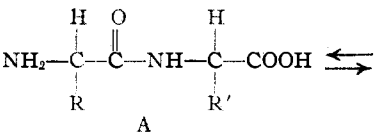
[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, COLUMBIA UNIVERSITY]

# Racemization of Tripeptides and Hydantoins[1]

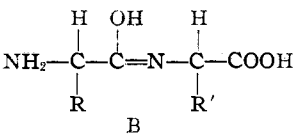
BY M. BOVARNICK AND H. T. CLARKE

In 1910 Dakin[2] first described the racemization of optically active hydantoins under the influence of mild alkali. At the same time he demonstrated that the presence of a hydrogen atom on the asymmetric carbon atom was a necessary condition for the occurrence of the racemization and further observed that neither the optically active amino acids themselves, their uramino acid derivatives, nor optically active dipeptides, were racemized under the conditions.[2a] He therefore concluded that the mechanism of racemization involved a keto–enol tautomerism and that it was essential that both the $\alpha$-amino group and the carboxyl group attached to the asymmetric carbon atom be bound up in order for the amino acid to undergo racemization by this method.[3] Extending this work, Dakin and others[4] later identified the terminal amino acids of protein peptide chains by making use of the assumption that, having free amino and carboxyl groups, they would not racemize on alkaline hydrolysis. Levene,[5] working with smaller peptide chains, substantiated the findings of Dakin and reached the conclusion that in a peptide composed of three optically active amino acids only the middle amino acid was racemized by alkali.

On comparing the formulas of dipeptides and tripeptides, a theoretical reason presents itself for the observed difference in racemizability of the two. In both there are two types of structures capable of undergoing tautomerization. One is the familiar keto–enol system, and the other is the amide–imide system. In the dipeptide only the non-racemizing tautomeric equilibrium



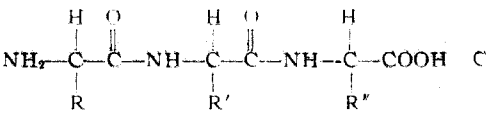
A



B

need be considered; the keto–enol tautomerization obviously does not take place to any appreciable extent as the dipeptides do not racemize.

In a tripeptide a wide variety of tautomeric forms is possible, of which only those represented below need be considered here. It is a well-recognized fact that the presence of a double bond in a molecule tends to favor the production (when this is at all possible) of other double bonds in conjugation with it. It was therefore thought that an explanation of the racemizability of the tripeptides might reside in the possibility that in these peptide chains a previous or simultaneous occurrence of an enolized peptide linkage (D), analogous to that outlined above (B) for a dipeptide, might be necessary to induce the formation of a second enolic double bond (E) whereby the asymmetry of the central constituent amino acid is destroyed.



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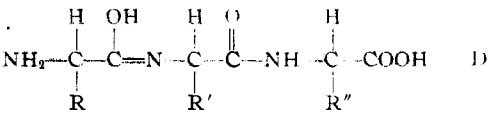
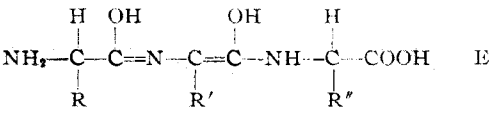
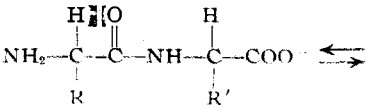


D



E

In order for this mechanism to be effective in the case of a dipeptide the following reaction would have to take place



(1) This report is from a dissertation submitted by Max Bovarnick in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

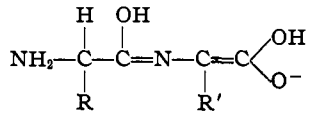
(2) Dakin, *Am. Chem. J.*, **44**, 48 (1910).

(2a) The optical stability of dipeptides may be further illustrated by the case of alanylglycine, which on treatment with normal sodium hydroxide at room temperature for two days showed no appreciable loss in activity [Levene and Pfaltz, *J. Biol. Chem.*, **70**, 219 (1926)], whereas in half-normal sodium hydroxide under the same conditions it was hydrolyzed to an extent of over 15% [Levene, Bass and Steiger, *J. Biol. Chem.*, **82**, 167 (1929)]. Racemization of the resulting amino acids can be effected by alkali only under very vigorous conditions, such as heating with 15% barium hydroxide at 155–160° for forty-eight hours [E. Fischer, *Z. physiol. Chem.*, **33**, 151, 173 (1901)].

(3) Dakin, *J. Biol. Chem.*, **13**, 357 (1913).

(4) Dakin and Dudley, *ibid.*, **15**, 263 (1913); Dakin and Dale, *Biochem. J.*, **13**, 248 (1919).

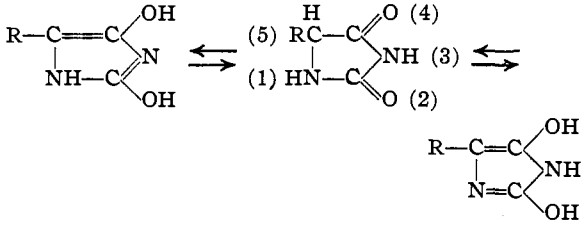
(5) Levene, Steiger and Marker, *J. Biol. Chem.*, **93**, 605 (1931).



Enolization involving carboxylate ions is not in harmony with the concept of resonance in these ions,[6] and the known non-racemizability of dipeptides conforms with its improbability.

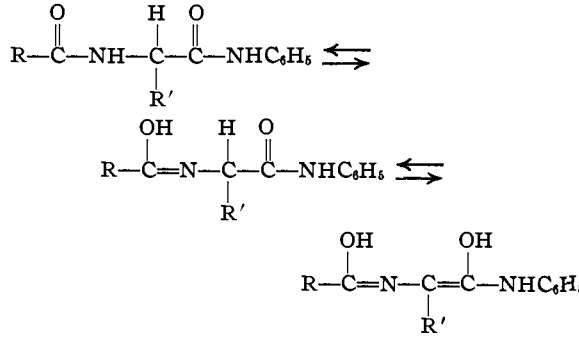
If the above hypothesis, as applied to tripeptides, is to be tenable, then replacement of the hydrogen in the system —CONH— by a methyl group should, by blocking the formation of the modification —C(OH)=N— and thereby preventing conjugation involving the asymmetric carbon atom, prevent racemization in the tripeptide.

In the case of hydantoins there are two possibilities for the occurrence of conjugation involving the asymmetric carbon atom



and if this be a factor controlling racemization, replacement of one of the H atoms in positions 1 or 3 of the ring by an alkyl or aryl group might retard racemization, and replacement of both should prevent it.

of racemization in suitable concentrations of alkali were measured. The latter derivatives contain an amino acid in which both the amino group and carboxyl group are modified. They differ from tripeptides in that they lack the terminal amino and carboxyl groups, but these are not essential for testing the theory as the requisite enolization can take place with equal probability



The derivatives studied were chosen because it was thought they might be more accessible than the tripeptides.

The results, given in Table I, have little quantitative significance since practical considerations precluded the use of standard concentrations of the optically active compounds and the precise evaluation of hydroxyl ion activity. Contrary to expectation, the loss of activity did not always follow a monomolecular course, as should have been the case if a single reaction had been involved.[9]

TABLE I

HALF RACEMIZATION TIME OF HYDANTOINS AND ACYL AMINO ANILIDES IN ALKALI

| | Compound | Molarity | Medium | Half-time, hours |
|---|---|---|---|---|
| I | N-Acetyl-tyrosyl anilide | 0.0255 | 0.37 *N* NaOH in 67% EtOH | 74 |
| II | N-Acetyl-N-methyltyrosyl anilide | .025 | .37 *N* NaOH in 67% EtOH | 9 |
| III | N-Acetyl-*p*-methoxyphenylalanyl anilide | .0227 | .37 *N* NaOH in 67% EtOH | 40 |
| IV | N-Benzoyl-*p*-methoxyphenylalanyl anilide | .0013 | .33 *N* NaOH in 2:1 BuOH–EtOH | 0.25 |
| V | N-Carbobenzoxy-*p*-methoxyphenylalanyl anilide | .025 | .37 *N* NaOH in 67% EtOH | ∞ |
| VI | N-Toluenesulfonyl-*p*-methoxyphenylalanyl methylanilide | .025 | .37 *N* NaOH in 67% EtOH | ∞ |
| VII | 5-*p*-Hydroxybenzylhydantoin[7] | .0046 | .002 *N* NaOH in 95% EtOH | 15 |
| VIII | 3-Phenyl-5-*p*-hydroxybenzylhydantoin[7] | .0222 | .002 *N* NaOH in 95% EtOH | 2.5 |
| IX | 1-Methyl-5-*p*-hydroxybenzylhydantoin | .030 | .002 *N* NaOH in 95% EtOH | 11.5 |
| X | 1-Methyl-3-phenyl-*p*-hydroxybenzylhydantoin | .0287 | .002 *N* NaOH in 95% EtOH | 0.5 |
| XI | 5-*p*-Methoxybenzylhydantoin | .0267 | .002 *N* NaOH in 95% EtOH | 45 |
| XIa | 5-*p*-Methoxybenzylhydantoin | .0046 | .002 *N* NaOH in 95% EtOH | 9 |
| XII | 3-Phenyl-5-*p*-methoxybenzylhydantoin[8] | .026 | .002 *N* NaOH in 95% EtOH | <0.1 |

Accordingly a series of optically active substituted hydantoins, and a series of α-acylaminoacyl anilides were prepared. For each series the rates

On comparing some of the rates of racemization, I with II, VII with IX and X, X with VIII,

(6) Pauling, *Proc. Nat. Acad. Sci.*, **18**, 293 (1932).

(7) Paal and Zitelmann, *Ber.*, **36**, 3344 (1903).

(8) Behr and Clarke, THIS JOURNAL, **54**, 1630 (1932).

(9) With the acylaminoacyl anilides, the values of *K* drifted upward for compounds I and IV, downward for II and III; with the hydantoins, relatively constant values were observed for VII, VIII, and XI, and those for the 1-methyl hydantoins IX and X showed an upward drift.

and XI with XII, it can be seen that the substitution of H by R groups not only fails to prevent racemization but in some cases even hastens it. These findings completely invalidate the hypothesis that the ease of racemization depends upon the possibility of conjugation.

An alternative explanation is that the racemization, whether or not it is identical with enolization, is similar to enolization in its dependence on the ionization of the hydrogen on the asymmetric carbon atom. That this ionization is the essential step in such processes of racemization or enolization has been demonstrated for various systems including the racemization of *l*-phenyl, β-α-butyl ketone;[10] mutarotation of an acetoacetic ester derivative;[11] bromination of ketones;[12,13] racemization of alkyl nitromethanes.[14] Even where racemization takes place[15] and enolization is improbable[16] or impossible,[17] there occurs an activation of the hydrogen which is most probably ionization.

This ionization is in turn dependent on two factors: (a) the alkalinity of the medium, and (b) the activating effects of the groups attached to the asymmetric carbon atom. It is obvious that the more alkaline the medium, the greater is the tendency of any hydrogen atom to ionize. The nature of the activating effect is more obscure. If its mechanism involves internal electron displacements,[18–20] then the adjacent activating groups must act by lowering the electron density around the asymmetric carbon atom to the requisite point where those electrons shared as a covalent pair by the hydrogen and carbon are so displaced toward the carbon as to enable the hydrogen to ionize under the influence of the hydroxyl ions. Activation would then depend on electron-attraction, and the problem of racemization of these compounds would resolve itself into a question of the relative electron-attracting effects of the various groups attached to the asymmetric carbon atom. On this basis we can, from our data and the known behavior of di- and tripeptides, uramino acids and hydantoins with respect to racemization of this type, draw certain conclusions about the relative activating effects of different radicals.

Whereas the effect of the carboxyl is not sufficient to induce racemization in either free or N-acylated amino acids under the conditions, the —CO—$NHC_6H_5$ group can induce racemization in the N-acetyl and N-benzoyl aminoacyl anilides (I, II, III, IV). Ring closure in the hydantoic acids is essentially substitution of the free carboxyl of a uramino acid by a CONR group, with the result that the non-racemizing uramino acids become racemizable. The greater ease of racemization of the hydantoins as compared with the open-chain compounds indicates that ring closure in itself has a large effect, but this cannot be interpreted from the data here presented.

Amino and methylamino groups are unable to induce racemization when free, as is shown by the failure of dipeptides and aminoacyl anilides to racemize under the conditions. However, acylation of the amino groups in these anilides does not necessarily lead to racemizability, for whereas the —$NHCOCH_3$ and —$NHCOC_6H_5$ groups are activating (I, IV), the —$NHCOOCH_2C_6H_5$ and —$NHSO_2C_7H_7$ groups have no such effect (V, VI).

In the hydantoins, replacement of the imide hydrogen atoms in position 3 by a phenyl group increases the rate of racemization (compare VII with VIII, IX with X, and XI with XII). This may be due either to an activating effect of the phenyl group or to the possibility that in the simple hydantoins the imide hydrogen atom dissociates sufficiently to decrease the (already low) hydroxyl ion concentration. Suppression of hydroxyl ion activity by ionization of the phenolic hydrogen atoms may be partially responsible for the slower rates of racemization of the tyrosine derivatives as compared with their methyl ethers (compare VII with XI, VIII with XII).

## Experimental

The observed optical rotatory powers of the various preparations recorded below do not necessarily represent the maximum possible values. In the racemization experiments carried out at 20–25° the half-times are based on the initial values observed for the alkaline solutions employed.

**Carbobenzoxymethoxyphenylalanine.**—To 20 g. of *p*-methoxyphenylalanine dissolved in 1 equivalent of 4 *N* sodium hydroxide were added alternately during the course of one-half hour with shaking and cooling 1 equivalent of

(10) Sheng, Ingold and Wilson, *J. Chem. Soc.*, 78 (1938).
(11) Kimball, THIS JOURNAL, **58**, 1967 (1936).
(12) Watson, *Chem. Rev.*, **7**, 173 (1930).
(13) Leuchs, *Ber.*, **46**, 2435 (1913).
(14) Kuhn, *ibid.*, **60**, 1297 (1927).
(15) Ashley and Shriner, THIS JOURNAL, **54**, 4410 (1932); Kipping, *J. Chem. Soc.*, 18 (1935).
(16) Kohler and Potter, THIS JOURNAL, **58**, 2166 (1936).
(17) Shriner, Struck and Jorison, *ibid.*, **52**, 2060 (1930).
(18) Ingold, *Chem. Rev.*, **15**, 225 (1934).
(19) Pauling, THIS JOURNAL, **57**, 2086 (1935).
(20) Hammett, *ibid.*, **59**, 96 (1937).

carbobenzoxy chloride and 1 equivalent of 4 *N* sodium hydroxide. Shaking was continued until the mixture was homogeneous. On dilution and acidification to congo red an amorphous white solid precipitated out. The crude product weighing 32 g., was recrystallized from ether–petroleum ether, yielding long, flattened needles, m. p. 106–107°; soluble in alkali, ether, acetone, alcohol, benzene; insoluble in water; rotation, $[\alpha]^{25}D$ +12° in 95% alcohol.

*Anal.* Calcd. for $C_{18}H_{19}O_5N$: C, 65.7; H, 5.8; N, 4.3. Found: C, 65.6; H, 5.8; N, 4.1.

**N-Carbobenzoxy-*p*-methoxyphenylalanyl Anilide** (V).—To 4.5 g. of carbobenzoxy-*p*-methoxyphenylalanine suspended in 150 cc. of dry ether was added 3.6 g. of finely powdered phosphorus pentachloride, and the mixture was allowed to stand at room temperature with occasional shaking until homogeneous (four hours). The ether was removed *in vacuo* and the oily residue quickly washed twice with dry petroleum ether. The amorphous residue was redissolved in 150 cc. of dry ether and 15 cc. of freshly distilled aniline in 50 cc. of dry ether was added. After twenty hours at room temperature the mixture was poured into cold dilute hydrochloric acid. The ether-soluble product was recrystallized twice from hot dilute acetone; yield 4.3 g., m. p. 171–173°; soluble in acetone, ether, alcohol; insoluble in water and carbon tetrachloride; rotation, $[\alpha]^{25}D$ +22.3° in acetone.

*Anal.* Calcd. for $C_{24}H_{24}O_4N_2$: C, 71.3; H, 5.9; N, 6.9. Found: C, 71.2; H, 6.1; N, 7.0.

***p*-Methoxyphenylalanyl Anilide.**—Hydrogen gas was bubbled through a suspension of 1 g. of carbobenzoxy-*p*-methoxyphenylalanine-anilide in 50 cc. of 70% alcohol in the presence of palladium catalyst until no more carbon dioxide was evolved. The mixture was filtered and the filtrate concentrated at room temperature to 10 cc. A crop of white glistening squares crystallized out. Another crop was obtained from the mother liquor on standing in the ice box overnight; yield 584 mg., m. p. 121–123°; soluble in alcohol, acetone; slightly soluble in water and ether; rotation, $[\alpha]^{25}D$ +34.3° in 95% alcohol.

*Anal.* Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.1; H, 6.7; N, 10.4. Found: C, 71.1; H, 6.8; N, 10.4.

**N-Acetyl-*p*-methoxyphenylalanyl Anilide** (III).—To 0.100 g. of *p*-methoxyphenylalanine anilide in 3 cc. of 50% acetone was added 0.3 cc. of freshly distilled acetic anhydride. After twenty hours another 0.3 cc. of anhydride was added, and the solution was allowed to stand at room temperature for twenty-four hours. On dilution with water and cooling in the ice box overnight clusters of needles separated out; yield 95 mg., m. p. 168–170°; soluble in alcohol and acetone; insoluble in water; rotation, $[\alpha]^{25}D$ +56.4° in 95% alcohol.

*Anal.* Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.2; H, 6.4; N, 9.0. Found: C, 69.1; H, 6.7; N, 9.1.

**Tyrosyl Anilide.**—A mixture of 282 mg. of *p*-methoxyphenylalanine anilide, 10 cc. of concentrated hydriodic acid (sp. gr. 1.7), and a few crystals of phosphonium iodide was allowed to stand in a sealed tube at room temperature for forty-eight hours. The contents were then diluted with water and taken to dryness at room temperature over phosphorus pentoxide. The glassy residue was dissolved in a small amount of water and the solution made alkaline to litmus with ammonia. On cooling overnight in the ice box needles separated out which were recrystallized from hot dilute alcohol; yield 160 mg., m. p. 145–147°; soluble in acetone, alcohol and acid; insoluble in water; rotation, $[\alpha]^{25}D$ +28.4° in 95% alcohol.

*Anal.* Calcd. for $C_{15}H_{16}O_2N_2$: C, 70.3; H, 6.3. Found: C, 70.2; H, 6.2.

**N-Acetyltyrosyl Anilide** (I).—A solution of 0.100 g. of tyrosine anilide in 3 cc. of 50% acetone was treated with acetic anhydride as previously described. On diluting with water and cooling in the ice box 98 mg. of crystalline material was obtained. This was recrystallized from dilute acetone in short rods, m. p. 236–237°; soluble in alcohol and acetone; insoluble in water; rotation, $[\alpha]^{25}D$ +61.0° in 95% alcohol.

*Anal.* Calcd. for $C_{17}H_{18}O_3N_2$: C, 68.5; H, 6.0. Found: C, 68.7; H, 6.1.

**N-*p*-Toluenesulfonyl-*p*-methoxyphenylalanine.**—A mixture of 6 g. of *p*-methoxyphenylalanine dissolved in 1 equivalent of 1 *N* sodium hydroxide and 2 equivalents of toluenesulfonyl chloride in 50 cc. of ether was shaken for one hour. One equivalent of 1 *N* sodium hydroxide was then added and the mixture shaken for another hour. This process was repeated two more times. The aqueous layer was strongly acidified with 5 *N* hydrochloric acid and an oil separated out which solidified on standing overnight. The solid was recrystallized from hot water in long white needles, m. p. 138–140°; soluble in hot water, alcohol, ether, acetone and benzene; yield 8 g.

*Anal.* Calcd. for $C_{17}H_{19}O_5NS$: N, 4.0. Found: N, 4.0.

**N-*p*-Toluenesulfonyl-*p*-methoxyphenylalanyl Methylanilide** (VI).—To a solution of 5.5 g. of N-*p*-toluenesulfonyl-*p*-methoxyphenylalanine in 200 cc. of dry ether was added 3.6 g. of finely powdered phosphorus pentachloride and the mixture allowed to stand at room temperature with occasional shaking for four hours. The ether was removed *in vacuo* and the oily residue quickly washed twice with dry petroleum ether. It solidified in clusters of needles. These were redissolved in 150 cc. of dry ether and a solution of 17 cc. of freshly distilled methylaniline in 50 cc. of dry ether was added. The mixture was allowed to stand at room temperature for two days and then poured into cold dilute hydrochloric acid. The ether layer was washed with dilute hydrochloric acid, bicarbonate, water, and dried over sodium sulfate. On concentrating, glistening platelets together with a small amount of needles came out. On recrystallization from ether–petroleum ether 5 g. of platelets was secured; soluble in alcohol, ether, acetone; insoluble in water; m. p. 120°; rotation, $[\alpha]^{25}D$ +18.8° in 95% alcohol.

*Anal.* Calcd. for $C_{24}H_{26}O_4N_2S$: C, 65.8; H, 5.9; N, 6.4. Found: C, 65.8; H, 5.9; N, 6.2.

The needles were not investigated.

**N-Methyl-N-*p*-toluenesulfonyl-*p*-methoxyphenylalanyl Anilide.**—A solution of 5 g. of N-*p*-toluenesulfonyl-O-N-dimethyltyrosine (prepared according to Fischer[21]) in 150 cc. of dry ether was treated with phosphorus pentachloride and aniline and worked up in the manner described above. After finally removing the ether, the glassy

(21) Fischer and Lipschitz, *Ber.*, **48**, 360 (1915).

residue was recrystallized twice from hot dilute alcohol. Clusters of long white prisms were obtained; yield 5.2 g.; m. p. 96–98°; soluble in ether, acetone, alcohol, benzene; insoluble in petroleum ether and water; rotation, $[\alpha]^{25}D$ +15.3° in 95% alcohol.

*Anal.* Calcd. for $C_{24}H_{26}O_4N_2S$: C, 65.8; H, 5.9; N, 6.4. Found: C, 65.8; H, 5.9; N, 6.3.

**N-Methyltyrosyl Anilide.**—A mixture of 4 g. of the above compound, 2.5 g. of phosphonium iodide, and 50 g. of concentrated hydriodic acid (sp. gr. 1.7) was shaken in a sealed tube at room temperature for six hours. The mixture was mixed with ice and allowed to stand for one hour. The thiocresol was filtered off; the filtrate was concentrated *in vacuo*, made alkaline with ammonia and allowed to stand in the ice box overnight. A semi-solid mass came out which was crystallized twice from hot dilute alcohol; yield 1.4 g., m. p. 139–140°; soluble in alcohol, acetone, and acid; slightly soluble in water; rotation, $[\alpha]^{25}D$ +46.8° in 95% alcohol.

*Anal.* Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.1; H, 6.7. Found: C, 71.0; H, 6.3.

**N-Acetyl-N-methyltyrosyl Anilide (II).**—A solution of 200 mg. of N-methyltyrosyl anilide in 6 cc. of 50% acetone was treated with 0.6 cc. of freshly distilled acetic anhydride, allowed to stand overnight at room temperature, and again treated with 0.6 cc. of acetic anhydride and allowed to stand another twenty-four hours at room temperature. On diluting with water and cooling in the ice box for a few days, clusters of rods separated out; yield 190 mg., m. p. 185–186°; soluble in acetone and alcohol; insoluble in water; rotation, $[\alpha]^{25}D$ −32.1° in 95% alcohol.

*Anal.* Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.2; H, 6.4; N, 9.0. Found: C, 69.1; H, 6.3; N, 8.9.

**N-Benzoyl-*p*-methoxyphenylalanyl Anilide (IV).**—To a solution of 74 mg. of *p*-methoxyphenylalanyl anilide in 5 cc. of benzene was added 44 mg. of freshly distilled benzoyl chloride. After standing at room temperature overnight, 0.15 cc. of 1.1 *N* sodium hydroxide was added and the mixture allowed to stand at room temperature for ten hours with occasional shaking. The solid which separated out was centrifuged down, washed with benzene and water, and then recrystallized from dilute acetone; yield 95 mg., m. p. 224–225°; long, white needles; soluble in acetone; very slightly soluble in alcohol and butyl alcohol; insoluble in water and benzene; rotation, $[\alpha]^{25}D$ +14.7° in acetone.

*Anal.* Calcd. for $C_{23}H_{22}O_3N_2$: C, 73.8; H, 5.9; N, 7.5. Found: C, 74.0; H, 6.1; N, 7.8.

**1-Methyl-5-*p*-hydroxybenzylhydantoin (IX).**—To a suspension of 1 g. of N-methyltyrosine[21] in 40 cc. of boiling water was added solid potassium cyanate until everything went into solution. The cooled solution was treated with 20% sulfuric acid until approximately one normal, and then refluxed for three hours. On cooling a white solid separated out. This was recrystallized twice from hot water, yielding 1.1 g. of flat platelets, m. p. 123–124°; soluble in hot water and alcohol; insoluble in cold water; rotation, $[\alpha]^{25}D$ −12.0° in 95% alcohol.

*Anal.* Calcd. for $C_{11}H_{12}O_3N_2$: C, 60.0; H, 5.5. Found: C, 59.7; H, 5.3.

**1-Methyl-3-phenyl-5-*p*-hydroxybenzylhydantoin (X).**—To a solution of 1 g. of N-methyltyrosine in 2 equivalents of half-normal sodium hydroxide was added 1 equivalent of phenyl isocyanate. The mixture was shaken for two hours, filtered, and the filtrate made acid to congo red. A white amorphous mass separated out which was recrystallized from hot dilute alcohol; yield 1.5 g., m. p. 153–155°; short thick rods; soluble in acetone, alcohol, and alkali; insoluble in water; rotation, $[\alpha]^{25}D$ −15.5° in 95% alcohol.

*Anal.* Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.9; H, 5.4. Found: C, 68.8; H, 5.5.

**5-*p*-Methoxybenzylhydantoin (XI).**—To a solution of 0.5 g. of *p*-methoxyphenylalanine in 25 cc. of boiling water was added 2 equivalents of solid potassium cyanate. The solution was cooled and made approximately normal with 20% sulfuric acid, and then refluxed for three hours. On cooling, white leaflets came out which were recrystallized from hot water; yield 0.47 g., m. p. 171–173°; soluble in hot water, acetone and alcohol; slightly soluble in cold water; rotation, $[\alpha]^{25}D$ −89.0° in 95% alcohol.

*Anal.* Calcd. for $C_{11}H_{12}O_3N_2$: C, 60.0; H, 5.5. Found: C, 59.8; H, 5.4.

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## Summary

Racemization of acylaminoacyl anilides and of hydantoins by alkali is not prevented by the introduction of groups which would restrain the formation of conjugated enolic double bonds. It is suggested that such racemization is a reflection of the electronic condition of the various groups attached to the asymmetric carbon atom.

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