amount of hydrogen had been absorbed. Evaporation of the filtered reaction mixture afforded a pale yellow oil, which on distillation *in vacuo* (115°, 0.1 mm.) yielded 1,3-dimethyl-2-phenylpiperidine as a colorless oil (118 mg., 88%). The base was characterized as its methiodide, obtained a colorless needles from methanol and ether; m.p. 176–177°.

Anal. Calcd. for $C_{14}H_{22}NI$: C, 50.76; H, 6.70; N, 4.23. Found: C, 50.46; H, 6.71; N, 4.32.

Oxidation of 1,3-Dimethyl-2-phenylpiperidine.—The piperidine derivative (71.3 mg.) dissolved in 10% sulfuric acid (2 ml.) was added to a refluxing solution of chromium trioxide (5.0 g.) in 10% sulfuric acid (12 ml.). Distillation was commenced immediately, distilled water being added from a dropping funnel to maintain the volume of the reaction mixture at about 12 ml. Distillation was continued for 3 hr. during which time 60 ml. of distillate was collected. This aqueous distillate was extracted with ether (2 × 40 ml.). The combined ether extracts were then extracted with water (2 × 40 ml.). These two water extracts were then back-extracted with ether (2 × 40 ml.). The combined ether extracts were then dried over sodium sulfate and evaporated, yielding crude benzoic acid (14.8 mg.). Sublimation twice afforded pure benzoic acid (4.8 mg.), m.p. 120–122°, not depressed on admixture with an authentic sample. The combined aqueous extracts were titrated to *p*H 8 with 0.0985 *N* sodium hydroxide solution (2.73 ml. required) and then evaporated to dryness. The white residue was refluxed with absolute ethanol, filtered and sodium acetate (11.1 mg.) precipitated by the addition of ether.

Schmidt Reaction on the Sodium Acetate.—Sodium acetate (6.1 mg.) was dissolved in warm concd. sulfuric acid (0.1 ml.). The mixture was then cooled to 0° and sodium azide (10 mg.) added. The reaction vessel was swept with carbon dioxide-free nitrogen, which was then passed through a 5% solution of potassium permanganate in 5% sulfuric acid (to remove sulfur dioxide) and then through a solution of barium hydroxide. The reaction flask was heated to 80° and maintained at this temperature for 1 hr. during which time barium carbonate (9.4 mg.) was precipitated in the barium hydroxide solution.

Decarboxylation of Nicotinic Acid. (a) With Barium Hydroxide.—Nicotinic acid (49.1 mg.) was intimately mixed with anhydrous barium hydroxide (110 mg.) and heated in a nitrogen stream. At about 325° pyridine distilled out of the reaction mixture and was collected as the picrate (32 mg., 26%).

(b) With Copper Chromite.—Nicotinic acid (34.3 mg.) was refluxed in quinoline (1 ml.) containing copper chromite catalyst (38.5 mg.) in a stream of nitrogen. The liberated carbon dioxide was passed into barium hydroxide solution yielding barium carbonate (53 mg., 98%).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MASSACHUSETTS, AMHERST, MASS.]

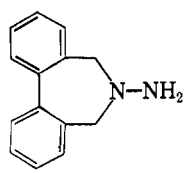
Synthesis and Oxidation of 2-Amino-2,3-dihydro-1H-benz[de]isoquinoline and 1,2,3,4-Tetrahydronaphtho[1,8-de][1,2]diazepine and Related Cyclic 1,2-Dibenzylhydrazines[1]

BY LOUIS A. CARPINO

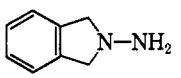
RECEIVED JANUARY 24, 1963

Contrary to expectations based on previous studies of the oxidation of cyclic 1,1-disubstituted hydrazines such as 6-amino-5,7-dihydrodibenzo[ce]azepine (I) and 2-aminodihydroisoindole (II), neither oxidation of 2-amino-2,3-dihydro-1H-benz[de]isoquinoline (III) nor alkaline degradation of the corresponding sulfonhydrazide led to the formation of acenaphthene. A general method for the synthesis of the three corresponding hydrazo compounds, 5,6,7,8-tetrahydrodibenzo[df][1,2]diazocine (XV), 1,2,3,4-tetrahydrophthalazine (XVI) and 1,2,3,4-tetrahydronaphtho[1,8-de][1,2]diazepine (X) was developed involving reaction of *t*-butyl hydrazodiformate with an appropriate bis-halomethyl derivative followed by cleavage of the carbo-*t*-butoxy group by means of hydrogen chloride. The oxidation of X gave a stable azo compound (XX), whereas the azo compound XXII derived from XV proved to be an unstable, heat-sensitive material. No stable azo compound could be isolated from the mercuric oxide oxidation of XVI. Thermal decomposition of 1,4-dihydronaphtho[1,8-de][1,2]diazepine (XX) yielded acenaphthene.

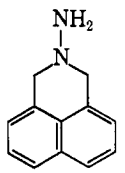
Just as 1,1-dibenzylhydrazine, on oxidation with mercuric oxide[2] and other oxidizing agents or alkaline degradation of the corresponding sulfonhydrazides,[3] yields bibenzyl, it would be expected that oxidation of the analogous cyclic systems I, II and III would yield 9,10-dihydrophenanthrene (IV), benzocyclobutene (V) and acenaphthene (VI), respectively. Indeed,



I

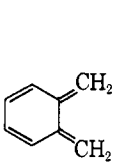


II

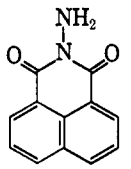


III

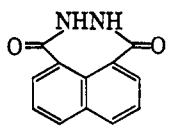
compound I gave IV in 95% yield on sulfonhydrazide degradation. Similarly, sulfonhydrazide degradation of II was shown by Baker, McOmie and Preston[4] to give benzocyclobutene in 14% yield along with some *o*-xylene and dibenzocycloöctadiene. It was subsequently shown[5] that this reaction as well as the corresponding mercuric oxide oxidation yields, in addition to V, the Errede dimer[6] of *o*-quinodimethane (VII). The present paper reports a study of the oxidation of



VII



VIII



IX

the naphthalene derivative III. Contrary to expectations, neither the oxidation of III nor the alkaline degradation of the corresponding sulfonhydrazide yielded any acenaphthene.

A synthesis of III was described in an earlier paper[7] utilizing two methods which implied the correctness of the structure indicated, namely (a) sodium borohydride–lithium bromide reduction of a hydrazide described as N-aminonaphthalimide (VIII) and (b) alkylation of *t*-butyl carbazate by means of 1,8-bis-(chloromethyl)-naphthalene followed by hydrogen chloride cleavage of the carbo-*t*-butoxy group. Neither method, however, is unequivocal and in view of the unexpected lack of conversion of III to acenaphthene on oxidation it was considered desirable to obtain further evidence for the structure of III.

The most likely alternative structure is the 7-ring hydrazo compound X. Although it is unlikely, method b could have led to the formation of X. The structure of the precursor hydrazide used in method a appears well established as VIII. An isomeric naphthalic hy-

(1) Supported by a grant from the National Science Foundation (NSF G-19506).

(2) M. Busch and B. Weiss, *Ber.*, **33**, 270 (1900).

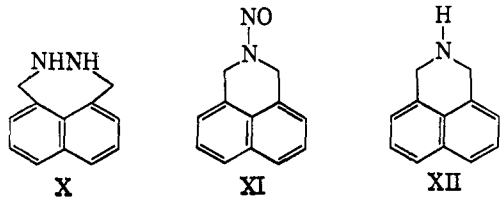
(3) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957).

(4) W. Baker, J. F. McOmie and D. R. Preston, *Chem. Ind.* (London), 1305 (1960); *J. Chem. Soc.*, 2971 (1961).

(5) L. A. Carpino, *J. Am. Chem. Soc.*, **84**, 2196 (1962).

(6) L. A. Errede, *ibid.*, **83**, 949 (1961).

(7) L. A. Carpino, A. A. Santilli and R. W. Murray, *ibid.*, **82**, 2728 (1960).



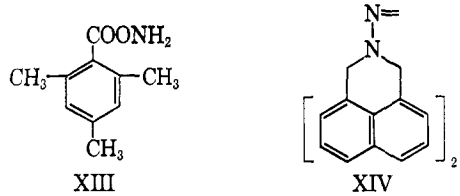
X XI XII

drazide (IX) has been obtained by reaction of naphthalic anhydride and hydrazine under certain conditions by some authors.[8,9] Attempts in our laboratories to obtain IX have always failed, only the compound described as VIII being obtained. The ease of reduction of the hydrazide used itself argues for structure VIII since 1,2-diacylhydrazines are not easily reduced even by the more potent reagent lithium aluminum hydride.[10]

Additional evidence has now been obtained to substantiate structure III for the earlier-described hydrazine by degradative experiments, alternate methods of synthesis, n.m.r. spectral studies and preparation of the isomeric hydrazo compound X.

Treatment of III with nitrous acid caused deaminative nitrosation yielding the nitrosamine XI, which was denitrosated to the amine XII by means of gaseous hydrogen chloride.

The structure of amine XII, m.p. 105–106°, was established by its formation from naphthalimide by lithium aluminum hydride reduction, albeit in very poor yield (1–2%). The same amine, reported m.p. 102–103°, had been obtained earlier by Späth, Kuffner and Kittel[11] by the electrolytic reduction of naphthalimide. Nitrosation of XII followed by reduction of the nitrosamine XI by means of aluminum amalgam in wet ether gave back III. The type of aluminum used was apparently critical as certain samples caused denitrosation, non-reaction or formation of unidentified basic products. Finally, hydrazine III was obtained directly from XII by amination utilizing O-mesitoylhydroxylamine (XIII), a general reagent[13] for the conversion of secondary amines to 1,1-disubstituted hydrazines.



XIII XIV

Examination of the n.m.r. spectrum of 2-amino-2,3-dihydro-1H-benz[de]isoquinoline (III) provides additional support in favor of the designated structure. The spectrum exhibits a group of lines associated with six aromatic protons centered at a δ-value of 7.34 and sharp lines for four methylene and two amino protons at 4.06 and 3.16, respectively. The methylene signal at 4.06 is expectedly shifted to a higher δ-value from the methylene peak in the spectrum of the corresponding acyclic analog, 1,1-dibenzylhydrazine (3.70). The methylene signal of amine XII appears at 4.31.

The n.m.r. spectrum of the *p*-toluenesulfonyl derivative of III confirms its structure also. Aside from the aromatic resonances centered at 7.5 the spectrum exhibited a series of three sharp lines at 6.0 (NH), 4.2 (CH_2) and 2.5 (CH_3).

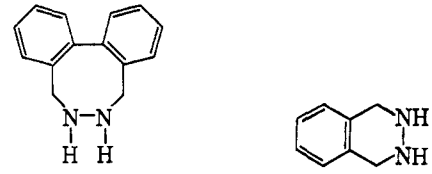
This combination of chemical and spectral evidence leaves little doubt as to the correctness of structure III. Synthesis of the isomeric compound X is discussed below. Having established the structure of III, it is necessary to explain the unusual result that hydrocarbon coupling products are formed from benzylic hydrazines I and II, but not from the similarly constituted III. Upon oxidation of III by means of mercuric oxide suspended in methylene dichloride and in a variety of other solvents the only product isolated, in poor yield, was a neutral substance (A) presumed to be the tetrazene XIV. The same substance was isolated in low yield using as oxidizing agents potassium permanganate in acetone or N-bromosuccinimide in the presence of pyridine. No tractable material could be isolated in the case of (a) N-bromosuccininide in the absence of pyridine, (b) benzoquinone,[14] (c) silver oxide[15] or (d) activated manganese dioxide.[16]

Examination of the n.m.r. spectrum of (A) was complicated by its low solubility in deuteriochloroform. However a saturated solution in this solvent was examined and found to exhibit only two weak resonance peaks at δ-values of 7.4 and 4.8, which can be ascribed to the aromatic and methylene protons of the tetrazene structure XIV. Unfortunately the solution was too dilute for a meaningful integration of the spectrum with the instrumentation available.

Treatment of the *p*-toluenesulfonyl derivative of III with refluxing 20% aqueous sodium hydroxide for 15 min. led to recovery of the unreacted sulfonhydrazide.[17] By contrast, the sulfonhydrazides of I and II in the presence of warm aqueous alkali are immediately decomposed with vigorous evolution of nitrogen.

One could rationalize the differences between I and II on the one hand and III on the other by postulating *o*-quinodimethanes as necessary intermediates in the formation of hydrocarbon products since III could not yield such a species. However from this viewpoint it would be difficult to see why cyclic systems such as I, II and III should differ so greatly from acyclic analogs such as 1,1-dibenzylhydrazine. Indeed, the result may be due to a simple steric effect. Further studies are clearly required in order to establish the basis for the differences observed in the oxidation of I, II and III.

As part of our interest in establishing definitely the structure of III it was considered desirable to develop an unequivocal synthesis of the isomeric hydrazo compound X. In addition, the analogs XV and XVI of I and II were prepared in order to compare the



XV XVI

oxidation of these systems with that of I, II and III. Oxidation of the hydrazo compounds should give rise, initially at least, to the corresponding azo compounds.

A general method for the synthesis of such cyclic 1,2-disubstituted hydrazines involves reaction of the corresponding bis-(halomethyl)-arenes with the dipotassium salt of *t*-butyl hydrazodiformate followed by

(8) A. Bistrzycki and J. Risi, *Helv. Chim. Acta*, **8**, 810 (1925).

(9) E. S. Vasserman and G. P. Miklukhim, *J. Gen. Chem. USSR*, **10**, 202 (1940) [*Chem. Abstr.*, **34**, 7179 (1940)].

(10) R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 2463 (1956).

(11) E. Späth, F. Kuffner and F. Kittel, *Ber.*, **72**, 1109 (1939). These workers corrected an earlier[12] erroneous description of the amine as having m.p. 70°.

(12) E. Späth and F. Breusch, *Monatsh.*, **50**, 349 (1928).

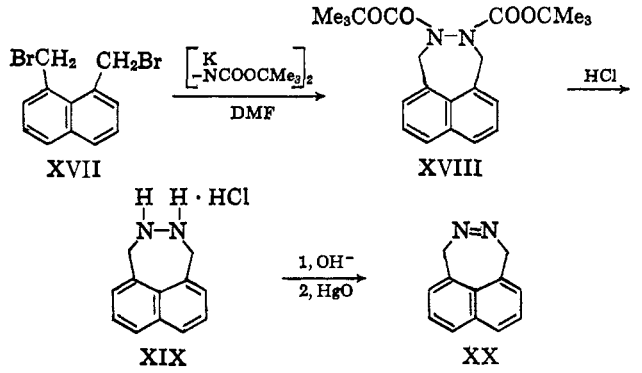
(13) L. A. Carpino, *J. Am. Chem. Soc.*, **82**, 3133 (1960).

(14) H. Wieland and H. Fressel, *Ann.*, **392**, 133 (1912).

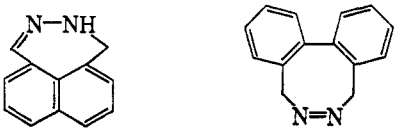
(15) W. Schroeder and L. Katz, *J. Org. Chem.*, **19**, 718 (1954).

(16) H. Morrison, S. Danishefsky and P. Yates, *ibid.*, **26**, 2617 (1961).

(17) Longer periods of refluxing led to the formation of a high-melting nitrogen-containing compound, the structure of which is currently under examination.



hydrogen chloride cleavage of the carbo-*t*-butoxy group. The method is illustrated for the naphthalene derivative in the equations leading from XVII to XIX. Although the free base X proved to be somewhat unstable, it could be liberated from the stable hydrochloride XIX and immediately oxidized by means of mercuric oxide to the azo compound XX. Other oxidizing agents such as ammoniacal hydrogen peroxide[18] or selenium dioxide, both of which can be used successfully in the oxidation of 1,2-dibenzylhydrazine to α,α'-azotoluene, lead to the formation of an isomer of XX, presumably the corresponding hydrazone XXI. Compound XXI is also obtained by treatment of XX with hydrochloric acid.



XXI XXII

N.m.r. studies support structure XX for the mercuric oxide oxidation product of X. Apart from the complex of lines due to the aromatic protons, the spectrum of XX showed a single sharp line at a δ-value of 5.8 ascribed to the methylene protons. That this large shift of 1.25 δ-units from the corresponding absorption (4.55) in the spectrum of the free hydrazo compound X is entirely reasonable for methylene bonded to azo nitrogen is shown by comparison of the δ-values associated with the methylene protons of the model compounds α,α'-azotoluene (5.0) and 1,1-dibenzylhydrazine (3.7).[19]

The spectrum of a freshly prepared sample of the 7-ring hydrazo compound X exhibited, aside from the aromatic proton resonances, three sharp peaks at 5.8, 4.55 and 3.70. The peak of medium height at 5.8 is attributed to the presence of a quantity of the azo compound XX arising from air oxidation. In fact when air was passed through the deuteriochloroform solution of X for one hour in the test capillary and the spectrum re-run, the peaks at 4.55 ($-CH_2-$) and 3.7 (NH) disappeared and were replaced by a single strong line at 5.8, the spectrum having become identical with that of XX prepared by mercuric oxide oxidation. The infrared spectrum of XX showed no absorption in the N–H region.

Examination of the n.m.r. spectrum of the rearrangement product of XX confirmed its structural assignment as the corresponding hydrazone XXI. The spectrum showed a sharp line for the benzyl protons at 4.5, a very weak hump due to the amino hydrogen almost undetectable above the noise level at 6.5, and a complex of lines associated with the aromatic protons centered at 7.7. Since no other lines were present it was presumed that the aldimine proton was buried among the aromatic hydrogens. This was verified by integration of the spectrum which led to the ratio 2:1:7 for the ten protons. Presence of the NH group was verified by examination of the infrared spectrum of XXI, which exhibited a wide band of medium intensity at 3.1 μ. As a model compound the n.m.r. spectrum of the benzal derivative of benzylhydrazine was also examined. In this case the benzyl protons again appeared as a sharp line at 4.5. The amino proton led to an easily detected broad band at 5.7. Again the aldimine proton appeared in the region of the aromatic protons centered at 7.6. Similarly the n.m.r. spectrum of the benzal derivative of 1,1-dibenzylhydrazine exhibited only one sharp line due to 4 protons at 4.6 (CH_2) in addition to the series of lines due to 16 protons for the aromatic and aldimine resonances centered at 7.6. Apparently this overlap occurs only in the case of the hydrazones since the aldimine protons in the spectrum of benzalazine appeared at 8.8, clearly separated from the series of aromatic peaks centered at 7.8.

Methods similar to those used in the synthesis of X were used in the synthesis of XV and XVI. Oxidation of the latter by means of mercuric oxide was accompanied by immediate gas evolution, even at 0°, and formation of the Errede dimer of *o*-quinodimethane. No intermediate azo compound could be isolated under the conditions employed. Oxidation of XV by means of activated manganese dioxide at 0° yielded the very sensitive azo compound XXII which detonated on heating. It was not sufficiently stable to be submitted for elemental analysis. A sample submitted for n.m.r. analysis in deuteriochloroform decomposed rapidly in the probe while the spectrum was being run. The resulting spectrum appeared to be that of 9,10-dihydrophenanthrene contaminated by an unknown impurity. The naphthalene-derived azo compound XX proved to be more stable toward loss of nitrogen. However, when XX was heated to the boiling point at atmospheric pressure, acenaphthene was isolated in a yield of 59%.[20] Thus, as expected, the three hydrazo compounds undergo similar oxidative decomposition reactions differing only in the ease with which the hydrocarbon products are formed.

Experimental[21-23]

Dimethyl Naphthalene-1,8-dicarboxylate.—The following method is considerably more convenient for large scale work than the alkylation[24] of naphthalic anhydride. A mixture of 284 g. of naphthalic anhydride, 426 g. of phosphorus pentachloride and 450 ml. of phosphorus oxychloride was refluxed for 34 hours and the solvent then removed by distillation from a water-bath by means of a water aspirator. The residual liquid was poured slowly into 1.4 l. of methanol while cooling in an ice-bath and swirling vigorously. The resulting brei was allowed to stand for 0.5 hour at room temperature, diluted with water to 4 l., filtered and washed with water and recrystallized from about 800 ml. of methanol which gave 214.5 g. (61.4%) of cream-colored crystals, m.p. 99–101° (lit.[24] m.p. 102°).

1,8-Bis-(bromomethyl)-naphthalene (XVII).—The following modification of the procedure of Bergmann and Szmuszkovicz[25] was found to be more convenient in the synthesis of this and related bisbromomethyl compounds. A mixture of 86.5 g. of 1,8-bis-(hydroxymethyl)-naphthalene (prepared in 75% yield by the method of Bergmann and Szmuskovicz[25] except that benzene was omitted as co-solvent so as to avoid formation of a

(18) J. Thiele, *Ann.*, **376**, 239 (1910).

(19) Although 1,2-dibenzylhydrazine was not examined, the 1,1-analog should represent a reasonable model.

(20) Compare A. F. Bickel and W. A. Waters, *Rec. trav. chim.*, **69**, 312 (1950).

(21) Melting and boiling points are uncorrected.

(22) Elemental analyses are by Drs. Weiler and Strauss, Oxford, Eng.

(23) N.m.r. spectra were determined in deuteriochloroform solution using tetramethylsilane as internal standard and recorded on a Varian DP-60 spectrometer. Peak positions are recorded in δ-units. See N. S. Bhacca, L. F. Johnson and J. N. Shoolery, "N.M.R. Spectra Catalog," Varian Associates, 1962, p. 1.

(24) T. A. Geissman and L. Morris, *J. Am. Chem. Soc.*, **66**, 716 (1944).

(25) E. D. Bergmann and J. Szmuszkovicz, *ibid.*, **75**, 2760 (1953).

tacky product) and 700 ml. of methylene dichloride was stirred mechanically and 90 ml. of phosphorus tribromide added dropwise over 20–30 min. During the first half of the addition the solution refluxed spontaneously. After stirring for 5 hours at room temperature, 125 ml. of water was added dropwise with stirring over 20–30 min. which again caused refluxing and evolution of much hydrogen bromide. After stirring for an additional 2 hours, 200 ml. of water was added and the layers separated and the organic layer washed with another 250-ml. portion of water. The organic layer was allowed to evaporate from a flat dish and the residue recrystallized from 400 ml. of a ligroin (b.p. 60–70°)–benzene (1:3) mixture. There was obtained 118 g. (81.7%), m.p. 131.5–133.5° (lit.[25] m.p. 130–131.5°), of the dibromide.

2-Nitroso-2,3-dihydro-1H-benz[de]isoquinoline (XI).—In a solution of 40 ml. of water in 300 ml. of glacial acetic acid there was suspended 24 g. of the hydrochloride of III at room temperature. Slowly, over a period of 8–10 min., a solution of 16 g. of sodium nitrite in the minimum amount of water was added. Spontaneous warming occurred as the solid gradually dissolved. Dilution with water to a final volume of 1 l. gave 17.5 g. (81%) of cream-tan flakes, m.p. 106–110°. The crude solid was dissolved in 550–600 ml. of hot ligroin (b.p. 88–98°), the solution filtered from a small amount of purple residue and allowed to cool. The gray flakes amounted to 14.5 g. (67.2%), m.p. 113–115°. The silvery-white analytical sample had m.p. 113–114.5°, δ_{CH_2} 5.7, 5.3.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.14. Found: C, 73.00: H, 5.15; N, 14.19.

2,3-Dihydro-1H-benz[de]isoquinoline (XII).—Without recrystallizing from ligroin the crude, air-dried N-nitroso compound XI obtained as described above from 11.5 g. of the hydrochloride of III was dissolved in 100 ml. of nitromethane and dry hydrogen chloride passed through the solution for a few minutes, whereupon a flaky cream-colored solid precipitated. There was added 100–150 ml. of ether and the mixture let stand for 10 min. and filtered. The resulting air-dried hydrochloride was dissolved in 250 ml. of water by warming very slightly, the solution treated with decolorizing carbon and the filtrate made alkaline with potassium hydroxide. The white solid was extracted into two 60–75-ml. portions of ether and the filtered, bluish extracts allowed to evaporate spontaneously from a flat dish. The air-dried greenish solid was recrystallized from a mixture of ligroin fractions of b.p. 30–60° and 60–70° (1:2) which deposited 5 g. (56.8%) of cream-colored needles with a greenish cast, m.p. 105–107°. Several additional recrystallizations from ligroin (b.p. 60–70°) gave an analytical sample as white needles, m.p. 105–106°. The base rapidly became yellow in the air.

Anal. Calcd. for $C_{12}H_{11}N$: C, 85.17; H, 6.55. Found: C, 85.08; H, 6.59.

The hydrochloride XII·HCl crystallized from ethanol as white, silky needles. In a melting point tube the compound sintered at about 270° and decomposed to a black tar at about 320–325°.

Anal. Calcd. for $C_{12}H_{12}NCl$: C, 70.07; H, 5.88. Found: C, 70.44; H, 5.83.

The *p*-toluenesulfonyl derivative, obtained in the usual way, had m.p. 178–179.5° (ethanol–dimethylformamide, 1:1).

Anal. Calcd. for $C_{19}H_{17}NSO_2$: C, 70.56; H, 5.30. Found: C, 70.84; H, 5.26.

A trace (1–2%) of amine XII, m.p. 102–105°, was isolated from the reduction of naphthalimide by means of lithium aluminum hydride in ether. The compound was identified by conversion to the N-nitroso compound, m.p. and mixture m.p. 112–113°.

Reduction of 2-Nitroso-2,3-dihydro-1H-benz[de]isoquinoline.—Reduction of 4.4 g. of the nitroso compound XI by means of 4 g. of aluminum amalgam prepared from Baker and Adamson aluminum (8–20 mesh), 0.6 ml. of water and 150 ml. of ether by the general method previously described[7] gave 2 g. (40.8%) of the hydrochloride of 2-amino-2,3-dihydro-1H-benz[de]isoquinoline (III), m.p. 235–237° dec. Conversion to the free base gave long white needles, m.p. and mixture m.p. with an authentic sample, 69–71°.

The aluminum amalgam reduction appeared to depend critically on the type and nature of the aluminum. Various samples led to the formation of the denitrosated material XII, m.p. 105–106°, an unknown compound of m.p. 82–84° or recovery of the unreacted N-nitroso compound.

Amination of 2,3-Dihydro-1H-benz[de]isoquinoline (XII).—A solution of 2.1 g. of O-mesitoylhydroxylamine (XIII)[13] in 20 ml. of methylene dichloride was treated with 3.94 g. of 2,3-dihydro-1H-benz[de]isoquinoline (XII) and the solution heated in a water-bath at 35–40° for 1 hour and then let stand at room temperature for 7 hours. The red-brown solution was evaporated in a water-bath at 45° with the aid of a water aspirator. The resulting cream-red solid was dissolved in 10 ml. of acetic acid and 4.7 ml. of water at 45–50° and 1.16 g. of benzaldehyde added. After heating in the water-bath at 45–50° for 1 hour, the mixture was diluted with 100 ml. of water and the mixture extracted with three 25-ml. portions of ether (a solid remaining undissolved in both the ether and water layers was removed by filtration). The ether was removed by means of an air jet, 225 ml. of 10% sulfuric acid was added and the mixture steam distilled until the benzaldehyde was removed. The residual aqueous solution was treated with decolorizing carbon, basified, extracted with ether and the dried ether solution treated with hydrogen chloride gas. The yellow hydrochloride III·HCl which precipitated amounted to 1 g. (38.6%), m.p. 220–225°. Recrystallization from ethanol–ether gave 0.6 g. (23%) of yellow crystals, m.p. 232–234° dec. (lit.[7] m.p. 233–237° dec.). Solution of the hydrochloride in water, basification, extraction and recrystallization from ligroin (b.p. 60–70°) gave snow-white needles of III, m.p. and mixture m.p. with an authentic sample[7] 70–72°. The benzal derivative had m.p. and mixture m.p. 118–120°.

Oxidation of 2-Amino-2,3-dihydro-1H-benz[de]isoquinoline (III).—To a solution of 1.4 g. of 2-amino-2,3-dihydro-1H-benz[de]isoquinoline (III) in 75 ml. of methylene dichloride there was added in one portion 12 g. of "brown" mercuric oxide.[7] The mixture was swirled continuously for 2.5 minutes and filtered into a flat dish. Spontaneous evaporation left 0.25 g. of a crystalline cream-colored solid (at the rim of the vessel a ring of brown-black material was deposited which was subsequently separated from the main portion of the material which deposited on the bottom of the dish). Recrystallization from nitromethane–dimethylformamide (1:1) gave 0.2 g. (15%) of creamish crystals, m.p. 193–194° dec. The brown-black material left at the rim of the dish (0.2 g.) was shown to be a less pure sample of the same substance, m.p. 195–198° dec., presumably the **tetrazene XIV**.

Anal. Calcd. for $C_{24}H_{20}N_4$: C, 79.09; H, 5.53; N, 15.38. Found: C, 79.03; H, 5.46; N, 15.20.

The same substance, identified by mixture melting point determination, was the only product isolated when the oxidation was carried out with potassium permanganate in acetone or N-bromosuccinimide and pyridine in ethanol. It was noted that only when the mercuric oxide oxidation was carried out rapidly could the above tetrazene be isolated. Long contact times led to the formation of black tarry substances. Oxidation by means of activated manganese dioxide or benzoquinone also led to the formation of tars and resins. In no case was any acenaphthene isolated.

***t*-Butyl 1,2,3,4-Tetrahydronaphtho[1,8-d,e][1,2]diazepine-2,-3-dicarboxylate (XVIII).**—To a solution of 16.8 g. of potassium metal in 500 ml. of *t*-butyl alcohol there was added 50 g. of *t*-butyl hydrazodiformate[3] and the solution evaporated to dryness from a water-bath at 65–70° with the aid of a water aspirator. The residue was treated with 375 ml. of dimethylformamide, the resulting mixture stirred mechanically for 5 minutes and 67.5 g. of 1,8-bis-(bromomethyl)-naphthalene (XVII) added over 1–2 minutes. The mixture, which became very hot spontaneously, was stirred at room temperature without cooling for 20 hours. The mixture was diluted with water to 2 l. and extracted with three 150-ml. portions of ether. After washing the extracts with water, spontaneous evaporation from a flat dish left a tacky semi-solid material. Trituration with ice-cold methanol gave 34.5 g. (41.7%) of crystalline white solid, m.p. 115–123°. Recrystallization from ligroin (1:1 mixture of 60–70° and 88–98° fractions) gave 30.5 g. (36.9%) of white crystals, m.p. 128–129°. The analytical sample (same solvent) had m.p. 128–129.5°, δ_{CH_2} 5.1.

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34. Found: C, 68.25; H, 7.02.

1,2,3,4-Tetrahydronaphtho[1,8-d,e][1,2]diazepine Hydrochloride (XIX).—A solution of 10 g. of XVIII in 200 ml. of ether and 75 ml. of methanol was treated with dry hydrogen chloride gas for 15–20 min., the flask stoppered with a Saran-wrapped cork and the solution allowed to stand at room temperature for 10–15 hours. There separated 5 g. (87%) of the hydrochloride as crystalline white flakes, m.p. 238–240° dec. (sintering at 225°). Recrystallization from ethanol–ether and 95% ethanol gave tiny crystals which sintered and melted indistinctly between 221–236°.

Anal. Calcd. for $C_{12}H_{13}N_2Cl$: C, 65.30; H, 5.93. Found: C, 65.30; H, 6.32.

The dibenzoyl derivative was prepared by Schotten–Baumann acylation followed by recrystallization from ethanol; m.p. 180–182°.

Anal. Calcd. for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14. Found: C, 79.15; H, 5.14.

1,2,3,4-Tetrahydronaphtho[1,8-d,e][1,2]diazepine (X).—By very slight warming there was dissolved 1.1 g. of XIX in 50 ml. of water, the solution treated with charcoal and the filtrate basified with excess potassium hydroxide. The crystalline white solid which separated was filtered at once, dried in the air for 2–3 hours,

and recrystallized by rapid solution in 10–15 ml. of ligroin (b.p. 88–98°), filtration and cooling to room temperature. There separated 0.3 g. (32.7% of tiny white needles, m.p. 71–94°. This material could not be obtained in analytically pure form by recrystallization. Indeed, continued recrystallization from ethyl acetate yielded the corresponding azo compound, m.p. 132–136°, identified by comparison of the infrared spectrum with a sample (see below) prepared by mercuric oxide oxidation of the hydrazo compound X.

1,4-Dihydronaphtho[1,8-d,e][1,2]diazepine (XX).—There was dissolved 5.5 g. of XIX in 250–300 ml. of water by slight warming. The solution was treated with decolorizing carbon and then with 10 g. of solid sodium bicarbonate followed by extraction with three 60-ml. portions of ether. The ether extracts were dried briefly over magnesium sulfate, filtered and treated with 15 g. of commercial yellow mercuric oxide. The mixture was swirled by hand for 5 minutes, filtered into a beaker and allowed to stand in the slight draft of a hood. When the volume had been reduced to one-half of the original, the solution was poured into a clean beaker and the crystals remaining were scraped out and air-dried. The orange-yellow solid (0.7 g., 15.4%) was recrystallized from ethyl acetate which gave 0.5 g. (11%) of well formed orange crystals, m.p. 134–139°. Continued recrystallization from ethyl acetate did not lessen the melting point range significantly. An analytical sample, thrice recrystallized from ethyl acetate, had m.p. 132–137°.

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.08; H, 5.53; N, 15.38. Found: C, 79.25; H, 5.73; N, 15.32.

Evaporation of the original decanted ether solution left 0.6 g. (13.2%) of brown-black tacky solid which on recrystallization was shown to be an impure sample of the azo compound.

3,4-Dihydronaphtho[1,8-d,e][1,2]diazepine (XXI).—There was dissolved 4.2 g. of XIX in 230 ml. of water by slight warming and 3 g. of solid sodium bicarbonate added. The precipitated oil was extracted into four 30-ml. portions of methylene dichloride and the dried (magnesium sulfate) and filtered extracts were treated with 2.3 g. of powdered selenium dioxide and placed on a continuous shaking machine for 3 hours. The mixture was filtered from the caked selenium residue into a flat dish and allowed to evaporate overnight. The residual brown solid (2.3 g.) was dissolved in the minimum amount of warm ethyl acetate, filtered and cooled in an ice-bath. There was deposited 1.2 g. of brown solid, m.p. 122–127°. A further 0.5 g. of the compound, m.p. 122–127°, was obtained from the filtrate. The combined hydrazone (1.7 g., 49%) was recrystallized from 50–60 ml. of ligroin (b.p. 88–98°) which gave 1 g. (28.8%) of transparent flakes, m.p. 127–129°.

In order to remove a trace of selenium metal the hydrazone was dissolved in dilute hydrochloric acid, the solution treated with charcoal and basified with potassium hydroxide. The precipitated solid was filtered and recrystallized from ligroin (b.p. 88–98°) which gave yellow flakes, m.p. 128–130°.[26]

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.08, H, 5.53; N, 15.38. Found: C, 78.79; H, 5.43; N, 15.40.

Di-*t*-butyl 1,2,3,4-Tetrahydrophthalazine-2,3-dicarboxylate.—A solution of 4.5 g. of potassium metal dissolved in 150 ml. of *t*-butyl alcohol was treated with 13.5 g. of *t*-butyl hydrazodiformate.[3] After 2–3 minutes 15.3 g. of *o*-xylylene dibromide was added to the still warm solution. An immediate milky precipitate formed. After stirring at room temperature for 8 hours, dilution with 1 l. of water and storage in an ice-box, there was obtained 17.5 g. (63%) of white solid, m.p. 70–110°. Recrystallization from about 65 ml. of ligroin (b.p. 60–70°) gave 13 g. (46.8%) of white crystals, m.p. 110–113°. This material was pure enough for conversion to the hydrochloride by hydrogen chloride cleavage. The analytical sample (ligroin, b.p. 60–90°) had m.p. 118–120°.

Anal. Calcd. for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84. Found: C, 65.03; H, 7.68.

1,2,3,4-Tetrahydrophthalazine Hydrochloride (XVI·HCl).—Cleavage of 13 g. of the dicarbo-*t*-butoxylated tetrahydrophthalazine described above by solution in 100–125 ml. of nitromethane, followed by passage of hydrogen chloride gas for 10 min. and dilution with one volume of ether gave 6.5 g. (98%) of 1,2,-3,4-tetrahydrophthalazine hydrochloride, m.p. 227–231°. Recrystallization gave feathery white crystals, m.p. 236–238° (lit.[27] m.p. 231°). An attempt to obtain the free base by treating an aqueous solution of the hydrochloride with potassium hydroxide, extraction with ether and evaporation of the ether gave a snow-white crystalline material which rapidly became tacky on standing in air. A portion of the crude base was derivatized by the Schotten–Baumann technique which gave the dibenzoyl derivative as white crystals on recrystallization from ethanol; m.p. 210–212° (lit.[27] m.p. 207–208°).

(26) Subsequently it was shown that better yields were obtainable by solution of the crude product directly in dilute hydrochloric acid, then filtration and precipitation with alkali followed by recrystallization from ligroin.

(27) S. Gabriel and G. Pinkus, *Ber.*, **26**, 2210 (1893).

Oxidation of 1,2,3,4-Tetrahydrophthalazine.—A solution of 22 g. of 1,2,3,4-tetrahydrophthalazine hydrochloride in 15–20 ml. of water was treated with an excess of potassium hydroxide and the precipitated oil extracted into two 60-ml. portions of methylene dichloride. The dried (magnesium sulfate) solution was cooled in an ice-bath and treated with 3 g. of "brown" mercuric oxide[7] until gas evolution ceased. The mixture was filtered and a portion evaporated to yield a yellow oil which was shown by comparison of infrared spectra to be the same as that obtained by oxidation of N-aminodihydroisoindole.[5] The main portion of the methylene dichloride solution was treated slowly with a solution of 0.5 ml. of bromine in 5 ml. of methylene dichloride. Evaporation of the solvent left 2,2′-bis-(bromomethyl)-bibenzyl, a tacky yellow solid which was triturated with methanol, filtered and recrystallized from nitromethane, to give 0.8 g. (33.6%) of white needles, m.p. 136.5–138.5° (lit.[28] m.p. 137–138°).

5,6,7,8-Tetrahydrodibenzo[d,f][1,2]diazocine Hydrochloride (XV·HCl).—A solution of 11.6 g. of potassium metal in 350 ml. of *t*-butyl alcohol was treated with 34.5 g. of *t*-butyl hydrazodiformate[3] and after stirring for 5 min. the *t*-butyl alcohol was removed by distillation from a water-bath with the aid of a water aspirator. There was then added 500 ml. of dimethylformamide, the solid broken up and stirred mechanically for 3–4 min. and 51 g. of 2,2′-bis-(bromomethyl)-biphenyl[29] added in one portion. The mixture was stirred at room temperature for 24 hours, diluted with water to 2 l. and extracted with four 50-ml. portions of methylene dichloride. After drying (magnesium sulfate), the solvent was removed from a water-bath with the aid of a water aspirator and the residual yellow oil dissolved in 200 ml. of methanol and 700 ml. of ether and treated with a stream of hydrogen chloride gas for 35 min. The stoppered solution was allowed to stand at room temperature for 7 hours and the white crystals filtered and washed with ethanol–ether (1:1). The yield of hydrochloride was 14 g. (37.8%), m.p. 271–281° dec. Since all of the hydrochloride had not separated, the filtrate was again treated with hydrogen chloride gas for 30 min. which yielded another 8.5 g. of white solid, the total yield being 22.5 g. (60.5%). The analytical sample (ethanol–ether) had m.p. 282–284° dec.

Anal. Calcd. for $C_{14}H_{15}N_2Cl$: C, 68.14; H, 6.13. Found: C, 68.29; H, 6.22.

5,6,7,8-Tetrahydrodibenzo[d,f][1,2]diazocine (XV).—A mixture of 2.47 g. of the hydrochloride of XV and 125 ml. of water was treated with an excess of potassium hydroxide and the free base extracted with four 25-ml. portions of ether. Most of the insoluble material eventually dissolved in the two-phase system. The ether solution was evaporated rapidly[31] at once by means of an air jet. During the evaporation the solution was seeded[32] in order that the solid separate as rapidly as possible. The resulting solid was triturated with ligroin (b.p. 30–60°) at room temperature and the resulting mixture evaporated again by means of an air jet. The residual white solid amounted to 1.87 g. (89%), m.p. 101–125°. An analytical sample was obtained by several recrystallizations from nitromethane which deposited well formed crystals (blocks, cubes, square plates, etc.), m.p. 92–125°. Continued recrystallization did not improve the melting point range.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.33. Found: C, 79.74; H, 7.04; N, 13.22.

5,8-Dihydrodibenzo[d,f][1,2]diazocine (XXII).—A solution of 0.4 g. of XV in 25 ml. of methylene dichloride was cooled in an ice-bath and 0.8 g. of activated manganese dioxide[16] added in small portions over a period of 2 min. The mixture was swirled by hand for an additional 3 min. while still cooling in the ice-bath and then filtered into a flat dish and the solution evaporated by means of an air jet. The yellow solid was redissolved in a little methylene dichloride to remove some black manganese dioxide, filtered and evaporated rapidly a second time. The residual yellow crystals were scraped onto a filter paper and allowed to dry for 2–3 minutes by pressing gently into the paper. The yield was 0.2 g. (50.5%), m.p. 63–65° dec. (vigorous gas evolution). The n.m.r. spectrum was taken immediately. When freshly prepared samples of the azo compound were dropped onto a hot-plate the material exploded with a loud report. Samples which were left in the air for 5–7 hours became oily and no longer exploded when dropped onto a hot-plate. While the n.m.r.

(28) E. D. Bergmann and Z. Pelchowicz, *J. Am. Chem. Soc.*, **75**, 4281 (1953).

(29) Prepared in 81% yield from 2,2′-bis-(hydroxymethyl)-biphenyl[30] by the method described above for the corresponding 1,8-naphthalene derivative.

(30) D. M. Hall, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.*, 711 (1950).

(31) If the solution was allowed to stand for several hours before removal of the solvent it became orange and only an orange effervescent oil remained upon subsequent evaporation.

(32) Seed crystals were obtained by separate evaporation of a small portion of the solution.

spectrum was being taken in deuteriochloroform the sample tube popped its cork and vigorous gas evolution was noted. The spectrum was run several times during the first 15 min. after which it became constant and appeared to be that of 9,10-dihydrophenanthrene contaminated by an unidentified impurity which exhibited a strong peak at approximately 7.3 δ. Positive identification was made by comparison of the infrared spectrum with that of an authentic sample.

Thermal Decomposition of 1,4-Dihydronaphtho[1,8-d,e][1,2]-diazepine (XX).—In a semimicro distillation apparatus 0.4 g. of XX was heated gently with a free flame. The solid melted to an orange liquid and on continued heating sudden and vigorous decomposition occurred with the release of a cloud of smoke. The black liquid remaining in the pot was distilled into the receiver by means of the free flame. The distillate solidified as a black solid (0.2 g., 59.2%). Recrystallization from ethanol–water (decolorizing carbon) gave nearly white crystals, m.p. 93.5–94.5°. The melting point was not depressed on admixture with an authentic sample of acenaphthene.

When the azo compound was heated in diglyme (b.p. 162°) or triglyme (b.p. 210°), isomerization to XXI was noted as proved by mixture melting point determination.

Isomerization of 1,4-Dihydronaphtho[1,8-d,e][1,2]diazepine (XX).—A solution of 0.5 ml. of concentrated hydrochloric acid and 3 ml. of water was warmed with 0.2 g. of XX for 2–3 min. until solution occurred. Excess solid potassium hydroxide was added and the cream-colored powder filtered and dried in air. The yield was 0.17 g. (85%), m.p. 129–130°, identified as XXI by comparison with a sample prepared by selenium dioxide oxidation of X.

1-Benzal-2-benzylhydrazine.—A mixture of 10.4 g. of benzalazine, 4.66 g. of dry lithium chloride, 5.94 g. of potassium borohydride and 80 ml. of tetrahydrofuran was refluxed for 24 hours with stirring.[33] The mixture was decomposed by the addition of water and the tetrahydrofuran layer separated and allowed to evaporate spontaneously. Snow-white flakes (9.5 g., 91%) remained, m.p. 64–72° dec. Recrystallization from methanol gave 7.6 g. (72%) of the pure hydrazone, m.p. 70–73.5° dec. (softening at 69.5°, lit.[34] m.p. 69–70°). Since the hydrazone decomposed readily on standing as noted by previous workers, the n.m.r. spectrum was run at once.

Acknowledgment.—We are indebted to Prof. Thomas Stengle for the n.m.r. spectra and discussions concerning their interpretation.

(33) The procedure is based on the work of M. Davis [*J. Chem. Soc.*, 3981 (1956)], who showed that tertiary amides could be reduced under these conditions.

(34) A. Wohl and C. Oesterlin, *Ber.*, **33**, 2736 (1900).

[CONTRIBUTION FROM THE ROCKEFELLER INSTITUTE, NEW YORK 21, N. Y.]

Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide[1]

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A new approach to the chemical synthesis of polypeptides was investigated. It involved the stepwise addition of protected amino acids to a growing peptide chain which was bound by a covalent bond to a solid resin particle. This provided a procedure whereby reagents and by-products were removed by filtration, and the recrystallization of intermediates was eliminated. The advantages of the new method were speed and simplicity of operation. The feasibility of the idea was demonstrated by the synthesis of the model tetrapeptide L-leucyl-L-alanylglycyl-L-valine. The peptide was identical with a sample prepared by the standard *p*-nitrophenyl ester procedure.

The classical approach to peptide synthesis has yielded impressive successes in recent years in the preparation of several biologically active peptides.[2] With the development of new reagents and techniques the synthesis of most small peptides has been placed within easy reach.[3] However, these procedures are not ideally suited to the synthesis of long chain polypeptides because the technical difficulties with solubility and purification become formidable as the number of amino acid residues increases. A new approach to peptide synthesis has been investigated in an effort to overcome some of these difficulties. The present report deals with the basic idea behind the new method and with a demonstration of its feasibility through the synthesis of a simple model tetrapeptide.

The general concept underlying the new method is outlined in Fig. 1. It depends on the attachment of the first amino acid of the chain to a solid polymer by a covalent bond, the addition of the succeeding amino acids one at a time in a stepwise manner until the desired sequence is assembled, and finally the removal of the peptide from the solid support. The reason for this approach is that when the growing peptide chain is firmly attached to a completely insoluble solid particle it is in a convenient form to be filtered and washed free of reagents and by-products. Thus the intermediate peptides are purified, not by the usual recrystallization procedures, but by dissolving away the impurities. This greatly simplifies the manipulations and shortens the time required for the synthesis of the peptides. It is hoped that such a method will lend itself to automation and provide a route to the synthesis of some of the higher molecular weight polypeptides which have not been accessible by conventional procedures.

The Polymer.—The first requirement was for a suitable polymer. It had to be insoluble in all of the solvents which were used and have a stable physical form which permitted ready filtration. It also had to contain a functional group to which the first protected amino acid could be firmly linked by a covalent bond. Many polymers and modes of attachment were investigated. Among the polymers were cellulose, polyvinyl alcohol, polymethacrylate and sulfonated polystyrene. The one which worked best was a chloromethylated copolymer of styrene and divinylbenzene. The resin, in the form of 200–400 mesh beads, possessed a porous gel structure which allowed ready penetration of reagents, especially in the presence of swelling solvents. Although diffusion and steric hindrance were no doubt important factors, they were not serious enough to prevent the desired reactions from proceeding to completion. The reaction rates were slower than corresponding ones in solution, but conditions were found which permitted all of the reactions to occur at useful rates in spite of the fact that the growing peptide chain was in the completely insoluble solid phase at all times. It was for this reason that the term solid phase peptide synthesis was introduced to describe the new method.

(1) (a) Supported in part by Grant A 1260 from the U. S. Public Health Service. (b) An abstract of this work was presented at the 46th Annual Meeting of the Federation of American Societies for Experimental Biology, April, 1962; R. B. Merrifield, *Fed. Proc.*, **21**, 412 (1962).

(2) (a) V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts, P. G. Katsoyannis and S. Gordon, *J. Am. Chem. Soc.*, **75**, 4879 (1953); (b) R. B. Merrifield and D. W. Woolley, *ibid.*, **78**, 4646 (1956); (c) H. Schwarz, M. Bumpus and I. H. Page, *ibid.*, **79**, 5697 (1957); (d) R. A. Boissonnas, S. Guttmann and P. A. Jaquenoud, *Helv. Chim. Acta*, **43**, 1349 (1960); (e) K. Hofmann, H. Yajima, N. Yanaihara, T. Liu and S. Lande, *J. Am. Chem. Soc.*, **83**, 487 (1961); (f) C. H. Li, J. Meienhofer, E. Schnabel, D. Chung, T. Lo and J. Ramachandran, *ibid.*, **83**, 4449 (1961); (g) H. Kappeler and R. Schwyzer, *Helv. Chim. Acta*, **44**, 1136 (1961).

(3) See J. P. Greenstein and M. W. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1961.