

IX is outlined in the accompanying chart (R = 3-indazole).

The method of preparation of II is a modification of that of Schad,⁹ who employed both sulfur dioxide and stannous chloride in the reduction of the diazonium salt. It was found in the present work that the same yield (30%) is obtained when the sulfur dioxide is omitted. Both the dimethylamide (III) and the piperidide of II were prepared and reduced to the corresponding amines by lithium aluminum hydride.¹⁰ Neither of these bases could be made to alkylate acetaminomalonic ester. Conversion of the amines to their methiodides, however, produced active alkylating agents. Thus, V reacted smoothly with acetaminomalonic ester to give ethyl α -acetamino- α -carbethoxy- β -(3-indazole)-propionate (VI) in yields of 67–74%. Saponification converted the ester to the substituted malonic acid (VII), which was decarboxylated by heating alone or in a water suspension. α -Acetamino- β -(3-indazole)-propionic acid (VIII) was converted to the desired amino acid (IX) by hydrolysis with barium hydroxide, followed by treatment with dilute sulfuric acid to precipitate barium sulfate. The final product, DL- α -amino- β -(3-indazole)-propionic acid, is a white crystalline solid. Its solubility in water is of the order of 0.8 g. per 100 ml. at 29° and 12 g. per 100 ml. at 100°. In 95% ethanol its solubility is of the order of 0.1 g. per 100 ml. at 29°.

To compare the basicity of IX with that of DL-tryptophan, the pK_a values of both amino acids in aqueous solution were estimated from data obtained by electrometric titration.¹¹ The values of pK_a for compound IX and tryptophan were 2.20 ± 0.10 and 2.38 ± 0.10 , respectively, and for pK_a , 8.95 ± 0.10 and 9.30 ± 0.10 , respectively. Thus it is apparent that the additional nitrogen atom of the indazole system does not greatly affect the basicity of the amino acid.

Experimental^{12,13}

Attempted Mannich Reaction with Indazole.—(a) Gramine Procedure. The method of Kuhn and Stein⁶ was followed. Only unchanged indazole was isolated from the reaction mixture. (b) Solvent Procedure. The method was that of van de Kamp and Mosettig,⁷ the reaction time being extended to two hours. Unchanged indazole was recovered. (c) Forced Procedure. The procedure of Snyder and Brewster⁸ was carried out with both indazole prepared by the method of Stephenson,¹⁴ and indazole hydrochloride. The latter experiment is described.

Indazole hydrochloride (2.2 g., 0.015 mole) was heated with 2.5 g. (0.03 mole) of dimethylamine hydrochloride and 2.2 g. (0.075 mole) of paraformaldehyde in a 300-ml. Kjeldahl flask at 150° for 1.5 hours. For the first 30 minutes there was ebullition, and the paraformaldehyde sublimed to the side of the flask. After that a red, polymeric mass formed. This solid was heated in 60 ml. of water, but much of it did not dissolve. When the filtrate from this aqueous mixture was cooled, 0.30 g. of a bright red neutral solid was deposited and removed by filtration. No basic product could be isolated.

(9) P. Schad, *Ber.*, **26**, 217 (1893).

(10) A. Uffer and E. Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).

(11) The authors are indebted to Dr. Carl S. Vestling for these determinations.

(12) All melting points are corrected.

(13) Microanalyses by Miss Emily Davis, Mrs. Jean Fortney, Miss Rachel Kopel, Mrs. Katherine Pihl and Mr. Maurice Dare.

(14) E. F. M. Stephenson, *Org. Syntheses*, **29**, 73 (1949).

N-Benzylindazole.—The procedure of von Auwers and Schaich¹⁵ was followed. From 5.0 g. (0.043 mole) of indazole, 10.7 g. (0.085 mole) of benzyl chloride and 1.5 g. (0.065 gram atom) of sodium in 40 ml. of absolute ethanol was obtained 0.98 g. of the 1-isomer, melting at 61–62° and 1.66 g. of the 2-isomer, melting at 68–70°. The total yield was 2.64 g. (30%).

The three procedures used with indazole were repeated with N-benzylindazole, but no compound corresponding to the Mannich base was isolated.

N-Methyl-5-nitroindazole.—In a solution of 2.0 g. (0.036 mole) of potassium hydroxide in 25 ml. of water was dissolved 1.0 g. (0.006 mole) of 5-nitroindazole, prepared by the method of Porter and Peterson.¹⁶ To this solution was added 2.5 g. of dimethyl sulfate. A brown oil settled to the bottom of the flask. The mixture was heated at 60–80° on the steam-bath for 15 minutes and then cooled. The oil crystallized as a yellow powder, melting at 109°. Recrystallization from benzene and high-boiling petroleum ether produced 0.71 g. (65%) of N-methyl-5-nitroindazole.

Each of the three procedures used with indazole failed to effect the Mannich condensation on this derivative.

Attempted Chloromethylation of Indazole (a) With Formaldehyde.—A mixture of 2.3 g. (0.02 mole) of indazole, 0.9 g. (0.03 mole) of paraformaldehyde, 2.5 g. of glacial acetic acid, 3 ml. of concentrated hydrochloric acid and 1.5 ml. of sirupy phosphoric acid was heated at 90–100° for four hours. The reaction mixture was poured into 20 ml. of ice-water, the aqueous layer was decanted from the paste, and the latter was washed three times with 20-ml. portions of water. The paste was extracted with three 30-ml. portions of boiling ethanol, and the combined extract was evaporated to dryness, leaving 0.30 g. of a yellow oil, which did not crystallize when triturated with ether or on standing in the ice-box for two weeks. This oil was extracted with 20 ml. of 6 N hydrochloric acid, and the acid neutralized with 10% sodium hydroxide. Less than 0.1 g. of white powder, which was not identified, was isolated from the solution.

This procedure was also applied to 5-nitroindazole with similar results. In this experiment some high-melting solid (above 250°), which did not contain chlorine, was obtained.

(b) With Chloromethyl Ether.—A mixture of 2.3 g. (0.02 mole) of indazole in 8 ml. of carbon disulfide was cooled to 0° and 2.6 g. (0.032 mole) of chloromethyl ether was added. To this solution was added over a period of one hour 1.6 g. (0.006 mole) of stannic chloride. The flask was shaken continuously during the addition and frequently for another hour after the addition was complete. The reaction mixture was poured into ice-water and the organic layer was separated and dried over calcium chloride. On evaporation this layer yielded 0.3 g. of a thick colorless liquid which was soluble in acid. However, because of the low yield obtained, this reaction was not further pursued.

3-Indazolecarboxylic Acid (II).—To a 15-l. crock equipped with an efficient motor-driven stirrer was added 191 g. (1.9 moles) of concentrated sulfuric acid in 2 l. of water. This solution was cooled to 0° by the addition of crushed ice. In a warm (50°) solution of 41 g. (1.05 moles) of sodium hydroxide in 650 ml. of water was dissolved 147 g. (1.0 mole) of isatin, m.p. 199–200°. This dark-red solution was cooled to 0° and mixed with a solution (also at 0°) of 69 g. (1.0 mole) of sodium nitrite in 250 ml. of water. The combined solutions were then added to the rapidly stirred sulfuric acid solution from a dropping funnel, the tip of which extended below the surface of the acid solution. The rate of addition was rapid, but such that the temperature never rose above 4°; more crushed ice was added when needed. (To reduce the foaming which occurred as the solutions were mixed a few milliliters of ether was added when necessary. This procedure was continued throughout the period of stirring.) After the addition was complete the brownish-yellow solution was stirred for 15 minutes. A cold (0°) solution of stannous chloride dihydrate (540 g. 2.4 moles) in 850 ml. of concentrated hydrochloric acid was then added from a dropping funnel to the stirred diazo solution. The mixture was stirred for another hour after the addition was complete. The crude product, a yellow to brown paste, was collected on a buchner funnel. It can

(15) K. von Auwers and W. Schaich, *Ber.*, **54**, 1738 (1921).

(16) H. D. Porter and W. D. Peterson, *Org. Syntheses*, **20**, 73 (1940).

be purified by either repeated treatments with Darco and recrystallizations from glacial acetic acid⁹ or by one or two recrystallizations from a large volume (*ca.* 12 l.) of water. In the latter case the mother liquor must be evaporated to about one-third its initial volume to permit recovery of a high percentage of the product; alternatively, the mother liquor may be used for the recrystallization of a subsequent lot. In both methods a large quantity of insoluble material (mostly inorganic) was discarded in the initial crystallization. Two recrystallizations from water gave 53.3 g. of a yellow powder, m.p. 265–265.5° (33%). One further recrystallization produced short pale-yellow needles, m.p. 268–268.5° (lit.¹⁷ 260–261°).

N,N-Dimethyl-3-indazolecarboxylic Acid Amide (III).

(a) From Methyl 3-Indazolecarboxylate.—In a large excess of aqueous dimethylamine (18 ml. of 25% solution, 0.1 mole) was dissolved in 1.76 g. (0.01 mole) of methyl 3-indazolecarboxylate, prepared by the method of von Auwers and Dereser.¹⁷ The solution was stirred at room temperature for 24 hours, after which the dimethylamine and one-half the water were removed by distillation under reduced pressure. The residual solution was cooled in an ice-bath, whereupon 0.55 g. of brown crystals was deposited. Three recrystallizations from nitromethane, including a treatment with Darco, gave 0.45 g. (25%) of III as fine white crystals, melting at 187–189° (over-all yield from II, 15%).

Anal. Calcd. for C₁₀H₁₁N₃: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.60; H, 5.77; N, 22.27.

(b) From 3-Indazolecarbonyl Chloride.—A slurry of 28.3 g. (0.175 mole) of 3-indazolecarboxylic acid and 83.3 g. (0.70 mole) of purified thionyl chloride was heated under gentle reflux for two hours. The excess thionyl chloride was removed by distillation under reduced pressure. The flask containing the resulting red-orange solid was cooled in an ice-bath and to it was added a cold solution of dimethylamine (23.6 g., 0.525 mole) in 200 ml. of dry benzene. After 10 minutes of cooling and swirling the slurry was filtered, the crude amide remaining on the filter. Concentration of the filtrate by vacuum distillation to one-third its initial volume produced a little more of the crude amide, which was combined with the main portion. Two crystallizations from nitromethane including treatments with Darco, gave 18.9 g. (57%) of tan needles, m.p. 187–188.5°.

3-Dimethylaminomethylindazole (IV).—In the pot of a Soxhlet extractor was placed a slurry of 8.5 g. (0.25 mole) of lithium aluminum hydride in 500 ml. of tetrahydrofuran, previously dried over sodium wire. In the thimble was placed 24.8 g. (0.13 mole) of III. The extractor was allowed to run for nine hours, at the end of which time the thimble was empty and the solvent had assumed a yellow color. The excess lithium aluminum hydride was decomposed with a saturated solution of water in ether. A single liquid phase was present at all times and the aluminum hydroxide did not become as gelatinous as it did in the presence of a water phase. The mixture obtained in this way was filtered immediately through a sintered glass funnel containing a Filter-Cel mat. (It was found that if the mixture was allowed to stand, the aluminum hydroxide became much more gelatinous, making the subsequent filtration extremely tedious.) The filtrate was dried over magnesium sulfate and then concentrated by distillation to a volume of *ca.* 30 ml. After standing at 5° for an hour, the solution deposited 15.0 g. of large, white, rhombic crystals of IV, m.p. 125–126°.

Anal. Calcd. for C₁₀H₁₃N₃: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.39; H, 7.59; N, 24.01.

The aluminum hydroxide residue, which turned coral red on standing, was extracted with tetrahydrofuran in a Soxhlet extractor until the color disappeared. The solvent was distilled leaving *ca.* 4 g. of crude IV. This was dissolved in nitromethane treated with Darco, and allowed to crystallize. The over-all yield of pure product was 18.3 g. (80%).

It was found that the extraction procedure was much more efficacious for large quantities than the solution procedure described below for the piperidide, since both amides are insoluble in common neutral solvents.

Methiodide of 3-Dimethylaminomethylindazole (V).—

To 15 ml. of absolute ethanol were added 1.80 g. (0.0125 mole) of methyl iodide and 1.75 g. (0.01 mole) of IV. The solution was heated on a steam-cone for a few minutes, then

placed in an ice-box. After an hour the flask was scratched and a copious white precipitate of V formed immediately. The precipitate was sucked dry on a buchner funnel and recrystallized twice from absolute ethanol. There was obtained 2.60 g. (82%) of white crystals, m.p. 192–193°. An analytical sample of V was prepared from a portion of the amine purified by vacuum sublimation. This sample of V was crystallized once from absolute ethanol and also melted at 192–193°.

Anal. Calcd. for C₁₁H₁₆N₃I: C, 41.65; H, 5.09; N, 13.25. Found: C, 41.40; H, 4.99; N, 13.05.

Piperidide of 3-Indazolecarboxylic Acid.—To 10 ml. of piperidide was added 3.52 g. (0.02 mole) of methyl 3-indazolecarboxylate. This solution was refluxed for one hour, cooled to room temperature and diluted with water to precipitate the crude amide as a yellow powder. Treatment with Darco and three recrystallizations from nitromethane resulted in 2.2 g. (48%) of white platelets of the piperidide, melting at 201.5–203.5°.

Anal. Calcd. for C₁₃H₁₈N₃: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.28; H, 6.82; N, 18.31.

3-Piperidinomethylindazole.—To a 1-l. three-necked flask equipped with a dropping funnel, mercury-sealed Hershberg stirrer and a reflux condenser protected by a calcium chloride tube were added 200 ml. of dry tetrahydrofuran and 0.92 g. (0.02 mole) of lithium aluminum hydride. To this slurry was added slowly a warm solution of 2.29 g. (0.01 mole) of the piperidide of 3-indazolecarboxylic acid in 150 ml. of the same solvent. There was evidence of reaction, the temperature rising sufficiently for the solvent to reflux gently. After the addition was completed the reaction flask was heated to hold the solution at the reflux temperature for two hours. The solution was then cooled to room temperature and to it was added 30 ml. of water (dropwise) followed by 10 ml. of 6 *N* sulfuric acid. The aqueous layer was drawn off, made alkaline with sodium hydroxide and extracted with 50-ml. portions of the solvent. The extract was dried over magnesium sulfate and evaporated to dryness, yielding a pink solid, melting at 109–111°. From 2.29 g. of the amide was obtained 1.6 g. (75%) of the amine, which on recrystallization from nitromethane yielded white crystals, m.p. 112–113°.

Anal. Calcd. for C₁₃H₁₇N₃: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.60; H, 8.12; N, 19.37.

The methiodide of 3-piperidinomethylindazole was obtained in a manner similar to that for V. From 2.15 g. (0.01 mole) of 3-piperidinomethylindazole was obtained 2.7 g. of crystals melting at 161.5–164.5° (76%). Five recrystallizations from absolute ethanol gave a stable white compound, melting at 170–171°.

Anal. Calcd. for C₁₄H₂₀N₃I: C, 47.07; H, 5.64. Found: C, 47.40; H, 6.32.

3-Hydroxymethylindazole.—In the apparatus described for the reduction of the piperidide, methyl 3-indazolecarboxylate was reduced by lithium aluminum hydride in tetrahydrofuran to 3-hydroxymethylindazole. From 4.40 g. (0.025 mole) of the ester and 2.76 g. (0.06 mole) of the hydride was obtained 2.65 g. (72%) of silver platelets, melting at 138–139°.

Anal. Calcd. for C₈H₉ON₂: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.01; H, 5.42; N, 19.19.

In another experiment the preparation of 3-hydroxymethylindazole was attempted by the use of sodium and ethanol as a reducing medium for the methyl 3-indazolecarboxylate. This method failed.

Attempted Preparation of 3-Chloromethylindazole.—3-Hydroxymethylindazole (0.75 g., 0.005 mole) was added to 2.4 g. (0.02 mole) of purified thionyl chloride. The mixture was heated on a steam-cone for twenty minutes, the excess thionyl chloride then being removed by vacuum distillation. There remained a solid which did not melt at 300°.

Attempted Preparation of 3-Bromomethylindazole.—To 6 ml. of 48% hydrobromic acid containing 1 ml. of concentrated sulfuric acid was added 1.04 g. (0.007 mole) of 3-hydroxymethylindazole. This solution was heated under reflux for four hours. On cooling it precipitated 0.60 g. of brown crystals which darkened at 290°.

Replacement of the hydroxyl group was also essayed with phosphorus tribromide in tetrahydrofuran solvent, but no basic material was obtained.

Ethyl α -Acetamino- α -carbethoxy- β -(3-indazole)-propionate (VI).—In a three-necked flask equipped with an air-tight, ground-glass jointed stirrer, a Graham coil condenser surmounted by a calcium chloride tube, and a nitrogen inlet, were placed 50 ml. of absolute ethanol and 0.46 g. (0.02 gram atom) of sodium. To this solution was added 4.34 g. (0.02 mole) of acetaminomalonic ester in 15 ml. of absolute ethanol, and, after a few minutes of stirring, 6.34 g. (0.02 mole) of V dissolved in 30 ml. of warm absolute ethanol. The stirred solution was heated under reflux and a gentle stream of dry nitrogen was passed through the system. The reaction was allowed to continue, usually about 20 hours, until moist pink litmus paper held at the condenser mouth was no longer turned blue by escaping trimethylamine. The alcohol was removed by distillation under reduced pressure. The residual yellow oil was taken up in a 1:1 mixture of chloroform and ether, and the precipitated sodium iodide was removed by filtration. The organic layer was washed with water, dried over magnesium sulfate, and finally concentrated under reduced pressure, leaving a yellow paste. This was dissolved in 95% ethanol, treated with Darco, and water was added to incipient crystallization. After standing for 2 hours at 5° white needles of VI which had been deposited were removed by filtration. A second crop of VI was obtained by adding more water to the filtrate. The combined crops were recrystallized again from ethanol-water. There was obtained 5.1 g. (74%) of VI, as short white needles, m.p. 84–87°.

Anal. Calcd. for $C_{16}H_{21}N_3O_5$: C, 58.77; H, 6.09; N, 12.10. Found: C, 58.53; H, 6.39; N, 12.18.

By the same procedure, from 6.34 g. (0.02 mole) of V and 4.06 g. (0.02 mole) of formylaminomalonic ester there was obtained 4.5 g. (67.5%) of ethyl α -formylamino- α -carbethoxy- β -(3-indazole)-propionate as white needles, m.p. 140–140.5°.

Anal. Calcd. for $C_{17}H_{19}N_3O_5$: C, 57.66; H, 5.75; N, 12.61. Found: C, 57.55; H, 5.75; N, 12.75.

α -Acetamino- α -carboxy- β -(3-indazole)-propionic Acid (VII).—A mixture of 4.0 g. (0.012 mole) of VI and 2.4 g. (0.06 mole) of sodium hydroxide in 25 ml. of water was heated under reflux for four hours. The solution was then cooled in an ice-bath and 9 ml. of concentrated hydrochloric acid was added slowly so that the temperature did not exceed 25°. The solution was held at 5° overnight, white crystals of VII precipitating during this time. The product was washed with water and recrystallized from ethanol. The white granular solid shrinks at 131–135°, and melts at 222–223° (dec.).

Since a mixture of VII and VIII melts at 222–223° (dec.), which is the melting point of VIII alone, it is apparent that decarboxylation occurs in the range in which shrinkage of VII is observed.

Anal. Calcd. for $C_{13}H_{13}N_3O_5 \cdot H_2O$: C, 50.45; H, 4.89; N, 13.59. Found: C, 50.49; H, 5.15; N, 13.63.

α -Amino- β -(3-indazole)-propionic Acid (IX).—In a Wood's metal bath heated to 150–170° was placed a 50-ml. erlenmeyer flask containing 2.6 g. of the dry malonic acid VII. A gentle stream of dry nitrogen was passed into the flask and the heating was continued for one hour. The yellowish powdery product was dissolved in ethanol and treated with Darco. The alcohol solution was concentrated to one-third its initial volume, mixed with an equal volume of water, and allowed to stand overnight at 5°. The large yellow crystals which were deposited were mixed with 5.5 g. of barium hydroxide octahydrate in 20 ml. of water and boiled under reflux for 24 hours in an atmosphere free of carbon dioxide. At the end of this period 100 ml. of boiling water was added to the reaction mixture and while the solution was maintained at the boiling point, 1 *M* sulfuric acid was added until the pH, as indicated by Nitrazine paper,¹⁸ was 4.5–5.0. The precipitate of barium sulfate was removed by filtration. The filtrate was concentrated under reduced pressure to ca. 15 ml., whereupon a white solid separated. This was removed by filtration, treated with Darco and recrystallized thrice from water, yielding 1.4 g. of white needles of IX (yield 74% from VII). The pure amino acid darkens at 239° and melts at 249–250° (dec.). The compound gives a positive ninhydrin test.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.51; H, 5.40; N, 20.58; α -amino-nitrogen,¹⁹ 6.8. Found: C, 58.77; H, 5.52; N, 20.75; α -amino-nitrogen, 6.7, 6.8.

The malonic acid also decarboxylated when dissolved in water and heated at the reflux temperature for four hours. During this period the less soluble VIII precipitated. In one such experiment VIII was isolated and recrystallized twice from 20% ethanol, giving fine white needles, m.p. 222–223°.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.20; H, 5.50; N, 16.89.

(18) Nitrazine Paper, sold by E. R. Squibb and Sons, New York, indicates hydrogen ion concentration in the range pH 4 to 8.

(19) The authors are indebted to Mrs. June Hearn for carrying out the ninhydrin analysis for α -amino-nitrogen.

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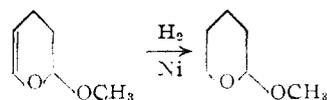
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Some Reactions of 2-Alkoxy-3,4-dihydro-2H-pyrans

BY RAYMOND I. LONGLEY, JR., WILLIAM S. EMERSON AND THEODORE C. SHAFER

2-Alkoxy-3,4-dihydro-2H-pyrans have been hydrogenated to 2-alkoxytetrahydropyrans and hydrogenolyzed to 5-alkoxy-pentanol. The dihydropyrans have been converted to 1,5-pentanediols by hydrolysis and hydrogenation in both two- and one-step operations. The diols have been dehydrogenated to δ -lactones by both liquid and vapor phase procedures. The δ -lactones also have been prepared by treating the corresponding dialdehydes with aqueous alkali. Treatment of the δ -lactones with ammonia has yielded piperidones, which in turn have been alkylated and vinylated.

The selective hydrogenation of the now readily available 2-alkoxy-3,4-dihydro-2H-pyrans¹ offers a variety of synthetic possibilities. At 125° in the presence of Raney nickel, hydrogenation of 2-ethoxy-3,4-dihydro-2H-pyran and of 2-methoxy-3,4-dihydro-2H-pyran yielded 77 and 92%, respectively, of the corresponding 2-alkoxytetrahydro-



(1) R. I. Longley, Jr., and W. S. Emerson, *THIS JOURNAL*, **72**, 3079 (1950).

pyrans. At 250–255° in the presence of copper chromite some hydrogenolysis occurred. Thus 2-ethoxy-3,4-dihydro-2H-pyran yielded, besides 39% of 2-ethoxytetrahydropyran, 13% of 5-ethoxy-pentanol. 2-*n*-Butoxy-3,4-dihydro-2H-pyran yielded tetrahydropyran (I), 22% of 2-*n*-butoxytetrahydropyran (II) and 19% of 5-*n*-butoxypentanol (III). This type of hydrogenolysis has been

