glacial acetic acid. *p*-Nitrophenyl esters of other amino acids with unprotected amino groups have been acylated previously without any apparent loss of optical activity.[10,11]

Ethyl N-acetyl-S-benzyl-L-cysteinylglycinate and methyl N-acetyl-S-benzyl-L-cysteinyl-L-tyrosinate were prepared from the corresponding N-carbobenzoxy dipeptides by acetylation of their decarbobenzoxylation products, a synthetic pathway in which there is considered to be no significant danger of racemization.[2,6,12] Ethyl N-acetyl-S-benzyl-L-cysteinylglycinate then was prepared from *p*-nitrophenyl N-acetyl-S-benzyl-L-cysteinate and ethyl glycinate hydrochloride. Likewise, methyl N-acetyl-S-benzyl-L-cysteinyl-L-tyrosinate was prepared from the active ester and methyl L-tyrosinate. The analytically pure products were isolated in 49 and 81% yield, respectively. Their melting points and optical rotations were in close agreement with the corresponding values for the products obtained by the more conventional synthetic procedure. Although the complete absence of racemization has not been demonstrated, these experiments indicate that the *p*-nitrophenyl ester of N-acetyl-S-benzyl-L-cysteine can be used for the preparation of optically active N-acetyl peptides. It remains to be established, of course, whether the *p*-nitrophenyl esters of other optically active N-acetyl amino acids can be used in peptide synthesis with similar retention of optical activity.

Experimental

All melting points were determined in capillary tubes and are corrected.

N-Acetyl-S-benzyl-L-cysteine.—This compound was prepared by a modification of a procedure reported earlier

(1) M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 2504 (1959).
(2) M. Bodanszky and V. du Vigneaud, *ibid.*, **81**, 5688 (1959).
(3) M. Bodanszky, J. Meienhofer, and V. du Vigneaud, *ibid.*, **82**, 3195 (1960).
(4) J. Meienhofer and V. du Vigneaud, *ibid.*, **83**, 142 (1961).
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(6) St. Guttmann and R. A. Boissonnas, *Helv. Chim. Acta*, **41**, 1852 (1958).
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(8) M. Rothe and F. W. Kunitz, *Ann.*, **609**, 88 (1957).
(9) M. Bodanszky, *Acta Chim. Acad. Sci. Hung.*, **10**, 335 (1957).
(10) M. Goodman and K. C. Stueben, *J. Am. Chem. Soc.*, **81**, 3980 (1959).
(11) B. Iselin and R. Schwyzer, *Helv. Chim. Acta*, **43**, 1760 (1960).
(12) K. Hofmann, T. A. Thompson, H. Yajima, E. T. Schwartz, and H. Inouye, *J. Am. Chem. Soc.*, **82**, 3715 (1960).