[CONTRIBUTION FROM THE RESEARCH DIVISION, ELECTROCHEMICALS DEPARTMENT, E. I. DU PONT DE NEMOURS AND CO., INC.]

Synthesis and Resolution of Tryptophan[1]

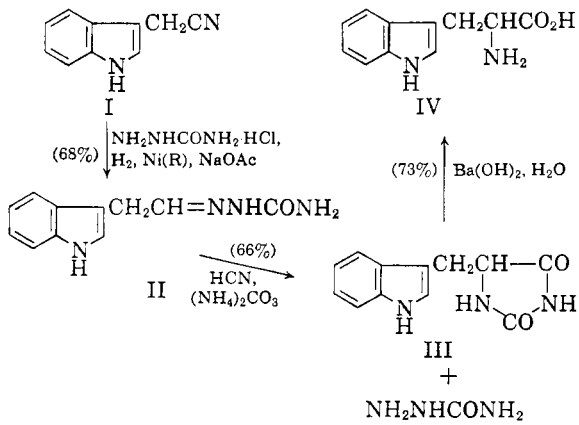
J. N. COKER, W. L. KOHLHASE, M. FIELDS, A. O. ROGERS, AND M. A. STEVENS[2]

Received August 9, 1961

DL-Tryptophan has been prepared in three steps from 3-indoleacetonitrile in 33% over-all yield. The two intermediates in this synthesis are 3-indoleacetaldehyde semicarbazone and 5-(3′-indolylmethyl)hydantoin. Preparation of the biologically active L-tryptophan was accomplished efficiently using L-lysine to resolve the readily prepared *N*-acetyl-DL-tryptophan.

L-Tryptophan is one of the eight amino acids essential to human growth and maintenance.[3–7] It is also needed in the diets of all vertebrates studied to date. A variety of synthetic routes to tryptophan have been developed of varying degrees of complexity. We wish to report a relatively simple new route to DL-tryptophan which starts with 3-indoleacetonitrile. The L-amino acid is then obtained by resolution of the DL-amino acid in the form of its *N*-acetyl derivative using L-lysine as the resolving agent.

Synthesis of DL-*tryptophan.* The preparation of DL-tryptophan (IV) from 3-indoleacetonitrile (I) was accomplished in three steps. The two intermediates in this synthesis are 3-indoleacetaldehyde semicarbazone (II) and 5-(3′-indolylmethyl)hydantoin (III).



The hydrogenation of 3-indoleacetonitrile (I) to 3-indoleacetaldehyde semicarbazone (II) was carried out by the procedure of Plieninger and Werst.[8] Treatment of the nitrile with hydrogen, semicarbazide hydrochloride, sodium acetate, and Raney nickel in aqueous methanol at room temperature and pressures near atmospheric yielded the semicarbazone as a white crystalline solid in 68% yield. The product after washing with cold water was sufficiently pure for use in the next step of the synthesis. Reaction of the semicarbazone with aqueous ammonium carbonate and hydrogen cyanide at 100° under autogenous pressure gave 5-(3′-indolylmethyl)hydantoin (III) in 66% yield. This material separated as a white crystalline solid when the reaction mixture was cooled; the filtrate from this reaction contained semicarbazide which was recoverable. Hydrolysis of the hydantoin was accomplished by a reported procedure[9] in the presence of hot aqueous barium hydroxide solution under autogenous pressure. DL-Tryptophan (IV) was isolated in 73% yield by extraction of the hydrolysis mixture with wet *n*-butyl alcohol. It was identified by its melting point, by infrared analysis in comparison with an authentic sample of DL-tryptophan, and by paper chromatographic analysis also using a tryptophan standard.

Initial efforts to characterize 3-indoleacetaldehyde semicarbazone (II)[10] were complicated by its relatively wide melting range. The product obtained directly from the hydrogenation reaction melted at 142–145°. However, upon repeated recrystallization of this material from methanol or water, this melting range was increased to 180–182°. A reasonable explanation for this behavior is that the semicarbazone exists in the form of *syn* and *anti* isomers. The lower melting, more soluble, metastable product, believed to be the *syn* isomer, is the principal material formed in the hydrogenation of 3-indoleacetonitrile. This product then isomerizes to the more stable, less soluble *anti* isomer on standing or by recrystallization from methanol. The greater reactivity of the lower melting isomer is indicated by the fact that it was converted to 5-(3′-indolylmethyl)hydantoin in

(1) Presented at the 140th National Meeting, American Chemical Society, Chicago, Ill., September 3–8, 1961.

(2) Present address: 3, Carrwood Road, Wilmslow, Cheshire, England.

(3) W. C. Rose *et al.*, *J. Biol. Chem.*, 211, 815 (1954).

(4) L. E. Holt, Jr., A. A. Albanese, J. E. Brumback, Jr., C. Kadji, and D. M. Wangerin, *Proc. Soc. Exptl. Biol. and Med.*, 48, 728 (1941).

(5) R. J. Block and D. Bolling, *J. Am. Dietet. Assoc.*, 20, 69 (1944).

(6) W. C. Rose, W. J. Haines, and D. T. Warner, *J. Biol. Chem.*, 206, 421 (1954).

(7) T. B. Osborne and L. B. Mendel, *J. Biol. Chem.*, 17, 325 (1914).

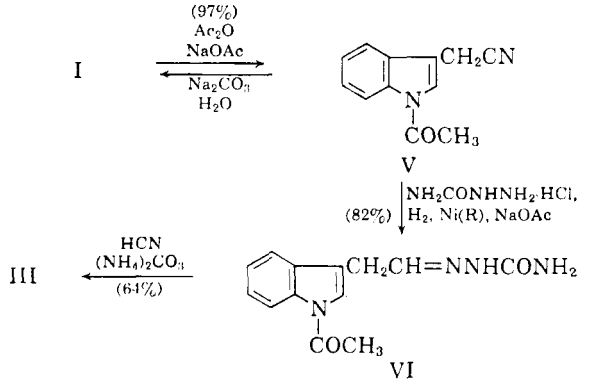
(8) H. Plieninger and G. Werst, *Chem. Ber.*, 88, 1956 (1955).

(9) J. E. Livak, S. C. Clemson, and E. C. Britton, U. S. Patent 2,527,366.

(10) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3172 (1952).

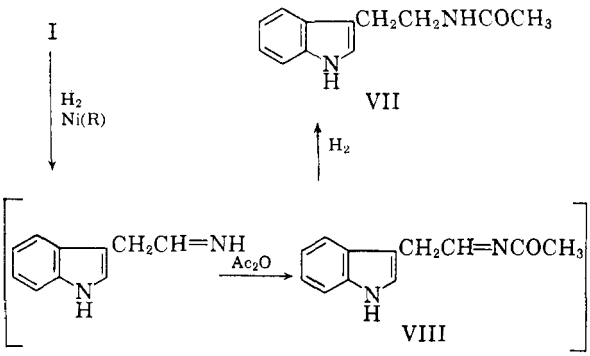
higher yield than the higher melting isomer (*i.e.*, 66% *vs.* 38%). This observation suggests that the semicarbazone should be converted to the hydantoin with the minimum of handling in order to obtain highest yields of the latter material.

3-Indoleacetonitrile (I) is a low-melting (34–36°) solid which can be crystallized only with difficulty. It is purified most efficiently by high vacuum distillation (b.p. 160°/0.02 mm.)[11], a tedious operation except on a small scale. The purification of 3-indoleacetonitrile has been simplified by converting it to its stable, easily recrystallized 1-acetyl derivative (V). The latter compound was prepared in nearly quantitative yield by the procedure of Plieninger and Werst[12] by treatment of the parent nitrile with sodium acetate–acetic anhydride. It could then be used in either of two ways. Brief treatment with aqueous alkali carbonate regenerated the parent nitrile in excellent yield, and this product could be hydrogenated to the semicarbazone without further purification. A somewhat more direct procedure involved the direct hydrogenation of the 1-acetyl derivative to 1-acetyl-3-indoleacetaldehyde semicarbazone (VI). This hydrogenation was accomplished in 82% yield under conditions identical to those employed with 3-indoleacetonitrile. Reaction of the 1-acetyl semicarbazone with hydrogen cyanide and ammonium carbonate gave 5-(3′-indolylmethyl)hydantoin (III) in 64% yield, the acetyl group being removed by hydrolysis during the reaction.



Free 3-indoleacetaldehyde is a relatively unstable compound and cannot be used conveniently as a precursor of tryptophan. However, it can be converted into typical aldehyde derivatives.[10,12] These have been found to be entirely equivalent to 3-indoleacetaldehyde semicarbazone for preparing tryptophan. Using the procedures of Plieninger and Werst,[8,12] both 3-indoleacetaldehyde and the more stable 1-acetyl-3-indoleacetaldehyde have been prepared and treated with the standard aldehyde reagents. Stable derivatives of the aldehyde obtained in this way include 3-indoleacetaldehyde phenylhydrazone, 3-indoleacetaldehyde oxime, 1-acetyl-3-indoleacetaldehyde oxime, and 1-acetyl-3-indoleacetaldehyde phenylhydrazone. These materials were all converted into 5-(3′-indolylmethyl)-hydantoin. This work is described in another paper[13] where the general nature of the hydantoin-forming reaction is reported.[14]

Efforts to reduce 3-indoleacetonitrile in the presence of acetic anhydride to an imine derivative of 3-indoleacetaldehyde have not been successful. The only product obtained was 3-(2-acetaminoethyl)indole (VII). The formation of this product instead of the desired *N*-acetylimine (VIII) indicates that the hydrogenation does not take place in controllable steps under the acidic conditions employed. The preparation of an acetal of



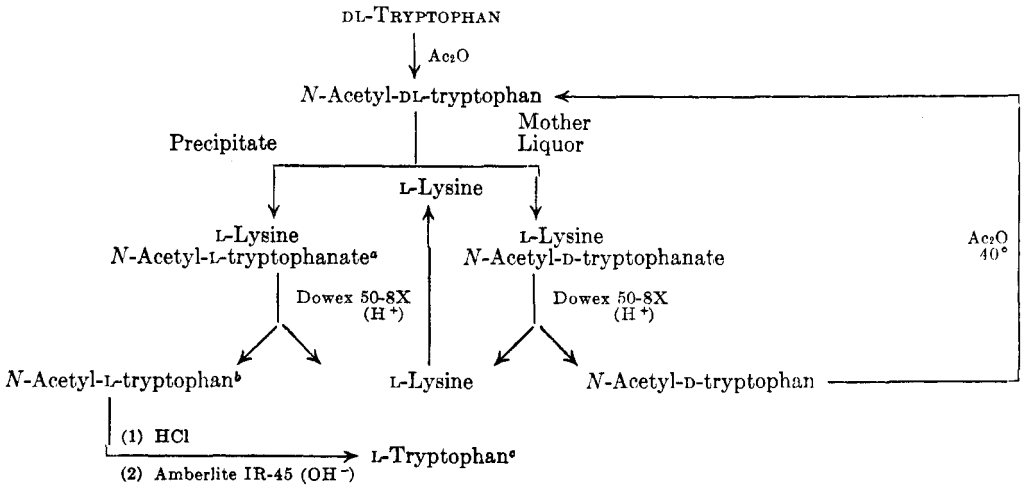
3-indoleacetaldehyde by the hydrogenation of 3-indoleacetonitrile in ethylene glycol with an acid catalyst (*e.g.*, ammonium chloride, *p*-toluenesulfonic acid) likewise could not be demonstrated. In the reactions carried out in the presence of *p*-toluenesulfonic acid, small amounts of the *p*-toluenesulfonic acid salt of tryptamine were isolated.

None of the hydrogenations performed in the presence of hydroxylamine, hydrazine, or phenylhydrazine yielded the expected 3-indoleacetaldehyde derivatives. Under the conditions used, hydroxylamine inhibited the hydrogenation of the nitrile. Slow hydrogenation occurred in the presence of hydrazine, but the reaction yielded no characterizable products. Normal rates of hydrogenation were noted in experiments with phenylhydrazine or ethylenediamine, but again no characterizable products could be isolated. Several hydrogenations were made in the presence of hydrogen cyanide and ammonium carbonate and the mixture of products subjected to alkaline hydrolysis without further work-up. Low yields of tryptophan, established by paper chromatographic analysis, were produced in these reactions. A very low yield of tryptophan was formed in a run in which one equivalent of hydrogen was added to 3-indoleacetonitrile, followed by immediate treatment with hydrogen

(11) W. Salzer and H. Andersag, German Patent 722,809.
(12) H. Plieninger and G. Werst, *Chem. Ber.*, 89, 2783 (1956).
(13) Manuscript in preparation.
(14) J. N. Coker, M. Fields, and A. O. Rogers, U. S. Patents 2,889,332; 2,893,997; 2,921,941; 2,937,184.

SCHEME I

CONVERSION OF DL-TRYPTOPHAN TO L-TRYPTOPHAN



[a] Obtained in 96% optical purity in 34% conversion. [b] Obtained in 91% optical purity in 79% yield. [c] Obtained in 95% optical purity in 89% yield.

cyanide and ammonium carbonate. Efforts to improve the yield of tryptophan precursor in the latter two reactions were not successful.

Resolution of DL-*tryptophan.* Evidence is that only L-tryptophan is active as a human dietary supplement; the unnatural D-isomer appears to be completely inactive.[3] A procedure for converting DL-tryptophan efficiently into the natural L-isomer is therefore desirable. The resolution of the free amino acid does not appear to be practical since the compound is not sufficiently acidic to combine with most basic resolving agents. The required diastereoisomer formation takes place readily, however, with tryptophan derivatives in which either the acid or primary amino group is masked. A derivative suited for use with basic resolving agents is *N*-acetyl-DL-tryptophan. This derivative is prepared by treating the free amino acid with acetic anhydride.[15] It has been resolved into its L-isomer using resolving agents such as quinine,[16] brucine,[17] and *p*-nitrophenyl-2-amino-1,3-propanediol.[18] One advantage gained from the use of the *N*-acetyl derivative in such resolutions stems from the ability of its optical antipodes to undergo racemization under relatively mild conditions. Thus the unwanted *N*-acetyl D-isomer should be readily convertible into the desired *N*-acetyl L-isomer.

During the course of the reported work, we have found that L-lysine is an excellent resolving agent for *N*-acetyl-DL-tryptophan, yielding the *N*-acetyl-L-amino acid as the lesser soluble diastereoisomer.[19] Operating in methanol–water the latter material was obtained in an optical purity of 96% at a conversion of 34%. The component amino acids were isolated from this salt by means of a sulfonic acid-type resin (Dowex 50), the L-lysine being absorbed when a solution of the resolution salt was passed over the acid form of the resin. *N*-Acetyl-L-tryptophan remained in the effluent and was recovered by evaporation. L-Lysine was recovered from the resin by elution with ammonium hydroxide. When the resin was used in the ammonium form the lysine still was absorbed on the column, but in this case the effluent contained ammonium *N*-acetyl-L-tryptophanate. Both L-lysine and *N*-acetyl-D-tryptophan should be recoverable from the more soluble isomer, L-lysine *N*-acetyl-D-tryptophanate, in the manner just described.

According to the literature racemization of *N*-acetyl-L-tryptophan can be accomplished readily by heating the material at 35–40° with acetic anhydride and aqueous alkali.[20] This reaction should proceed with the same facility with the chemically equivalent D-isomer and is therefore included as a part of the over-all resolution scheme. The hydrolysis of *N*-acetyl-L-tryptophan to the free L-amino acid is likewise reported in the literature.[18] In our work L-tryptophan of 95% optical purity was isolated in an 89% yield by removing the excess acid on an amino resin (Amberlite IR-45) and concentrating the resulting solution.

EXPERIMENTAL[21]

DL-*Tryptophan from 3-indoleacetonitrile.*[22] *3-Indoleacetaldehyde semicarbazone.* 3-Indoleacetonitrile (32.0 g., 0.21 mole) was dissolved in 125 ml. methanol.[23] To this solution

(15) C. P. Berg, W. C. Rose, and C. S. Marvel, *J. Biol. Chem.*, 85, 207 (1929).

(16) C. P. Berg, *J. Biol. Chem.*, 100, 79 (1933).

(17) A. C. Shabica and M. Tischler, *J. Am. Chem. Soc.*, 71, 3251 (1949).

(18) L. Velluz, et al., *Bull. soc. chim. France*, 20, 904 (1953).

(19) M. Fields and M. A. Stevens, U. S. Patent 2,865,928.

(20) V. Du Vigneaud and R. R. Sealock, *J. Biol. Chem.*, 96, 511 (1932).

(21) All melting points are uncorrected.

was added semicarbazide hydrochloride (23.0 g., 0.21 mole), Raney nickel (30 g., 50% ethanol slurry), sodium acetate trihydrate (23.0 g., 0.17 mole), and water (125 ml.). The mixture was shaken with hydrogen at 50 p.s.i. in a Burgess-Parr shaker assembly. After 4–5 hr. the mixture had absorbed approximately one equivalent of hydrogen, and the reaction was stopped. The mixture was diluted with methanol (300 ml.), heated to boiling, and filtered with the aid of Celite (5 g.). After concentration of the blue filtrate to about 1/4 its original volume, cooling produced grayish white crystals. After separation by filtration, the product was washed with cold water (three 50-ml. portions) and air-dried; it weighed 30 g. (0.14 mole, 68%). It was sufficiently pure for conversion to 5-(3′-indolylmethyl)hydantoin but could be recrystallized from water or methanol. Two recrystallizations of this product from water raised its melting point from 140–145° to 175.5–176.5°. This material was further characterized by infrared and elemental analysis.

Anal. Calcd. for $C_{11}H_{12}ON_4$: C, 61.09; H, 5.59; N, 25.92. Found: C, 60.68; H, 5.52; N, 25.98.

5-(3′-Indolylmethyl)hydantoin. An oxygen-free mixture of freshly prepared 3-indoleacetaldehyde semicarbazone (10 g., 0.047 mole, m.p. 140–145°), ammonium carbonate (7.5 g., 0.078 mole), water (70 ml.), and hydrogen cyanide (1.5 g., 0.056 mole) in a Hastelloy B-lined tube (325 ml.) was shaken at 100° for 4 hr. The resulting mixture was cooled to 5–10° and the white crystalline solid present collected by filtration, washed with cold water (four 30-ml. portions), and dried overnight *in vacuo* over calcium chloride. The dried product weighed 7.0 g. (0.031 mole, 66%), and was sufficiently pure for hydrolysis to DL-tryptophan. Further purification was accomplished by two recrystallizations from water yielding a product which melted at 216.5–217°. This material was further characterized by infrared, chromatographic, and elemental analysis.

Anal. Calcd. for $C_{12}H_{11}O_2N_3$: C, 62.90, H, 4.80; N, 18.37. Found: C, 62.88; H, 5.10; N, 18.25.

The hydantoin was also prepared, using the above conditions, from recrystallized 3-indoleacetaldehyde semicarbazone (m.p. 180–182°); the yield of product from this reaction amounted to only 38%.

DL-*Tryptophan.* 5-(3′-Indolylmethyl)hydantoin (1.7 g., 0.007 mole; m.p. 209–210°), barium hydroxide octahydrate (3.5 g., 0.011 mole), and water (75 ml.) were heated under nitrogen at autogenous pressure in a Hastelloy B-lined shaker tube for 1 hr. at 150°. A small amount of light brown precipitate was removed from the reaction mixture and discarded. The filtrate was treated with ammonium oxalate (1.6 g., 0.013 mole), the precipitated barium oxalate removed, and the filtrate concentrated to about 1/2 its original volume under aspirator vacuum. Extraction with *n*-butyl alcohol (three 150-ml. portions) at 40–60°, concentration of the combined extract to 150 ml. by heating under reduced pressure, and cooling produced DL-tryptophan in the form of white platelets. Further concentration of the *n*-butyl alcohol solution yielded a second crop of crystals. The combined yield obtained amounted to 1.1 g. (0.0054 mole, 73%). The product melted at approximately 265° with decomposition in a manner identical to that of a pure sample of DL-tryptophan. It was characterized further by paper chromatography and infrared analysis against DL-tryptophan standards. Treatment of the compound with hot ethanolic picric acid solution produced the picrate in the form of orange-red crystals, m.p. 191–192°.

Recovery of semicarbazide from the hydantoin-forming reaction. The filtrate and washings from the reaction producing 5-(3′-indolylmethyl)hydantoin were combined and evaporated to dryness *in vacuo* below 37°. This removed unchanged hydrogen cyanide and ammonium carbonate. The residue (4.2 g.) was extracted with distilled water (25 ml.) at 0° and the extracts decanted, combined, and evaporated to dryness *in vacuo*. The light brown product (3.3 g.) was extracted with absolute ethanol (17 ml. in several portions). Addition of dry hydrogen chloride to the extracts precipitated semicarbazide hydrochloride which was collected by filtration and air dried. The yield amounted to 1.83 g. (63.4%). An appreciable quantity of semicarbazide hydrochloride is believed to have remained in the ethanol in which it is appreciably soluble. Two recrystallizations from aqueous ethanol gave a white product (0.28 g.) which showed the same melting characteristics (m.p. 170–173° when heated rapidly) as authentic semicarbazide hydrochloride. The compound was also characterized by x-ray diffraction and by elemental analysis.

DL-*Tryptophan from 1-acetyl-3-indoleacetonitrile.* 1-Acetyl-3-indoleacetonitrile (5.0 g., 0.020 mole), semicarbazide hydrochloride (2.8 g., 0.025 mole), and sodium acetate trihydrate (2.8 g., 0.021 mole) were warmed in methanol (100 ml.) until dissolved. After cooling to room temperature, Raney nickel (5.0 g., 50% methanol slurry)[24] was added and hydrogenation carried out at near atmospheric pressure and room temperature. After slightly more than one equivalent (0.022 mole) of hydrogen had been absorbed (in 2.6 hr.), the hydrogenation was stopped and the reaction mixture cooled to 0–5° to precipitate the product. The mixture of catalyst and product was removed by filtration, and the product extracted from this mixture with hot dimethyl sulfoxide (three 50-ml. portions). The hot extracts were combined, filtered through Celite filter aid, cooled to below 30°, and diluted with water (300 ml.) to precipitate the flocculant white semicarbazone (4.2 g., 0.0163 mole, 81.5%). After two recrystallizations from methanol, its melting point was raised from 186–187° to a constant value of 201–202°. The product was further characterized as 1-acetyl-3-indoleacetaldehyde semicarbazone by elemental analysis.

Anal. Calcd. for $C_{13}H_{14}O_2N_4$: C, 60.47; H, 5.43; N, 21.71. Found: C, 60.32; H, 5.43; N, 21.77.

The crude semicarbazone was converted to 5-(3′-indolylmethyl)hydantoin in 64% yield by the procedure described above.

Derivatives of 3-indoleacetaldehyde. Various derivatives of 3-indoleacetaldehyde and of 1-acetyl-3-indoleacetaldehyde were prepared by the following general procedure.

The aldehyde reagent, hydroxylamine hydrochloride or phenylhydrazine hydrochloride, was dissolved in alcohol along with an equivalent amount of either sodium acetate or sodium hydroxide. The crude aldehyde also in alcohol was added and the mixture either warmed gently for several hours or allowed to stand several days at room temperature. The mixture was then cooled to 0–5° and the aldehyde derivative collected by filtration. The derivative was recrystallized from alcohol–water and characterized by elemental analysis and melting point:

(1) 3-Indoleacetaldehyde oxime (m.p. 140–142°)
Anal. Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.23; H, 5.81; N, 16.21.
(2) 3-Indoleacetaldehyde phenylhydrazone (m.p. 112–113°)
Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 77.13; H, 6.13; N, 17.32.
(3) 1-Acetyl-3-indoleacetaldehyde oxime (m.p. 137–138°)
Anal. Calcd. for $C_{12}H_{12}O_2N$: C, 66.67; H, 5.56; N, 12.96. Found: C, 66.96; H, 5.82; N, 12.83.
(4) 1-Acetyl-3-indoleacetaldehyde phenylhydrazone (m.p 122–124°)

(22) Freshly prepared 3-indoleacetonitrile was obtained by a reported procedure [J. Thesing and F. Schülde, *Chem. Ber.*, **85**, 324 (1952)] as a viscous oil ($n^{20}D$ 1.6097) which on standing at 0–5° for several weeks crystallizes to a solid melting at 36–38°. The vacuum-distilled oily nitrile had a correct analysis. *Anal.* Calcd. for $C_{10}H_8N_2$: C, 76.89; H, 5.16; N, 17.95. Found: C, 77.02; H, 5.30; N, 17.87; S, 525 p.p.m.

(23) Ethanol was also used as the hydrogenation solvent with comparable results.

(24) Digested for 10 min. in boiling methanol just prior to use.

Anal. Calcd. for $C_{18}H_{17}ON_3$: C, 74.23; H, 5.89; N, 14.43. Found: C, 74.21; H, 5.75; N, 14.52.

Resolution of N-acetyl-DL-tryptophan. With 95% L-lysine. *N*-Acetyl-DL-tryptophan (12.3 g., 0.050 mole) was stirred into a solution of 95% L-lysine (7.3 g., 0.062 mole) in water (18.7 g.) and, when it had dissolved, methanol (50 ml.) was added. The solution was seeded with pure L-lysine *N*-acetyl-L-tryptophanate (0.5 g., 0.002 mole), then gently stirred for 3.5 hr. at 25°. During this period the solution turned slowly into a thick slurry. This slurry was poured into a 3-cm., coarse-grained, sintered glass funnel and filtered under vacuum. The product, after washing with 75% methanol-water and drying, weighed 4.9 g. (0.013 mole, 27% conversion). It had a specific rotation, $[\alpha]^{22}D$ +17.17 (*c*, 3.6, water). This compared with $[\alpha]^{22}D$ values of +3.45 (*c* 2.8, water) for L-lysine *N*-acetyl-DL-tryptophanate and +20.47 (*c* 5, water) for L-lysine *N*-acetyl-L-tryptophanate and indicates that the salt had an optical purity of 90.0%.

With 100% L-lysine. At 25°. Pure L-lysine (11.2 g., 0.095 mole) was dissolved in water (19.8 g.). *N*-Acetyl-DL-tryptophan (12.3 g., 0.050 mole) was dissolved in the lysine solution, and the L-lysine *N*-acetyl-DL-tryptophanate solution so formed was diluted with methanol (78 ml.), seeded with L-lysine *N*-acetyl-L-tryptophanate (*ca.* 1 mg.), then stirred at 25° for 2.25 hr. At the end of this period, the solution was passed through a sintered glass filter, and the solid so obtained was washed with a mixture of methanol (22 ml.) and water (4 ml.). The resolution salt after drying over calcium chloride overnight weighed 6.39 g. (0.0175 mole, 35% conversion). This salt was found to be 90.0% pure L-lysine *N*-acetyl-L-tryptophanate ($[\alpha]^{22}D$ +16.8, *c* 4.7, water).

At 45°. To a solution of L-lysine (8.0 g., 0.068 mole) in water (21.8 g.) were added successively *N*-acetyl-DL-tryptophan (12.3 g., 0.050 mole), methanol (75 ml.), a finely triturated slurry of L-lysine *N*-acetyl-L-tryptophanate (0.5 g., 0.001 mole) in methanol (10 ml.), and, lastly, an additional amount of methanol (5 ml.). The suspension so obtained was stirred at 45° for 6.67 hr. and then filtered. The filter cake was washed first with 92% methanol–water (25 ml.) and then with 96% methanol–water (25 ml.). The salt obtained in this resolution (6.25 g., 0.0175 mole, 34% conversion) was shown to be 96.0% pure L-lysine *N*-acetyl-L-tryptophanate ($[\alpha]^{22}D$ +19.27, *c* 2.9, water).

Isolation of N-acetyl-L-tryptophan from L-lysine N-acetyl-L-tryptophanate. For this separation a sample of L-lysine *N*-acetyl-L-tryptophanate having a specific rotation, $[\alpha]^{22}D$ +17.2 (*c* 2.8, water) and an optical purity of 91% was used. A sample (5.8 g., 0.016 mole) of this product was dissolved in 50% methanol–water (100 ml.) and then poured through a bed of washed Dowex 50-8X resin (50 ml., H^+ form, 20–50 mesh). After the L-lysine *N*-acetyl-L-tryptophanate solution had been run through the bed, the resin was washed with water (50 ml.). After standing overnight, the effluent and the wash solution deposited crystals of *N*-acetyl-L-tryptophan which were collected by filtration. Concentration of the filtrates by evaporation under vacuum produced an additional quantity of product. The total yield obtained was 2.9 g. (0.012 mole, 79% yield). The material had a specific rotation, $[\alpha]^{29}D$ +21.2 (*c* 0.85, ethanol) and on optical purity of 91.0%.

An equally effective way of separating the amino acid components of L-lysine *N*-acetyl-L-tryptophanate was to run a solution of the salt over Dowex 50 (NH_4^+ form) resin. In this case the effluent consisted of a solution of ammonium *N*-acetyl-L-tryptophanate. *N*-Acetyl-L-tryptophan was filtered from the solution after acidification.

In both of the above examples, the L-lysine component of the resolution salt was absorbed on the resin and could be recovered by elution by 20% ammonium hydroxide (100 ml. in each case). The ammonium hydroxide eluate was evaporated to remove the ammonia, and the L-lysine reused.

Hydrolysis of N-acetyl-L-tryptophan. *N*-Acetyl-L-tryptophan (10 g., 0.040 mole) was boiled under reflux with 2 *N* hydrochloric acid (50 ml.) for 2 hr., then cooled, diluted with an equal volume of methanol, and poured down a 2 × 80 cm. column of Amberlite IR-45 resin (OH^- form). The resin was washed first with methanol (300 ml.) and then with hot water (200 ml.). The effluent and wash solution were mixed and evaporated to dryness at about 50° to give L-tryptophan (7.4 g., 0.036 mole, 89%). The optical purity of this product was 96.0%.

WILMINGTON 98, DEL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MIAMI]

Studies of Thermal Decarboxylation of Iron Carboxylates. I. Preparation of Symmetrical Aliphatic Ketones[1,2]

ROBERT DAVIS AND HARRY P. SCHULTZ

Received September 12, 1961

The thermal decarboxylation of iron carboxylates has been demonstrated to be an excellent method for the preparation of symmetrical, straight chain, aliphatic ketones. Some anomalous results are also reported.

The intermolecular decarboxylation of alkaline earth salts of carboxylic acids is frequently cited as a general method useful for the preparation of carbonyl compounds. A recently published critique[3] of this reaction presents evidence that yields are low and the expected carbonyl compounds are mixed with a variety of homologous compounds. Easterfield and Taylor[4] reported the syntheses of symmetrical ketones in yields of 60–80% by the reaction of straight chain fatty acids with iron filings, followed by distillation. They worked successfully with carboxylic acids of eighteen to thirty carbon atoms, but reported negative results

(1) Abstracted in part from the M.S. thesis of Robert Davis, University of Miami (1961).

(2) Presented before the 140th Meeting of the American Chemical Society, Chicago, Ill., Sept. 3–8, 1961.

(3) H. Schultz and J. Sickels, *J. Chem. Educ.*, **38**, 300 (1961).

(4) T. Easterfield and C. Taylor, *J. Chem. Soc.*, **99**, 2298 (1911).