amino acids.[2] A maximum of 50% hydrolysis of the racemate was achieved in a few hours, which was not altered by addition of fresh enzyme and further incubation. The liberated L-amino acid was separated from the digest as usual, and recrystallized as glistening prisms from 50% alcohol; N calcd. 11.8, found 11.7; $[\alpha]^{25}\text{D}$ +10.0° (4.00% in H_2O); yield 80% on the chloroacetyl derivative. The chloroacetyl-D-allothreonine in the mother liquor was extracted, hydrolyzed with 2 *N* HCl, and isolated in 62% yield after neutralization and recrystallization from 50% alcohol; N found 11.7; $[\alpha]^{25}\text{D}$ −9.8° (4.00% in H_2O).

The optical rotation values of the allothreonine isomers are in agreement with those given by West and Carter[6] and by Elliott,[7] and the assignment of their configuration is in accord with that recently reported by Elliott[7] on the basis of organic chemical procedures.

We thank Dr. H. E. Carter for a gift of DL-allothreonine.

[6] West and Carter, *J. Biol. Chem.*, **122**, 611 (1938).

[7] Elliott, *J. Chem. Soc.*, 62 (1950).

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH JESSE P. GREENSTEIN
BETHESDA, MARYLAND LEON LEVINTOW

RECEIVED MAY 4, 1950

OBSERVATIONS OF THE MANNICH REACTION WITH OPTICALLY ACTIVE SUBSTITUTED MANDELIC ACIDS

Sir:

We have found that the Mannich reaction involving *d*-*o*-nitromandelic acid ($[\alpha]^{20}\text{D}$ +346° in ethanol), formaldehyde and piperidine, yielded the expected Mannich base α-piperidinomethyl-*o*-nitromandelic acid in an optically active form ($[\alpha]^{20}\text{D}$ +439° in ethanol). The *l*-acid gave a product whose rotation was $[\alpha]^{20}\text{D}$ −449° in ethanol. The lack of racemization appears to render inadmissible the enolization step postulated by Alexander and Underhill[1] for all compounds that undergo the Mannich reaction which have a methynyl group on a carboxyl group. Their investigation concerned the Mannich reaction with ethylmalonic acid, formaldehyde and dimethylamine.

The possibility of oxygen alkylation rather than carbon alkylation required by the Mannich reaction was eliminated by means of Zerewitinoff tests performed on the Mannich base.

A series of reactions with *d*-*o*-nitromandelic acid at various *p*H values and temperatures indicated that the condensation occurred too rapidly to permit a satisfactory study of its kinetics. The results obtained at 20° and 0° were virtually identical. Reaction occurred without apparent change in rate at *p*H values of 7.2, 8.5 and 9.3, while at *p*H 3.1 (piperidine hydrochloride), it failed to occur.

The investigation of this reaction and other similar reactions is continuing and will be reported in the near future.

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[1] E. Alexander and E. Underhill, THIS JOURNAL, **71**, 4014 (1949).

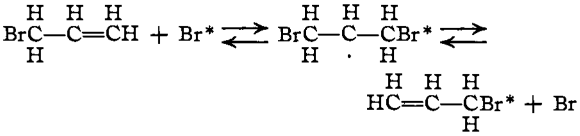
THE CHEMISTRY DEPARTMENT
SYRACUSE UNIVERSITY GERALD F. GRILLOT
SYRACUSE 10, NEW YORK RAYMOND I. BASHFORD, JR.

RECEIVED JANUARY 14, 1950

ISOTOPIC EXCHANGE OF ATOMIC BROMINE WITH ALLYLIC VINYLIC HALIDES[1,2]

Sir:

Recent work[3,4] indicates that most bromine atoms produced by slow neutron capture attain thermal energy before exchanging with gaseous hydrogen bromide. An efficient organic reagent for radioactive atoms is very desirable and it occurred to us that vinylic and allylic halides might serve this purpose by the following type of exchange



$$\mathrm{Br}\underset{\mathrm{H}}{\overset{\mathrm{H}}{\mathrm{C}}}-\overset{\mathrm{H}}{\mathrm{C}}=\overset{\mathrm{H}}{\mathrm{C}}\mathrm{H} + \mathrm{Br}^* \rightleftarrows \mathrm{Br}\underset{\mathrm{H}}{\overset{\mathrm{H}}{\mathrm{C}}}-\underset{\cdot}{\overset{\mathrm{H}}{\mathrm{C}}}-\underset{\mathrm{H}}{\overset{\mathrm{H}}{\mathrm{C}}}\mathrm{Br}^* \rightleftarrows \mathrm{H}\overset{\mathrm{H}}{\mathrm{C}}=\overset{\mathrm{H}}{\mathrm{C}}-\underset{\mathrm{H}}{\overset{\mathrm{H}}{\mathrm{C}}}\mathrm{Br}^* + \mathrm{Br}$$

Such reagents should be quite efficient since the exchange velocity depends primarily upon addition at the double bond, with a small or zero energy of activation.

We have found that neutron bombardment of gaseous mixtures consisting of 1–25 mm. of bromoolefin and 180 mm. of hydrogen bromide yields 80% organic activity. This high efficiency, which is practically independent of bromoölefin concentration over the range studied, has been interpreted elsewhere.[4]

Other experiments have demonstrated the efficiency of these olefins as reagents for Br* in the liquid state. Liquid ethyl bromide containing approximately one volume per cent. of a bromoölefin was subjected to thermal neutron bombardment. Additional bromoölefin and its addition product (*e.g.*, allyl bromide and 1,2-dibromopropane) were added after bombardment and separated by distillation. The addition product was invariably inactive, and the bromoolefin contained 25–50% of the total activity. This efficiency for the nascent Br* is maintained down to concentrations as low as 0.01 volume per cent. α,β-Dibromoethylene, 2-bromopropene and allyl chloride have been equally effective.

We have previously reported[2] the temperature coefficient of competitive exchange of nascent Br* with α,β-dibromoethylene and allyl bromide when both are present during neutron bombardment. We have recently found that the significance of this result has been obscured by a

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[1] Work supported in part by A.E.C. Contract No. At(11-1)38.

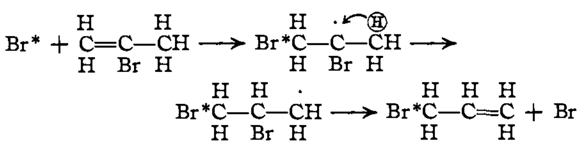
[2] Presented at the 116th Meeting of the A.C.S., Atlantic City, September, 1949.

[3] W. H. Hamill and R. R. Williams, Jr., *J. Chem. Phys.*, **16**, 1171 (1948).

[4] R. R. Williams, Jr., and W. H. Hamill, *ibid.*, in press.

complicating isomerization of the allyl bromide. When any one of the three isomeric bromopropenes is present (∼one per cent.) during neutron bombardment of bromobenzene, a mixture of active isomers is formed and may be separated by addition and fractionation of the carriers. In samples prepared and bombarded in open vessels, the activity distribution is approximately 22% 1-bromopropene, 3% 2-bromopropene and 75% allyl bromide, regardless of the bromoölefin present during bombardment. The distribution in air-free samples is now under investigation, and is apparently quantitatively but not qualitatively different.

The observed isomerizations among the bromopropenes can be described in terms of hydrogen atom and electron shifts in the free radicals formed by bromine atom addition. In one of the simplest cases, isomerization of allyl bromide to 2-bromopropene, we postulate



$$Br^* + \underset{H}{\overset{H}{C}}=\underset{Br}{\overset{H}{C}}-\underset{H}{CH} \longrightarrow Br^*\underset{H}{\overset{H}{C}}-\underset{Br}{\overset{\cdot}{C}}-\underset{H}{CH} \longrightarrow$$

$$Br^*\underset{H}{\overset{H}{C}}-\underset{Br}{\overset{H}{C}}-\underset{H}{\overset{\cdot}{C}H} \longrightarrow Br^*\underset{H}{\overset{H}{C}}-\overset{H}{C}=\underset{H}{\overset{H}{C}} + Br$$

Investigation of these and similar compounds is continuing.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NOTRE DAME
NOTRE DAME, INDIANA

WILLIAM H. HAMILL
RUSSELL R. WILLIAMS, JR.
HAROLD A. SCHWARZ[5]

RECEIVED APRIL 10, 1950

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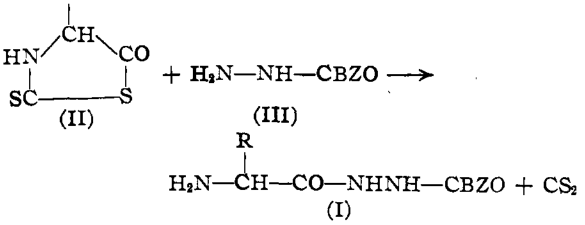
[5] A.E.C. Fellow.

STUDIES ON POLYPEPTIDES. II. THE PREPARATION OF α-AMINO ACID CARBOBENZOXYHYDRAZIDES

Sir:

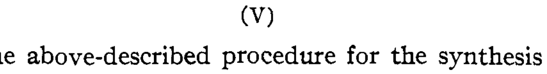
In connection with investigations on the synthesis of complex polypeptides[1] we have prepared a number of representatives of a new class of α-amino acid derivatives of the general structure (I), which we designate as α-amino acid carbobenzoxyhydrazides. The method of synthesis used involves the interaction of 4-substituted-2-thio-5-thiazolidone derivatives (II)[2] with carbobenzoxyhydrazine (III).[3]



CBZO = —OC—O—CH_2—C_6H_5

The α-amino acid carbobenzoxyhydrazides were isolated as the hydrochlorides. Thus the interaction of III with 2-thio-5-thiazolidone led to the formation of glycine carbobenzoxyhydrazide; hydrochloride m. p. 176–178° (*Anal.* Calcd. for $C_{10}H_{14}O_3N_3Cl$: C, 46.3; H, 5.4; N, 16.2; NH_2 N, 5.4; Cl, 13.7. Found: C, 46.5; H, 5.3; N, 15.8; NH_2 N, 5.3; Cl, 13.7). Similarly the reaction of *dl*-2-thio-4-methyl-5-thiazolidone, m. p. 124–126° with III afforded DL-alanine carbobenzoxyhydrazide; hydrochloride m. p. 197–199° (*Anal.* Calcd. for $C_{11}H_{16}O_3N_3Cl$: C, 48.3; H, 5.9; N, 15.4; NH_2 N, 5.1; Cl, 13.0. Found: C, 48.5; H, 6.0; N, 15.6; NH_2 N, 5.5; Cl, 13.1. From *l*-2-thio-4-isobutyl-5-thiazolidone, m. p. 94–95°, L-leucine carbobenzoxyhydrazide was prepared; hydrochloride, m. p. 167–169° (*Anal.* Calcd. for $C_{14}H_{22}O_3N_3Cl$: C, 53.2; H, 7.0; N, 13.3; NH_2 N, 4.4; Cl, 11.2. Found: C, 53.0; H, 6.8; N, 13.4; NH_2 N, 4.5; Cl, 10.9). The reaction of *l*-2-thio-4-(2-carboxyethyl)-5-thiazolidone, m. p. 151–152°, with III under our experimental conditions gave the carbobenzoxyhydrazide of *l*-2-pyrrolidone-5-carboxylic acid, m. p. 163–165° (*Anal.* Calcd. for $C_{13}H_{15}O_4N_3$; C, 56.3; H, 5.5; N, 15.2. Found: C, 56.5; H, 5.4; N, 15.0).

The α-amino acid carbobenzoxyhydrazides represent valuable intermediates for the synthesis of complex peptides, since by way of their free amino group they may be readily combined with other peptide structures, thus forming peptide carbobenzoxyhydrazides. For example, the interaction of glycine carbobenzoxyhydrazide with benzoyldiglycine azide afforded benzoyltriglycine carbobenzoxyhydrazide (IV), m. p. 225–228° (*Anal.* Calcd. for $C_{21}H_{23}O_6N_5$: N, 15.9; Found: N, 15.6). A series of peptide derivatives were prepared from carbobenzoxy dipeptide azides and glycine carbobenzoxyhydrazide. Carbobenzoxyglycyl-L-tyrosylglycine carbobenzoxyhydrazide, m. p. 175–177°, carbobenzoxyglycyl-L-leucylglycine carbobenzoxyhydrazide, m. p. 142–144°, and carbobenzoxy-L-α-glutamylglycylglycine carbobenzoxyhydrazide, m. p. 161–163°, may be mentioned. These tripeptide derivatives contain a potential hydrazide group which is liberated by hydrogenolysis. Thus the hydrogenation of (IV) in the presence of hydrochloric acid afforded benzoyltriglycine hydrazide; hydrochloride (*Anal.* Calcd. for $C_{13}H_{18}O_4N_5Cl$; C, 45.4; H, 5.3; N, 20.4; Cl, 10.3. Found: C, 45.6; H, 5.1; N, 20.4; Cl, 10.0), which reacted with nitrous acid to give the corresponding azide. Similarly, reduction of the above-mentioned dicarbobenzoxylated tripeptide hydrazides afforded the respective free tripeptide hydrazides, of the general structure (V)



$$H_2N\text{-}\overset{R_1}{CH}\text{-}CO\text{-}NH\text{-}\overset{R_2}{CH}\text{-}CO\text{-}NH\text{-}\overset{R_3}{CH}\text{-}CO\text{-}NH\text{-}NH_2$$

(V)

The above-described procedure for the synthesis

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[1] Magee and Hofmann, THIS JOURNAL, **71**, 1515 (1949).

[2] Cook, Heilbron and Levy, *J. Chem. Soc.*, 201 (1948); Levy, *ibid.*, 404 (1950).

[3] Rabjohn, THIS JOURNAL, **70**, 1181 (1948).