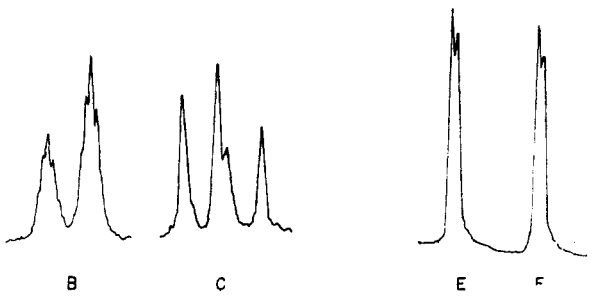

Fig. 2. Fine splitting in NMR spectrum of II

Confirmation of the double bond is obtained in band B (τ, 4.97) corresponding in position to an olefinic proton.[8] This is coupled to one adjacent hydrogen (10 c.p.s.) and shows further fine splitting (see Fig. 2) of the same magnitude as the methyl bands E and F. The unequal coupling with two methyl groups (1.5 for E and 1.3 c.p.s. for F) is due to the difference in the 1:3-*cis* and 1:3-*trans* coupling[12] and is consistent with the poorly resolved septets in band B. Band C can then be assigned to the proton coupled with the olefinic proton, as it shows the same spacing (10 c.p.s.) as in band B and is also at low field (τ, 5.6), being α to the carbonyl and β to the double bond.[11] If this deduction is correct then the fact that band C is a quartet is most simply explained by having the proton giving rise to band C coupled both to the olefinic proton (J = 10 c.p.s.) and to another proton (J = 8.75 c.p.s.).

The spectrum of the remaining protons is in bands A, D and under band E. The former is due to the aromatic protons which are similar to those of acetophenone and corresponds to ten protons. The spectrum of the tertiary hydrogen of the isopropyl group is only partially visible under band E as it is extensively split by the six hydrogens on the two methyl groups and also by adjacent hydrogen. Intensity measurements on band D show that it corresponds to three protons as compared with one each for B and C. The detailed analysis of this is not feasible by first-order treatment as the chemical shift is of the same order as the coupling constant resulting in an ABC system.[13]

The properties of the dimer II can be rationalized on the basis of the structure proposed. Although the double bond is only trisubstituted, models show considerable steric hindrance. The latter has been shown to confer unusual properties even to the disubstituted ethylene, 1,1-dineopentylethylene (III) which can be hydrogenated only at 130 atmospheres at 150° with Raney nickel.[14] The evolution of hydrogen bromide during attempts to brominate II[1] also finds parallel in the properties of III.[14] We have observed that the ethylenic linkage in II is attacked extremely slowly by potassium permanganate as has also been observed with III.

It is interesting that II is a β,γ-unsaturated ketone although it is formed under equilibrating conditions. This may be due to increased steric strain in going from an unconjugated to a conjugated structure. The structure II is consistent with the ultraviolet absorption spectrum which follows that of acetophenone. The formation of the monomer I can be easily visualized as a reverse Michael reaction[5] which needs no further comment.

ADDED IN PROOF: Dr. Kulka (personal communication) has now obtained acetone on ozonolysis of the dimer, in complete agreement with the structure proposed in this paper.

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Cleavage of Ethyl 2,2-Diphenyl-4-pentenoylglycinate by Oxidants and Acids

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Received May 16, 1960

The participation of amide groups in intramolecular displacement reactions has been utilized as a principle for the elaboration of selective methods to cleave peptide bonds next to γ,δ-unsaturated acids such as tryptophan[1,2] and tyrosine.[3] These degradative reactions may be used to advantage not only for analytical studies but also for the development of blocking groups in peptide synthesis. Indole-3-propionic[1] and phloretic acids[3] in principle are acceptable blocking groups for the synthesis of peptides that contain no functional groups whose rate of reaction with *N*-bromosuccinimide or *N*-bromoacetamide is faster than with that of the blocking groups. This note shows that by comparison observations on the use of a straightforward γ,δ-unsaturated acid such as 2,2-diphenyl-4-pentenoic acid (I) as a blocking group, though offering no immediate advantages with regard to yield, may serve as a guide for the development of groups removable not only by positive bromine but also by the controlled action of acid.

Bromination of acid I under anhydrous conditions has been found to lead to a bromolactone formulated as IV,[4] which has now also been obtained

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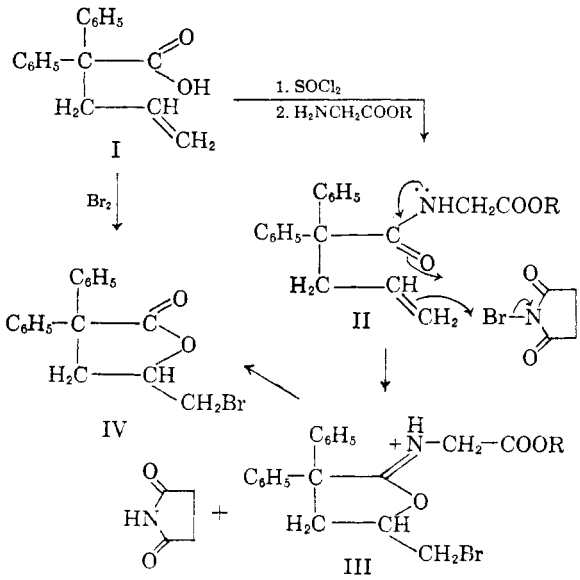

in 80% yield by the action of *N*-bromosuccinimide on the solution of the acid I in a mixture of acetonitrile and aqueous acetate buffer of *p*H 4.

The preparation of the corresponding amide II of glycine ethyl ester, unsuccessful by the mixed anhydride and carbodiimide methods, was achieved in 65% yield by the reaction of the acid chloride[4] of I with ethyl glycinate.

The cleavage of this peptide was carried out in ethanolic aqueous buffer solutions of varying *p*H or in dioxane or acetic acid saturated with hydrogen bromide. The colorimetric evaluation of the ninhydrin reaction according to Moore and Stein was used to follow the cleavage of the peptide bond. In buffer solutions of *p*H 4 cleavage to the extent of 20% was observed when the ratio of peptide to *N*-bromosuccinimide was about 1:1. Less than 5% or no cleavage occurred when glacial acetic acid was used as the reaction medium. By changing the *p*H of the buffer systems and using one mole of *N*-bromosuccinimide, the maximum yield of cleavage was constant (18–25%) between *p*H 1 and *p*H 6, and decreased steadily with higher *p*H, suggestive of alternate routes, *e.g.*, participation of nitrogen and formation of pyrrolidones.[5] The yields with acid alone in anhydrous systems did not exceed 32%.

Formation of stable iminolactones of type III has so far been observed only for tertiary amides derived from cyclohexylamine[5] dialkylamines and morpholine.[6]

EXPERIMENTAL

2,2-Diphenyl-4-hydroxy-5-bromopentanoic acid lactone (IV). To a solution of 500 mg. (1.98 mmoles) of 2,2-diphenyl-4-pentenoic acid (I) in a mixture of 25 ml. of acetonitrile and 25 ml. of 0.2*M* acetate buffer of *p*H 4 was added a solution of 374 mg. (2.1 mmoles; 5% excess) of *N*-bromosuccinimide. After 2 hr. at room temperature, the acetonitrile was evaporated and the neutral product was extracted into ether. The residue from the ether extract was crystallized from ethanol to give 480 mg. (73%) of lactone IV, m.p. 87–89° (reported[4] m.p. 87–88°). An additional 50 mg. was obtained from the mother liquors to give a total yield of 530 mg. (81%). In the infrared the compound has a peak at 5.65 μ, as would be expected for a five-membered lactone.

2,2-Diphenyl-4-pentenoylglycine ethyl ester (II). The crude acid chloride[4] from 1.09 g. (4 mmoles) of 2,2-diphenyl-4-pentenoic acid was allowed to react with a solution of 600 mg. (4.3 mmoles) of glycine ethyl ester and 1.1 ml. of triethylamine in chloroform for 2 days at 20°. The solution was extracted with 20 ml. of 1.0*N* hydrochloric acid and 20 ml. of 1.0*N* potassium bicarbonate, and evaporated to dryness. Crystallization from ethanol-water gave 870 mg. (65%) of II, m.p. 85–87°. Recrystallization, followed by drying *in vacuo* for 2 hr. at 55° afforded an analytical sample, m.p. 86.5–87.0°.

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.79; H, 7.11; N, 4.29.

Cleavage of the peptide. The cleavage of the peptide was carried out in aqueous buffer systems with 1 mole of *N*-bromosuccinimide or in anhydrous systems saturated with hydrogen bromide and was followed by the method described by Patchornik, *et al.*[1] Table I summarizes the results. Total hydrolysis of the peptide in 6.0*N* hydrochloric acid for 15 hr. at 105° gave a quantitative yield of glycine.

TABLE I

EFFECT OF *p*H ON THE CLEAVAGE OF 2,2-DIPHENYL-4-PENTENOYLGLYCINE ETHYL ESTER AS ASSAYED BY COLORIMETRIC EVALUATION OF NINHYDRIN-POSITIVE MATERIAL

*p*H	Buffer or Solvent System	Yield of Glycine Ethyl Ester, %
1	Hydrochloric acid	25
2	Citrate	25
3	Citrate	21
4	Acetate	18
5	Acetate	20
6	Phosphate	23
7	Phosphate	13
8	Borate	8
9	Borate	8
Anhydrous HBr	Dioxane, saturated, 25°, 2 hr.	32
Anhydrous HBr	Glacial acetic acid, saturated, 25°, 1 hr.	26

In contrast to indole-3-propionyl peptides[7] the pentenoyl peptide II is not cleaved by the action of periodic acid at *p*H 1.

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