phenethylamine (II) hydrochloride, $E_{1/2}$ = 0.194 v.; 4,5-dihydroxy-2-methoxyphenethylamine (I) hydrochloride, $E_{1/2}$ = 0.279 v., and the related 3,4,5-trihydroxyphenethylamine hydrochloride, $E_{1/2}$ = 0.300 v.

Enzymatic O-methylation Studies.—Enzymatic O-methylation of 2,5-dihydroxy-4-methoxyphenethylamine (II), 4,5-dihydroxy-2-methoxyphenethylamine (I) and 2,4,5-trihydroxyphenethylamine (XXXII) was attempted using 2 ml. of an enzyme preparation[20] containing the enzyme catechol-O-methyltransferase, 1 ml. of 0.5 *M* phosphate buffer, *p*H 7.9, 0.05 ml. of 0.5 *M* magnesium chloride, 5 μmole. Before addition of the substrate, the tubes were flushed with nitrogen and the incubation for 2 hrs. at 37° was carried out under nitrogen. Controls were also carried out in which no S-adenosylmethionine was present. After incubation the solutions were acidified with 0.5 ml. of 2 *N* hydrochloric acid and centrifuged at 10,000 rpm in a Servall centrifuge for 10 minutes. The decanted solutions were lyophilized, the residue extracted with 5 ml. of ethanol, the extract concentrated to dryness *in vacuo* and taken up in 0.4 ml. of ethanol. Paper chromatography (Table I) of these extracts showed methylation products for both 4,5-dihydroxy-2-methoxyphenethylamine (I) and 2,4,5-trihydroxyphenethylamine (XXXII) while 2,5-dihydroxy-4-methoxyphenethylamine (II) gave no reaction. The product from 4,5-dihydroxy-2-methoxyphenethylamine (I) gave a blue color with Gibb's reagent. The product from 2,4,5-trihydroxyphenethylamine (XXXII) gave a bright purple color with Gibb's reagent and no color with sodium molybdate.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

The Reaction of α-Chloro-α,α-diphenylacetanilide with Sodium Hydride

BY JOHN C. SHEEHAN AND JOHN W. FRANKENFELD

RECEIVED JUNE 12, 1961

The reaction of α-chloro-α,α-diphenylacetanilide with sodium hydride in an inert medium produced three compounds of the oxindole and indoxyl type; no α-lactam was isolated. Two oxindoles (3,3-diphenyloxindole and 1,3-diphenyloxindole) were identified by independent syntheses and the structure of the third product (2,2-diphenylindoxyl) was established by spectral data and by conversion to 3,3-diphenyloxindole by acidic reagents. The formation of oxindoles and indoxyls from α-haloanilides under basic conditions has not been reported previously.

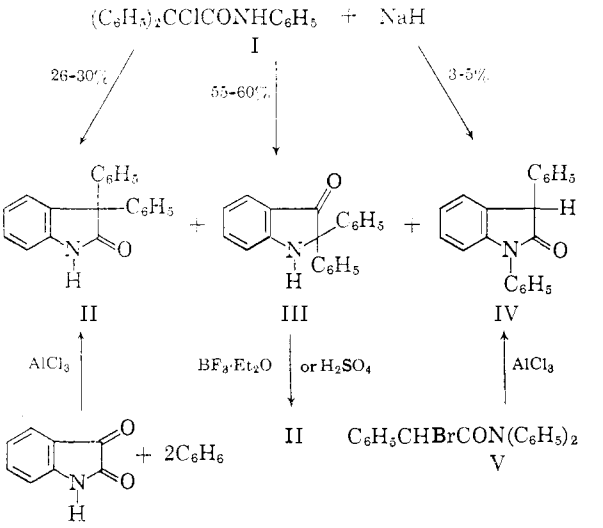
In a recent communication[1] the reaction of two α-haloanilides with sodium hydride was described and the reaction products were formulated as aziridinones (α-lactams). In view of our interest in small ring lactams we undertook to reinvestigate this work using α-chloro-α,α-diphenylacetanilide (I). In our hands the reaction took a different course leading to the formation of products which, although they resembled in physical and spectral properties the compounds reported previously,[1] have been identified as oxindole- and indoxyl-type compounds. No α-lactam was isolated from the reaction mixture. However, the formation of the products obtained may be rationalized by means of an α-lactam intermediate.

When α-chloro-α,α-diphenylacetanilide[2] (I, m.p. 87–88°) was treated with sodium hydride at 40–60° (under an inert atmosphere and with careful exclusion of oxygen) three compounds were obtained. These have been identified as 3,3-diphenyloxindole (II), 2,2-diphenylindoxyl (III) and 1,3-diphenyloxindole (IV).

This is the first reported example of the formation of oxindoles and indoxyls by the action of basic reagents upon α-haloanilides.

It was found that gradual addition of a twofold excess of sodium hydride to the α-chloroanilide I at 40–60°, followed by a brief period at 80°, provided the cleanest reaction. However, varying the reaction conditions considerably (including inverse mode of addition) did not affect the ratio of products materially. No reaction was observed below 40°.

The oxindole II crystallized readily from the reaction mixture leaving behind the more soluble III and IV. The infrared (bands at 3190, 1718, 1680, 1615 and 1589 cm.$^{-1}$) and ultraviolet (λ_{max}^{EtOH}



255 mμ, log ε 3.81) spectra suggested a 5-membered lactam fused to an aromatic system. One such compound, the formation of which can be rationalized easily, is the known[3a,b] 3,3-diphenyloxindole. This compound, prepared from isatin and benzene as described,[3a] proved to be identical to the reaction product II.

Fractional crystallization of the residue from ether and ether–petroleum ether mixtures yielded the indoxyl III and the second oxindole IV in the percentages shown. Compound IV (m.p. 114°) has infrared and ultraviolet spectra similar to those of 3,3-diphenyloxindole (II) except that the infrared ($CHCl_3$) clearly shows the absence of N–H absorption. These observations together with mechanistic considerations suggested the hitherto unknown 1,3-diphenyloxindole structure for IV. This oxin-

(1) S. Sarel and H. Leader, *J. Am. Chem. Soc.*, **82**, 4752 (1960).
(2) H. Klinger, *Ann.*, **389**, 253 (1912).
(3) (a) J. Wegmann and H. Dahm, *Helv. Chim. Acta*, **29**, 415 (1946); (b) C. H. Hassal and A. E. Lippman, *J. Chem. Soc.*, 1059 (1953).

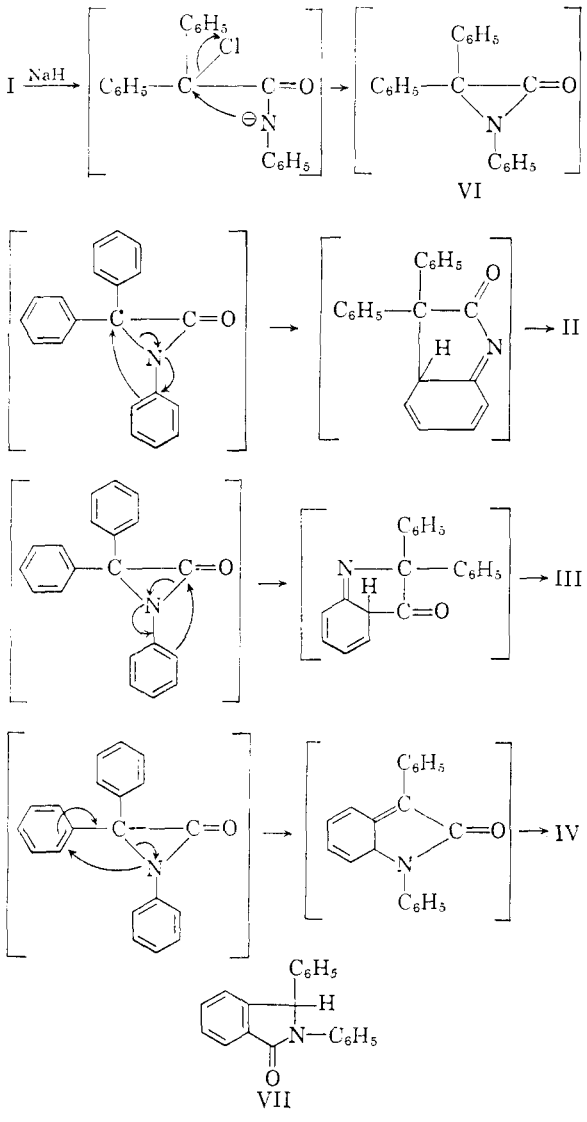
dole was synthesized by treating α-bromo-N,N-diphenylphenylacetanide[4] (V) with aluminum chloride in a manner commonly used to prepare oxindoles of known structure.[5] The substance obtained in this way was identical to compound IV. The n.m.r. spectrum of IV is consistent with 1,3-diphenyloxindole (see Experimental).

Analytical and molecular weight data established that the indoxyl III was isomeric with the oxindoles II and IV. The infrared spectrum ($CHCl_3$) exhibits N–H absorption at 3395 cm.$^{-1}$. No absorption attributable to aliphatic C–H is present (KBr). The fact that the N–H absorption, both in solution and in solid spectra, is not lowered because of hydrogen bonding suggested that the compound was an amino ketone rather than a lactam. (A lactam would be expected to absorb at around 3200 cm.$^{-1}$, as does 3,3-diphenyloxindole (II) for example, due to intermolecular hydrogen bonding;[6] while an amino ketone such as III, unable to form hydrogen bonds readily, should exhibit normal free N–H absorption.) Despite the presence of a secondary nitrogen the compound could not be acetylated even under conditions which readily attacked 3,3-diphenyloxindole. This observation suggested a high degree of steric hindrance about the nitrogen atom, as would be the case if two phenyl groups are attached to the carbon α to the nitrogen. From this evidence and from mechanistic considerations it seemed most likely that the third reaction product was the hitherto unknown 2,2-diphenylindoxyl (III). The n.m.r. spectrum of III verified the lack of aliphatic hydrogens and was consistent with this formulation (see Experimental).

Confirmation of the assignment was obtained by the facile conversion of III to 3,3-diphenyloxindole (II) under acidic conditions. Similar rearrangements are known to occur[7] with indoxyls containing groups of high migratory aptitude in the 2-position. Either boron fluoride etherate or sulfuric acid readily converted III to II in good yield.

Since rearrangements of the indoxyl to oxindole type may sometimes occur under basic conditions[7] it was necessary to consider the possibility that the oxindole II resulted from partial rearrangement of the indoxyl III by excess sodium hydride. In a separate experiment, however, III was found to be stable to excess sodium hydride under the conditions employed in the original reaction. This result, together with the observation that considerable variation in reaction conditions had little effect upon product ratios, indicates that II, III and IV are primary reaction products.

Mechanism of the Reaction.—A simple mechanism to account for the formation of all three compounds demands a symmetrical intermediate which can collapse to products in such a way as to sever the amide bond of I. Such an intermediate is the α-lactam VI.



A fourth compound, the known[8] 2,3-diphenylphthalimidine (VII), could conceivably arise from the α-lactam. However, none of this substance was isolated.

An alternate mechanism, not involving an α-lactam intermediate, may be employed to rationalize the formation of the two oxindoles (compounds II and IV). However, such a mechanism cannot account for the concurrent formation of 2,2-diphenylindoxyl (III).

Although the α-lactam is a likely intermediate in the reaction, all attempts at isolation failed. In order to run the reaction under milder conditions, the α-chloroanilide (I) was treated with the strong base, triphenylmethylsodium, at ice-bath temperature. The rapid disappearance of the red color of the base indicated that the reaction was occurring, but the infrared spectrum of the crude mixture showed no absorption in the 1820–1760 cm.$^{-1}$ region (expected[9] for an α-lactam). This α-lactam, if

(4) P. Pruitt, E. E. Richardson, L. M. Long and W. J. Middleton, *J. Am. Chem. Soc.*, **71**, 3479 (1949).

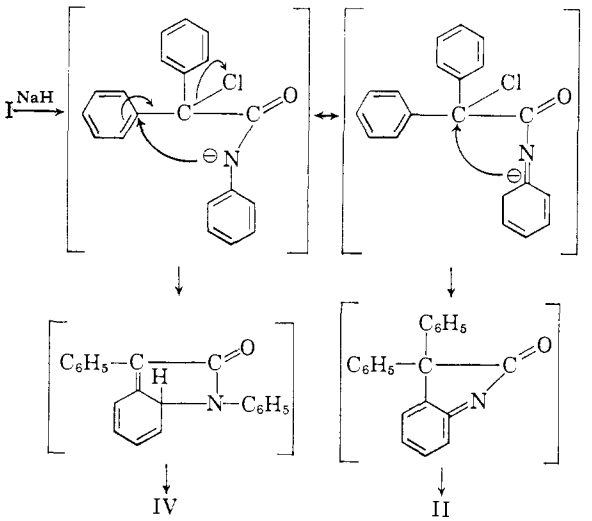
(5) See W. E. Sumpter, *Chem. Revs.*, **37**, 443 (1945), and references listed therein.

(6) L. J. Bellamy, "Infra-red Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 206–208.

(7) B. Witkop and A. Ek, *J. Am. Chem. Soc.*, **73**, 5664 (1951).

(8) H. Meyer, *Monatsh. Chem.*, **28**, 1219 (1907).

(9) γ-Lactams absorb at about 1750–1700 cm.$^{-1}$ and β-lactams at about 1760–1730 cm.$^{-1}$. See "The Chemistry of Penicillin," Princeton Univ. Press, Princeton, N. J., 1949, pp. 390–391.



formed, is apparently too reactive to be isolable by the techniques employed.

Acknowledgments.—The authors wish to express their appreciation to Mr. R. E. Chandler for many helpful discussions concerning the interpretation of infrared spectra and the reaction mechanism. Financial support from a contract with the Office of Naval Research (Biochemistry Branch) is gratefully acknowledged.

Experimental[10]

Reaction of α-Chloro-α,α-diphenylacetanilide (I) with Sodium Hydride.—This reaction was run under various conditions; those described are representative. All apparatus used was baked, assembled hot and flamed under a stream of pre-purified nitrogen to remove traces of oxygen. The solutions were de-gassed with a stream of nitrogen and a nitrogen atmosphere was maintained throughout the reaction.

To a vigorously stirred solution of 3 g. (0.0094 mole) of α-chloro-α,α-diphenylacetanilide[2] (I), m.p. 87–88°, in 120 ml. of dry benzene held at 40° by means of an oil-bath was added, slowly, 1.2 g. (0.025 mole) of sodium hydride (50% dispersion in oil). After the addition was complete (45 min.) the reaction temperature was raised to 75–80°. After 30 min. the reaction mixture was cooled to room temperature and kept there for 4.5 hours. The excess sodium hydride was destroyed by the cautious addition of 1 ml. of methanol.

Isolation of 3,3-Diphenyloxindole (II).—The benzene solution was washed with three 15-ml. portions of water, dried over magnesium sulfate and concentrated to one-quarter volume. Cooling afforded 0.48 g. of 3,3-diphenyloxindole (II), m.p. and mixture m.p. with an authentic sample prepared according to Wegmann and Dahm,[3a] 227–228°. Addition of petroleum ether to the filtrate and cooling gave a second crop of 0.15 g.; total yield 0.63 g. (29%); infrared spectrum (KBr): 3190, 1718, 1680, 1615, 1589 cm.$^{-1}$; ultraviolet spectrum: λ_{max}^{EtOH} 255 mμ, log ε 3.81. The infrared spectrum was superimposable with that of the authentic sample.

Anal. Calcd. for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.46; H, 5.31; N, 4.64.

The acetyl derivative of II was prepared from acetic anhydride in boiling pyridine; m.p. 176–177° (lit.[3b] m.p. 176–177°); infrared: 1750, 1705 cm.$^{-1}$ ($CHCl_3$).

Isolation of 1,3-Diphenyloxindole (IV).—The mother liquors after crystallization of II were concentrated to a yellow oil which was extracted with petroleum ether. After storage of the extract for a week in a refrigerator, IV (75 mg., 3.5%) crystallized. After recrystallization from ether–petroleum ether the m.p. was 113–114°, not depressed upon admixture with a synthetic sample prepared as described below. The infrared spectrum ($CHCl_3$) (1715, 1615, 1590 cm.$^{-1}$) is identical with that of the synthetic material; ultraviolet spectrum: λ_{max}^{EtOH} 248 mμ, log ε 4.09. The n.m.r. spectrum[11] shows two sharp peaks at 7.36 and 7.21 p.p.m., apparently due to the 10 protons on the two non-equivalent phenyl groups. The spectrum contains multiplets between 7.01 and 6.89 p.p.m. which may be assigned to four adjacent protons on the fused aromatic ring and a sharp singlet due to the tertiary proton at 4.59 p.p.m.

Isolation of 2,2-Diphenylindoxyl (III).—The yellow oil remaining after the petroleum ether extraction crystallized upon trituration with ether. The light yellow crystals were collected by filtration and washed with the mother liquor. Cooling the filtrate produced another small crop. The total yield of III, melting at 205°, was 1.22 g. (57%). After recrystallization from acetone or benzene–petroleum ether the compound was obtained as colorless plates, m.p. 213–214°; infrared spectrum ($CHCl_3$): 3395, 1705, 1589 cm.$^{-1}$. The ultraviolet spectrum showed complicated absorption between 220 and 280 mμ ($CHCl_3$ or EtOH) with no definite maxima. The n.m.r. bands, because of the scarcity of information concerning n.m.r. spectra of compounds of this type, are difficult to assign. However, the presence of two equivalent phenyl groups is suggested by a strong, sharp signal at 7.24 p.p.m. The spectrum also contains multiplets between 6.95 and 7.50 p.p.m., probably due to three adjacent protons on the aromatic ring fused to the five-membered, nitrogen-containing ring, and a peak at 7.91 p.p.m. which may be assigned tentatively to the fourth aromatic proton *ortho* to the carbonyl. A broad peak centered at 6.29 p.p.m. is probably due to the N-H proton. This signal unexpectedly occurs as a multiplet, perhaps because of long-range coupling with protons of one of the aromatic rings in the 2-position. Mol. wt. (cryoscopic in benzene): 260–280; calcd. for $C_{20}H_{15}NO$: 285.

Anal. Calcd. for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 83.87; H, 5.30; N, 4.84.

Attempts to prepare the **acetyl derivative of III** failed both with acetic anhydride in boiling pyridine and with acetyl chloride and triethylamine. The compound showed no reaction with 2,4-dinitrophenylhydrazine.

Rearrangement of III to II. (a) **By Boron Fluoride.**—Freshly distilled boron fluoride etherate (3 ml.) was added to 150 mg. of III and the resulting bright red solution was refluxed for 15 min. The solution, now colorless, was cooled and poured into cold water. The colorless crystals which resulted were collected on a filter, washed with water until the washings were neutral, and dried. The yield was 125 mg. (85%), m.p. 223–226°; mixture m.p. with authentic II, 225–226°. The infrared spectrum of the rearranged product was identical to that of II.

(b) **By Sulfuric Acid.**—A sample of III dissolved slowly in warm, concentrated sulfuric acid. Upon dilution with water II was obtained in 50% yield. After a single recrystallization from benzene–petroleum ether it melted at 227–228° (not depressed upon admixture with authentic II).

α-Bromo-N,N-diphenylphenylacetamide (V), prepared according to Pruitt and co-workers,[4] had m.p. 140–141° (lit.[4] m.p. 140°), infrared spectrum (KBr) 1670 cm.$^{-1}$ (C=O).

1,3-Diphenyloxindole (IV).—An intimate mixture of 4.2 g. (0.0114 mole) of V and 4.1 g. of aluminum chloride was heated in an oil-bath at 130° for 2.5 hr. After cooling, the dark mass was poured into ice-water and extracted with benzene. The dried benzene extracts were concentrated to a red oil which crystallized from ether as light tan plates, m.p. 112–113°. Recrystallization from ether–petroleum ether afforded colorless IV, m.p. 114°. The total yield amounted to 2.57 g. (79%); infrared spectrum ($CHCl_3$): 1715, 1615, 1590 cm.$^{-1}$; ultraviolet spectrum: λ_{max}^{EtOH} 248 mμ, log ε 4.09.

Anal. Calcd. for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.40; H, 5.60; N, 4.98.

As a model, **1-phenyloxindole** (m.p. 122°) was prepared as described by Stolle.[12] The infrared spectrum of this compound was very similar to that of IV.

(10) Melting points are corrected. The authors are indebted to Dr. S. M. Nagy and his associates for the microanalyses, to Mrs. N. Alvord for the infrared spectra and to Miss V. Kramar and Mr. J. Byrum for the ultraviolet spectra.

(11) The n.m.r. spectra were obtained on a Varian 4300b spectrometer operating at 60 megacycles. Peak positions are given as parts per million (p.p.m.) downfield from internal tetramethylsilane.

(12) R. Stolle, *Ber.*, **47**, 2120 (1914).

Reaction of α-Chloro-α,α-diphenylacetanilide (I) with Triphenylmethylsodium.—Oxygen and moisture were excluded from the system as described in the sodium hydride reaction. To a stirred solution of 0.285 g. (1 mmole) of α-chloro-α,α-diphenylacetanilide in 10 ml. of anhydrous ether maintained at −5 to 0° by means of an ice–salt-bath was added, dropwise, 0.9 mmole of a 1% solution of triphenylmethylsodium in anhydrous ether. The dark red color of the base was discharged immediately indicating a rapid reaction. After an additional 10 min. stirring, the ether was removed and replaced with chloroform. At no time during these operations was the temperature allowed to rise above 0°. The insoluble material was rapidly centrifuged and the yellow, supernatant solution was scanned in the infrared. No bands attributable to an α-lactam were observed. The same was true of the chloroform-insoluble material.

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A Sterically Controlled Synthesis of Amino Acids

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RECEIVED JUNE 12, 1961

Catalytic hydrogenation of α-acetamido-β,β-dimethylacrylic acid L-α-methylbenzylamide in the presence of Raney nickel gave the saturated amide. Hydrolysis of this amide afforded D-valine of 39% optical purity. Reduction of α-benzamido-β,β-dimethylacrylic acid L-α-methylbenzylamide followed by hydrolysis of the saturated amide produced D-valine of 18% optical purity. Similar treatment of the D-α-methylbenzylamide gave L-valine of 18% optical purity. D-Phenylalanine of 6% optical purity was produced by the hydrogenation and subsequent hydrolysis of α-benzamidocinnamic acid L-α-methylbenzylamide.

One route for the biosynthesis of α-amino acids is through reductive amination or transamination of α-keto acids. A remarkable feature of this reaction is the high degree of stereospecificity shown. Although the *in vivo* synthesis doubtless operates under enzymatic control and probably by interaction with asymmetric species, it seemed of interest to determine the degree of asymmetric induction produced under non-enzymatic conditions. In particular the catalytic hydrogenation of compounds of the type I was studied.

By application of the rules proposed by Cram[1] and Prelog[2] it should be possible to predict the isomer which will be formed predominantly in the conversion of an asymmetric amide of an α-acylamino-α,β-unsaturated acid to the amino acid. Assuming, like Prelog,[2] that hydrogen is adsorbed on the surface of the catalyst and that the substrate approaches the catalyst surface with the least hindered side, one can predict the enantiomer that will predominate by the induction due to the optically active center already present in the molecule. Thus, it can be seen (Fig. 1) that by the use of L-α-methylbenzylamine, D-amino acid should predominate. Conversely, the use of D-α-methylbenzylamine should lead to a predominance of L-amino acid. Leithe[3] has established the absolute configuration of (−)-α-methylbenzylamine by degrading the phenyl group to carboxyl and obtaining L-alanine. α-Methylbenzylamine was chosen as the optically active portion of the molecule to facilitate separation of the products after hydrolysis.

Aminolysis of 4-isopropylidene-2-methyl-5-oxazalone with L-α-methylbenzylamine afforded α-acetamido-β,β-dimethylacrylic acid L-α-methylbenzylamide (Ia). Hydrogenation of Ia in the presence of Raney nickel in methanol gave N-acetylvaline L-α-methylbenzylamide (IIa). Hydrolysis of IIa with 20% hydrochloric acid gave valine (III) in 90% yield. The valine thus obtained had a

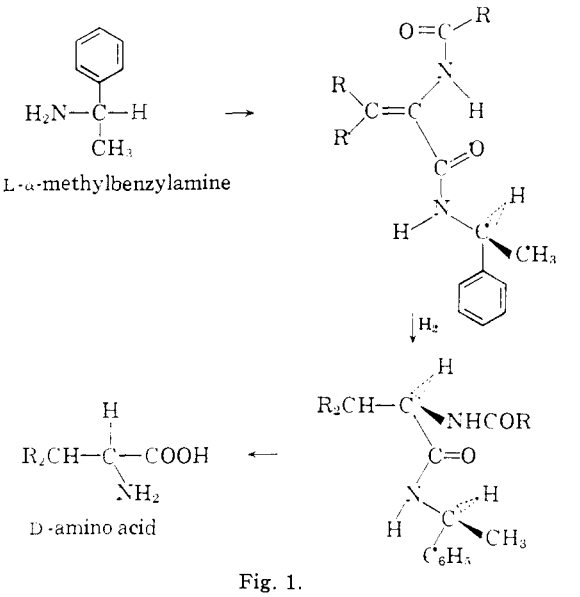

Fig. 1.

specific rotation of −11.3° in 6 *N* hydrochloric acid and −24.2° in glacial acetic acid. Based on the reported values for L-valine,[4] this corresponds to a 39% excess of D-valine.

Aminolysis of 4-isopropylidene-2-phenyl-5-oxazalone with L-α-methylbenzylamine in refluxing ethanol gave α-benzamido-β,β-dimethylacrylic acid L-α-methylbenzylamide (Ib). Hydrogenation of Ib over Raney nickel in methanol afforded a quantitative yield of N-benzoylvaline L-α-methylbenzylamine (IIb). Hydrolysis of IIb in 20% hydrochloric acid gave valine (III) in a yield of 90%. The valine obtained in this manner had a specific rotation of −5.2° in 6 *N* hydrochloric acid, −10.6° in glacial acetic acid, and −2.4° in water. These values correspond to an optical yield of 18% with the D-isomer once again in excess.

The same reaction sequence was carried out with D-α-methylbenzylamine. Hydrogenation of α-

(1) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

(2) V. Prelog, *Bull. soc. chim. France*, 987 (1956).

(3) W. Leithe, *Chem. Ber.*, **64**, 2831 (1931).

(4) J. P. Greenstein, S. M. Birnbaum and M. C. Otey, *J. Biol. Chem.*, **204**, 307 (1953).