cuted. A clue regarding the environment of the hydroxyl and methoxyl functions of cryptojaponol came from a study of the pyridine solvent shift of its proton magnetic resonance spectrum, $\delta_{CDCl_3} - \delta_{C_5H_5N} = 0.01$ ppm for the isopropyl methyl groups. Had the compound been a 11-methoxy-12-hydroxy isomer, the proximity of the hydroxyl and isopropyl groups would have led to strong deshielding of the latter in pyridine solution.[13] Structure **3c** was confirmed when hydrogenation of cryptojaponol and subsequent oxidation with *m*-chloroperbenzoic acid yielded royleanone methyl ether (**4**).[14] The synthesis of cryptojaponol (**3c**) was accomplished in the following manner. Chromic acid oxidation[9] of 11-methoxyferruginyl methyl ether (**1c**)[15] gave 11-methoxysugiyl methyl ether (**3d**). Demethylation of the latter with boron tribromide[16,17] and remethylation of the resultant catechol **3e** with diazomethane yielded the natural product (**3c**).

Experimental Section[18]

Dehydroabietane (1b).—A mixture of 200 mg of ferruginol (**1a**), 250 mg of 1-phenyl-5-chlorotetrazole, and 1.5 g of anhydrous potassium carbonate in 50 ml of acetone was refluxed for 18 hr. The cooled mixture was filtered and the filtrate evaporated under reduced pressure. Chromatography of the residue, 436 mg, on 6 g of Woelm neutral alumina, activity I, and elution with methylene chloride yielded 227 mg of oily ferruginyl 1-phenyl-5-tetrazoyl ether. A mixture of 160 mg of the ether and 200 mg of 10% palladium–charcoal in 20 ml of 95% ethanol was hydrogenated at 35 psi pressure for 48 hr. Filtration of the mixture and evaporation of the filtrate under reduced pressure yielded 160 mg of partly crystallized oil whose exhaustive extraction with petroleum ether gave 120 mg of clear oil. Chromatography of the latter on 6 g of silica gel and elution with petroleum ether afforded 33 mg of dehydroabietane (**1b**), mp and mmp 42–43°, ir and prm spectra identical with those of an authentic specimen,[7] while elution with methylene chloride led to recovery of 81 mg of starting ether.

Lactol 2a.—A solution of 125 mg of sugiyl methyl ether (**3b**) in 3 ml of dry *t*-butyl alcohol was added to a potassium *t*-butoxide solution (27 mg of potassium in 5 ml of dry *t*-butyl alcohol). Oxygen was bubbled into the mixture for 12 hr while it was being stirred and kept slightly above freezing temperature. Thereafter, 16 ml of 10% hydrochloric acid was added and the mixture extracted exhaustively with ether. The extract was dried over anhydrous sodium sulfate and evaporated. The solid residue, 110 mg, was chromatographed on an inverted dry column of silica gel G. Elution with chloroform gave first 35 mg of starting ketone **3b** and then 13 mg of lactol **2a**, mp and mmp 168–170°, ir and pmr spectra identical with those of the natural lactol.[8]

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.43; H, 8.31.

Royleanone Methyl Ether (4).—A mixture of 15 mg of cryptojaponol and 5 mg of 10% palladium–charcoal in 8 ml of ethanol was hydrogenated at atmospheric pressure and room temperature. Filtration of the mixture and evaporation of the filtrate yielded 14 mg of 7-deoxocryptojaponol, mp 164–165° (lit.[12] mp 163–164.5°). A solution of the latter and 10 mg of *m*-chloroperbenzoic acid in 5 ml of methylene chloride was left standing for 12 hr. A solution of 100 mg of sodium sulfite in 25 ml of water was added and the mixture stirred for 1 hr. The aqueous layer was extracted with methylene chloride, and the combined organic layer and extract was dried and evaporated. Thick layer chromatography of the residue, 8 mg, on silica gel G and elution with chloroform gave 3 mg of royleanone methyl ether (**4**), mp 118–120°, ir spectrum identical with that of an authentic sample.

Cryptojaponol (3c).—A solution of 530 mg of **1c**[15] and 500 mg of chromium trioxide in 60 ml of acetic acid and 15 ml of water was stirred at room temperature for 6 hr. It was poured into 250 ml of cold saturated brine solution and extracted with methylene chloride. The extract was washed with water, saturated sodium sodium bicarbonate, and brine solutions and dried. Solvent removal yielded 495 mg of oily ketone **3d** homogeneous on thin layer chromatography, 2,4-dinitrophenylhydrazone mp 215–217°.

Anal. Calcd for $C_{25}H_{36}O_6N_4$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.36; H, 6.83; N, 10.81.

A solution of 0.5 ml of freshly distilled boron tribromide in 5 ml of dry methylene chloride was added slowly to a solution of 250 mg of **3d** in 25 ml of methylene chloride at Dry Ice–acetone bath temperature. The solution was allowed to warm to room temperature slowly and then was evaporated under vacuum. Water, 50 ml, was added to the cooled solid residue and the mixture extracted with chloroform and with ether. The combined extracts were dried and evaporated. An ether solution of the solid residue (homogeneous on tlc and devoid of methoxy pmr signals) was treated with ethereal diazomethane. Evaporation of the solution and crystallization of the solid residue, 244 mg, from methanol gave cryptojaponol, mp and mmp 204–206°, ir and pmr spectral identical with those of an authentic sample.[19]

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.39; H, 9.09. Found: C, 76.69; H, 9.26.

Registry No.—**2a**, 24099-23-8; **3c**, 16755-52-5.

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(19) The authors are indebted to Professor T. Kondo for a gift of a specimen of the natural product.

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(18) Melting points were determined on a Reichert micro hot stage and are uncorrected.

Trichloroacetylation of Dipeptides by Hexachloroacetone in Dimethyl Sulfoxide under Neutral Conditions[1a]

C. A. PANETTA[1b] AND T. G. CASANOVA

Department of Chemistry, University of Mississippi, University, Mississippi 38677

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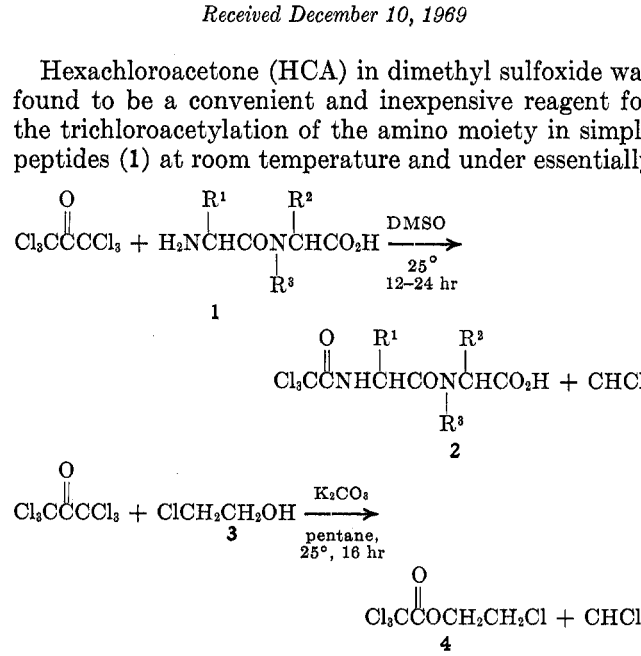
Hexachloroacetone (HCA) in dimethyl sulfoxide was found to be a convenient and inexpensive reagent for the trichloroacetylation of the amino moiety in simple peptides (**1**) at room temperature and under essentially



(1) (a) Presented at the 21st Southeastern Regional Meeting of the American Chemical Society, Richmond, Va., Nov 1969; (b) to whom inquiries should be addressed.

TABLE I

RESULTS OF NEUTRAL TRICHLOROACETYLATION EXPERIMENTS USING HEXACHLOROACETONE AND DIMETHYL SULFOXIDE[a,b]

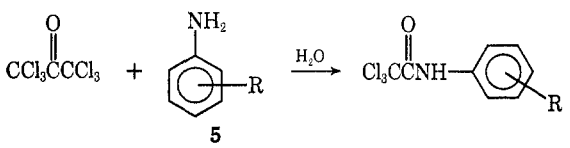
Name of dipeptide, 1	R¹	R²	R³	TCA-dipeptide, 2: Mp, °C[c]	Yield, %	Tlc R_f[d]	Ml of DMSO/mmol of dipeptide	New carbonyl group, ν (cm⁻¹)
Glycylglycine	H	H	H	142.0–142.5	28.5	0.20	3.54	1750
L-Leucyl-L-leucine	*i*-Bu	*i*-Bu	H	177.0–178.0	89.0	0.80	1.77	1710
Glycylsarcosine	H	H	Me	173.5–174.5	51.5	0.30	1.47	1746
L-Valyl-L-leucine	*i*-Pr	*i*-Bu	H	178.0–179.0	55.5	0.80	3.47	1715
L-Phenylalanyl-L-leucine	Benzyl	*i*-Bu	H	155.5–156.0	73.2	0.80	4.16	1708

[a] Moles of HCA:mole of dipeptide, 3–4:1. [b] Reaction period is 12 hr except for glycylglycine for which it is 24 hr. [c] Melting points are corrected. [d] 50:45:5 benzene:acetone:HOAc.

neutral conditions. The carboxylate group does not interfere with this novel reaction. The foregoing transformation was uncovered during a general investigation of the interaction of certain carbonyl compounds with peptides. Glycine, an amino acid, was also easily and rapidly transformed to its trichloroacetyl derivative under similar conditions. The common by-product in these reactions was chloroform which was detected and identified by vapor phase chromatography and by isolation and characterization. It was formed in good yield.

In 1960, Simmons and Wiley[2] reported a similar reaction between HCA and ethylenechlorohydrin (**3**) which afforded an ester of trichloroacetic acid (**4**). This reaction bears a close resemblance to the type described in this paper; however, the basic conditions reported by these workers were not necessary when a mixture of HCA and DMSO was used as the acylation reagent.

More recently, two Russian workers described the trichloroacetylation of aromatic amines, **5**, with HCA in an aqueous mixture.[3] The results of this procedure



5

were variable. When R was hydrogen, methoxy, or methyl, trichloroacetylation was accomplished at room temperature. When R was *m*- or *p*-chloro, heating was required, and when R was *o*-chloro or *o*-nitro, no reaction was observed.

Table I summarizes our work on the trichloroacetylation of dipeptides, **1**, using HCA in DMSO under neutral conditions. All of the products, **2** (TCA-dipeptides), were new compounds. TCA-glycylglycine was characterized by elemental analysis. TCA-glycylsarcosine and TCA-L-leucyl-L-leucine were identified by infrared spectral data and by thin layer chromatographic comparison with the product obtained from the reaction of the dipeptide and trichloroacetyl chloride in aqueous base. TCA-L-valyl-L-leucine and TCA-L-phenylalanyl-L-leucine were characterized by infrared spectral data. The yields were generally good except in the case of TCA-glycylglycine. The water solubility of this product made a more tedious and less efficient isolation procedure necessary. No attempt was made to establish the optimum time required for the greatest yields. Thin layer chromatography indicated that the reaction was essentially complete after 12 hr in most cases and probably required much less time than that. Lastly, the possibility of racemization of the optically active dipeptides, **1**, during this reaction was not investigated.

(2) H. E. Simmons and D. W. Wiley, *J. Amer. Chem. Soc.*, **82**, 2288 (1960).

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Experimental Section[4]

The thin layer chromatograms of the TCA-dipeptides, **2**, were run on microscope slides coated with 250-μ layer of Camag D-5 silica gel. Spotting was performed using 0.5–1.0 μl of a 1% solution and the solvent system was benzene–acetone–HOAc (50:45:5). The zones were detected as yellow areas on a purple background after spraying with a 0.5% aqueous $KMnO_4$ solution sometimes followed by heating. Cited R_f values are approximate.

N-Trichloroacetylglycylglycine (2, R¹, R², R³ = H).—A mixture of 0.749 g (5.67 mmol) of glycylglycine, 3.44 ml (6.0 g, 22.6 mmol) of hexachloroacetone, and 20 ml of dimethyl sulfoxide was magnetically stirred for 24 hr at room temperature in a flask equipped with a drying tube. Complete solution occurred after about 60 min. Gas–liquid chromatographic (ss column 0.25 in. × 2 m, 20% dodecyl phthalate on GC-22, 60–80 mesh, He carrier gas) analysis showed a peak with the same retention time as that of authentic chloroform. The yellow reaction solution was diluted with 60 ml of water and was then extracted with three 30-ml portions of *n*-BuOH. The butanol extract contained a fast zone (assumed to be the product) and a zone of DMSO. The product was separated from the DMSO by passing the mixture through a column of silicic acid (100 mesh) using acetone as the eluting solvent. The oily product was crystallized from methyl isobutyl ketone: yield 0.45 g (28.5%).

This product was identical in all respects (thin layer R_f values, melting point, and ir spectra) with that obtained from the reaction of glycylglycine with trichloroacetyl chloride or with trichloroacetic anhydride.

Anal. Calcd for $C_6H_7Cl_3N_2O_4$: C, 25.96; H, 2.52; N, 10.01; Cl, 38.36. Found: C, 26.17; H, 2.68; N, 10.16; Cl, 38.31.

General Procedure for the Preparation of Water-Insoluble TCA-Dipeptides, 2.—This method was employed for all of the dipeptides in Table I except glycylglycine.

N-Trichloroacetyl-L-leucyl-L-leucine (2, R¹, R² = *i*-Bu, R³ = H).—A mixture of 0.275 g (1.12 mmol) of L-leucyl-L-leucine, 0.60 ml (1.04 g, 3.94 mmol) of hexachloroacetone, and 2.0 ml of dimethyl sulfoxide was placed in a dry flask protected with a drying tube. After about 1 hr of magnetic stirring, a clear solution resulted. Glpc analysis again indicated the presence of chloroform in this solution (see previous procedure). Stirring was continued at room temperature for 11 hr, after which the reaction solution was poured into ten times its volume of crushed ice. The solid which precipitated was collected by filtration, thoroughly washed with cold water, and dried. The crystals weighed 0.39 g (89%) and were homogeneous according to thin layer chromatography. This product was then dissolved in a minimum amount of methyl isobutyl ketone and crystallization was induced by dilution with petroleum ether (bp 30–60°).

The identity of the above product was established from spectral data (see Table I), and by direct comparison of the thin layer R_f value of this product with that of the product obtained from the

(4) Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points were corrected.

reaction between L-leucyl-L-leucine and trichloroacetyl chloride in aqueous NaOH.

N-Trichloroacetylglycine.—Glycine, 1.00 g (13.35 mmol), 8 ml (13.98 g, 52.25 mmol) of hexachloroacetone, and 25 ml of DMSO were magnetically stirred at room temperature for 24 hr. The reaction solution was diluted with 85 ml of water and the reaction solution was diluted with 85 ml of water and the resultant mixture was extracted with three 50-ml portions of *n*-BuOH. The butanol extract was chromatographed on a silicic acid column. A mixture of benzene, acetone, and methanol (5:4:1) was the eluting solvent. A DMSO-free oil was obtained which crystallized from methyl isobutyl ketone and petroleum ether (bp 30–60°). The yield of product was 1.88 g (63.7%); mp 130.0–130.5° (lit.[5] 131–132°). This product was identical (thin layer R_f value, melting point, and ir spectra) with that obtained from the reaction of glycine with trichloroacetic anhydride.

Larger scale preparations of N-trichloroacetylglycine showed that the reaction with hexachloroacetone in DMSO is exothermic. In one such preparation (0.134 mol of glycine) the reaction solution was poured into about 100 ml of water and the resultant solution was distilled at atmospheric pressure. At 60° (vapor temperature) a distillate was collected which was identified as chloroform by its gas chromatography retention time and by its infrared spectrum: yield, 13.32 g (0.112 mol).

Registry No.—Hexachloroacetone, 116-16-5; 2 ($R^1 = R^2 = R^3 = H$), 24299-47-6; 2 ($R^1 = R^2 = i$-Bu; $R^3 = H$), 24299-25-0; 2 ($R^1 = R^2 = H$; $R^3 =$ Me), 24299-74-9; 2 ($R^1 = i$-Pr; $R^2 = i$-Bu; $R^3 = H$), 24299-26-1; 2 (R^1 = benzyl; $R^2 = i$-Bu; $R^3 = H$), 24299-27-2.

Acknowledgment.—Support of this work under a National Institutes of Health Research Grant No. I RO1 AM12761-01A1 MCHA is gratefully acknowledged.

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Synthesis of Derivatives of 2-Aminoproline and 5-Aminoproline

CARLO GALLINA, FRANCO PETRINI, AND AURELIO ROMEO

Centro di Studio per la Chimica del Farmaco e dei Prodotti Biologicamente Attivi (C.N.R.), Università di Roma, Rome, Italy

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Synthesis of α-amino acids containing a nitrogen or oxygen atom on the carbon linked with nitrogen have been described in reports from several laboratories, and some of these compounds are constituents of Ergot alkaloids. Proline derivatives of the type previously indicated have not yet been prepared, and we present here the synthesis of derivatives of 2-amino-DL-proline and 5-amino-DL-proline.

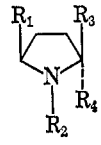
Addition of acetamide[1] to N-acetyl-Δ²-pyrroline-2-carboxylic acid[2] occurred on heating a mixture of the two substances, which produced a compound to which we attributed the structure of N,N′-diacetyl-2-amino-DL-proline (**1**). This structure is in accord with the spectral data and was confirmed through acid hydrolysis,[3] which gave α-keto-δ-acetylaminovaleric acid, recognized as the 2,4-dinitrophenylhydrazone.[2]

(1) Addition of acetamide to α-acylaminoacrylic acids has been reported: D. Shemin and R. Herbst, *J. Amer. Chem. Soc.*, **60**, 1954 (1938).

(2) K. Hasse and P. Homann, *Biochem. Z.*, **335**, 474 (1962).

(3) *trans*-N,N′-Diacetyl-3-amino-DL-proline, prepared by us [*Tetrahedron Lett.*, **35**, 3055 (1969)], was stable under the conditions employed in the hydrolytic degradation of **1**.

Starting material for synthesis of *cis*-N,N′-dicarbobenzyloxy-5-amino-DL-proline (**5**) was N-carbobenzyloxy-DL-pyrrolidine-2,5-dicarboxylic acid anhydride.[4] This compound was transformed to the corresponding monoazide **4** and gave **5** through the Curtius reaction. Catalytic hydrogenation (palladium on charcoal in acetic acid) of *cis*-N,N′-dicarbobenzyloxy-5-amino-DL-proline led to proline, which was recognized as the N-2,4-dinitrophenyl derivative.



(L forms only are shown)

Compd	R_1	R_2	R_3	R_4
1	H	$COCH_3$	COOH	$NHCOCH_3$
2	H	$COCH_3$	$COOCH_3$	$NHCOCH_3$
3	H	$COCH_3$	$CONHNH_2$	$NHCOCH_3$
4	CON_3	$COOCH_2C_6H_5$	COOH	H
5	$NHCOOCH_2C_6H_5$	$COOCH_2C_6H_5$	COOH	H

Experimental Section[5]

N,N′-Diacetyl-2-amino-DL-proline (1).—N-Acetyl-Δ²-pyrroline-2-carboxylic acid (1 g) and 2 g of acetamide were finely powdered and heated in a vacuum sublimator at 110° for 3 hr after removal of air under high vacuum. The excess acetamide was sublimed off and the residue was crystallized from methanol to give 1.15 g (75%) of **1**, mp 175–77°.

Anal. Calcd for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.20; H, 6.78; N, 12.95.

2,4-Dinitrophenylhydrazone of α-Keto-δ-acetylaminovaleric Acid.—A 90-mg portion of **1** was dissolved with stirring and was gently heated in 25 ml of a solution of 2,4-dinitrophenylhydrazine in 2 *N* HCl (4 mg/ml). When the reaction mixture was maintained at room temperature overnight, the hydrazone crystallized. The melting point of a sample recrystallized from acetic acid was 231° dec.

Anal. Calcd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28; N, 19.83. Found: C, 43.98; H, 4.45; N, 19.61.

N,N′-Diacetyl-2-amino-DL-proline Methyl Ester (2).—Methyl ester **2** was obtained by addition of ethereal diazomethane to the parent acid in methanol at 0°. Evaporation of the solvent and crystallization from ethyl acetate gave **2**: 90% yield; mp 140–141°; nmr ($CDCl_3$) δ 1.99 and 2.04 (two s, 3, $CH_3CON<$), 2–3 range (m, 4, C-3 and C-4 H of the ring), 3.79 (s, 3, CH_3OCO), 3.6–4.2 range (m, 2, C-5 H of the ring), 7.14 (broad signal, 1, NHCO). The assignments were made on the basis of the chemical shift and ratio of intensities values.

Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.71; H, 7.01; N, 12.32.

N,N′-Diacetyl-2-amino-DL-prolinehydrazide (3).—Methyl ester **2** (1 g) was dissolved in 8 ml of monohydrated hydrazine which was removed 5 min later under vacuum at 30°. The residue was crystallized from ethanol–ethyl ether to give the hydrazide in 80% yield, mp 171–172°.

Anal. Calcd for $C_9H_{16}N_4O_3$: C, 47.36; H, 7.07; N, 24.55. Found: C, 47.23; H, 7.09; N, 24.68.

***cis*-N,N′-Dicarbobenzyloxy-5-amino-DL-proline (5).**—N-Carbobenzyloxy-DL-pyrrolidine-2,5-dicarboxylic acid anhydride (1.24 g) was dissolved in 75 ml of warm acetone. The solution was cooled in ice and 750 mg of sodium azide in 5 ml of water was added with stirring and cooling, immediately followed by a further amount of water to dissolve the sodium azide which separated as a solid. After the mixture stirred for 1 hr at 0°, 20 ml of water was added and the acetone was evaporated off at 30°. The cooled aqueous solution was acidified to pH 4 with 2 *N* hydrochloric acid and extracted with ethyl ether, which was

(4) G. Cignarella and G. Nathansohn, *J. Org. Chem.*, **26**, 1500 (1961).

(5) Melting points were taken on a Culatti apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 221 infrared spectrophotometer. Nmr spectra were recorded on a Varian A-60 spectrometer, at room temperature, and are given in δ units relative to TMS as internal standard.