cyanomethyl - 5,8,9,10,13,14 - hexahydrophenanthrene as an intermediate and model compound for the synthesis of substances containing the morphine ring system has been developed.

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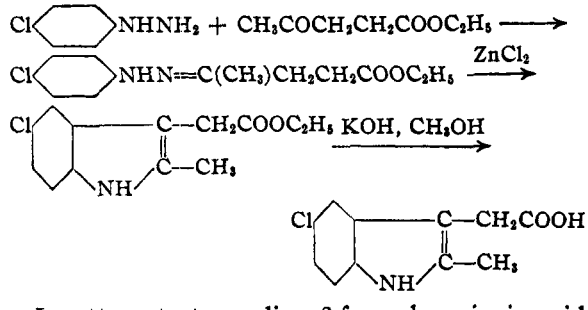
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Amino Acid Conversion Products. IV. Some Substituted 3-Indoleacetic Acids and Some Substituted Phenylhydrazones of β-Formylpropionic Acid[1]

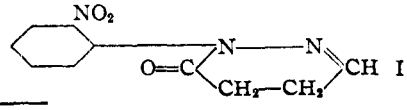
BY FRANK J. STEVENS[2] AND SIDNEY W. FOX

The natural plant growth hormone, 3-indoleacetic acid[3] (*heteroauxin*), and the substituted phenoxyacetic acids[4] have received much attention as stimulants of plant growth. A search of the literature does not reveal many syntheses of indoleacetic acid derivatives for phytological studies. The indoleacetic acid derivatives containing the types of substitution which have been useful in the phenoxyacetic acid series, are of especial interest. The present paper deals with the preparation of a number of such substances.

For the compounds reported here, the reactions involved are typified by the sequence below. In this example, the chlorophenylhydrazone of levulinic ester was converted *via* Fischer's ring closure[5] to the substituted indoleacetic acid



In attempts to cyclize β-formylpropionic acid phenylhydrazones, there was obtained in some cases an anhydride of the type reported as a by-product by Fischer in his experiments on cyclization of the phenylhydrazone of levulinic acid.[6] In the present study, ring closure of this type was obtained with the phenylhydrazone and *o*-nitrophenylhydrazone of β-formylpropionic acid. The product in the case of the nitrophenylhydrazone was 4,5-dihydro-2-(*o*-nitrophenyl)-3(2)-pyridazone, represented by I.



Of the compounds prepared in the present series, the 2-methyl-5-chloro derivative was more active in preliminary Pea Tests[7] than the 2-methyl-5-chloro and 2-methyl-7-chloro or 2-methyl-5,7-dichloro derivatives of 3-indoleacetic acid.

The indoleacetic acids reported all are substituted in the 2-position. For the corresponding unsubstituted indoleacetic acids obtained from β-formylpropionic acid, only the phenylhydrazones are recorded here. Ring closure has not been effected as readily with these latter compounds as with the derivatives of levulinic acid. The synthesis of indoleacetic acid itself, however, has been accomplished, and work is continuing on this series.

Experimental

All m.p.'s were corrected.

All nitrogen analyses were made by the micro Dumas method.

Levulinic Acid *o*-Nitrophenylhydrazone.—A hot solution of 7.65 g. (0.05 mole) of *o*-nitrophenylhydrazine[8] in 150 cc. of 20% acetic acid was added to 5.8 g. (0.05 mole) of levulinic acid (stores) in 200 cc. of hot water. The red-orange oil which precipitated crystallized upon cooling; yield 10.2 g. (81%). The solid was recrystallized from ethanol with the addition of water; m. p. 149–150°. Two more such recrystallizations raised the m. p. to 150–150.5°.

Anal. Calcd. for $C_{11}H_{13}O_4N_3$: N, 16.7. Found: N, 16.9, 16.3.

Ethyl Levulinate *o*-Nitrophenylhydrazone.—Dry hydrogen chloride was bubbled rapidly into a solution of 1.00 g. (0.0040 mole) of levulinic acid *o*-nitrophenylhydrazone in 60 cc. of absolute ethanol, and the solution was refluxed for two hours. The preparation was diluted with 200 cc. of water and extracted with four 50-cc. portions of ether. The combined ether extracts were washed with sodium bicarbonate solution and water. After drying with Drierite the ether was distilled off and the residue was recrystallized from ethanol; yield 0.88 g. (80%), m. p. 57.5–58.5°. Recrystallization from ethanol with the addition of water gave orange crystals of m. p. 58.5–59°. A mixed m. p. with the ester prepared from ethyl levulinate[9] and *o*-nitrophenylhydrazine showed no depression.

Anal. Calcd. for $C_{13}H_{17}O_4N_3$: N, 15.1. Found: N, 14.9.

2-Methyl-7-nitro-3-indoleacetic Acid.—To 20.0 cc. of a saturated solution of zinc chloride in concentrated hydrochloric acid solution, 2.0 g. (0.0071 mole) of the ester hydrazone was added and the mixture was refluxed

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(1) From the thesis submitted by Frank J. Stevens to the Graduate School of Iowa State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Thimann, *Ann. Rev. Biochem.*, **4**, 545 (1935).

(4) Zimmerman and Hitchcock, *Contrib. Boyce Thompson Inst.*, **12**, 321 (1941–1942).

(5) Fischer, *Ber.*, **19**, 1563 (1886).

(6) Fischer, *Ann.*, **236**, 147 (1886).

(7) Went and Thimann, "Phytohormones," Macmillan Company, New York, N. Y., 1937.

(8) Müller, Montigel and Reichstein, *Helv. Chim. Acta*, **20**, 1472 (1937).

(9) Grote, Kehrer and Tollens, *Ann.*, **206**, 221 (1881).

for one hour. The resultant solution was extracted with four 50-cc. portions of ether, and the combined extract was dried. The ether was distilled off and the residue refluxed with 25 cc. of 2% ethanolic sodium hydroxide for one hour. Twenty-five cc. of water was added and the alcohol was removed by distillation. The alkaline solution was then extracted with 100 cc. of ether, and the extract was discarded. The solution was made acid with dilute hydrochloric acid solution, and extracted with three 50-cc. portions of ether. The combined ether extracts were dried and the ether removed by distillation; yield 0.47 g. (28%), the material decomposed about 245°. Recrystallization from acetic acid with the addition of water gave a material that melted 265° (dec.). The substance was soluble in ethanol, acetic acid, and sodium bicarbonate solution, but insoluble in water.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: N, 12.0. Found: N, 11.9, 11.8.

Other treatments which were unsuccessfully tested for ring closure were: heating with zinc chloride alone, and in boiling xylene, and heating with aluminum chloride in hexane.

Ethyl Levulinate *o*-Chlorophenylhydrazone.—A hot solution of 17.9 g. (0.10 mole) of *o*-chlorophenylhydrazine hydrochloride,[10] 8.5 g. (0.104 mole) of sodium acetate, and 25 g. of acetic acid in 200 cc. of water was slowly added to 14.4 g. (0.10 mole) of ethyl levulinate in 300 cc. of hot water. The light yellow oil, which immediately precipitated, solidified after cooling. The precipitate was filtered and washed with water; yield 25.5 g. (95%). Recrystallization from ethanol with the addition of water gave a white crystalline precipitate of m. p. 58.5–59.5°. The material was unstable, however, and soon turned to a dark oil. Kögl and Kostermans[11] reported that levulinic acid *p*-tolylhydrazone behaved similarly. The chlorophenylhydrazone was not analyzed.

2-Methyl-7-chloro-3-indoleacetic Acid.—A mixture of 3.0 g. (0.012 mole) of freshly prepared *o*-chlorophenylhydrazone and 15 g. of zinc chloride was heated at 100° for one hour, and the melt was dissolved in 50 cc. of 1 *N* hydrochloric acid solution. The brown oil which separated was extracted with two 100-cc. portions of ether. The ether extract was dried with Drierite and evaporated. The residual brown oil was refluxed for forty minutes with 25 cc. of 10% methanolic potassium hydroxide.

After addition of 50-cc. of water, the methanol was removed under reduced pressure by distillation. The aqueous solution was extracted once with ether, and acidified with hydrochloric acid solution, whereupon a brown oil precipitated. This was taken up in ether and shaken with half-saturated sodium bicarbonate solution. The bicarbonate layer was separated and acidified. The brown oil which resulted was extracted from its aqueous suspension with four 50-cc. portions of ether. The combined ether extracts were dried with Drierite and the ether was distilled off under reduced pressure. The residue was dissolved in acetic acid, decolorized with Norit and concentrated in a vacuum desiccator over sodium hydroxide. The solid obtained was 0.8 g. (30%) with a m. p. of 157–159°. The material was recrystallized thrice from benzene, and once from benzene with addition of hexane after decolorization. There resulted white slender needles of m. p. 164–164.5°.

Anal. Calcd. for $C_{11}H_{10}O_2NCl$: C, 59.06; H, 4.51; N, 6.26; neut. equiv., 223.5. Found: C, 59.45; H, 4.47; N, 6.12, 6.36; neut. equiv. (phenolphthalein), 226, 225. A 7.5-g. portion of ester hydrazone, treated as above, yielded 2.7 g. (43%) of crude product.

The products gave a test with Ehrlich reagent which was negative in the cold but positive upon warming.

Ethyl Levulinate *p*-Chlorophenylhydrazone.—This compound was prepared in 63% yield in the same way as the *o*-chlorophenylhydrazone by use of the *p*-chlorophenylhydrazine.[8] The unstable product, when freshly prepared, had a m. p. of 104–106°. An earlier preparation of this compound[12] recorded a m. p. of 112–113°.

2-Methyl-5-chloro-3-indoleacetic Acid.—Six grams (0.022 mole) of crude ester was mixed thoroughly with 36 g. of zinc chloride and heated in an oil-bath at 125–135° for one hour. The solidified melt was distributed between 80 cc. of 1 *N* hydrochloric acid and 100 cc. of ether. The acid layer was further extracted with ether until a negative test with Ehrlich reagent was obtained (three 100-cc. portions of ether). The combined ether extracts were evaporated, after drying, and the residue was refluxed for twenty minutes with a solution of 3.0 g. of potassium hydroxide in 25 cc. of methanol.

The solvent was diluted with 50 cc. of water, and the alcohol removed under vacuum. The solution was extracted with 100 cc. of ether and the extract was discarded. The solution was then acidified with hydrochloric acid and the oily liquid was extracted with ether until the indole test was negative. The substance was shaken from the ether into 100 cc. of half-saturated sodium bicarbonate solution, which was separated and carefully acidified. The oily precipitate was extracted with four 100-cc. portions of ether. The extract was dried and the ether was distilled off from a residue of 2.2 g. (45%) of m. p. 183–186° (dec.). Recrystallization from benzene with addition of hexane gave 1.8 g. of m. p. 190° (dec.). Another recrystallization did not raise the m. p.

Anal. Calcd. for $C_{11}H_{10}O_2NCl$: C, 59.06; H, 4.51; N, 6.26; neut. equiv., 223.5. Found: C, 58.94; H, 4.34; N, 6.36, 6.37; neut. equiv., 221, 224.

The acid was soluble in alcohol, ether and benzene, insoluble in water and hexane.

Ethyl Levulinate 2,4-Dichlorophenylhydrazone.—A hot solution of 9.3 g. (0.044 mole) of 2,4-dichlorophenylhydrazine hydrochloride,[13] 30 g. of acetic acid and 4.5 g. of sodium acetate in 100 cc. of water was added to a solution of 7.5 g. (0.052 mole) of ethyl levulinate in 200 cc. of water. The light brown oil which separated crystallized on cooling. The crystals were collected, washed with ethanol, and dried in a vacuum desiccator. The yield was 12.2 g. (91%), m. p. 74–76° (dec.). This hydrazone, also, decomposed in the air.

2-Methyl-5,7-dichloro-3-indoleacetic Acid.—Ten grams (0.033 mole) of ester hydrazone was heated with 50 g. of anhydrous zinc chloride at 165–170° for one hour. The solidified melt was distributed between 100 cc. of ether and 100 cc. of 1 *N* hydrochloric acid. The acid solution was extracted with three 100-cc. portions of ether. The combined ether extracts were dried and the ether was evaporated. The residue was refluxed with 5 g. of potassium hydroxide dissolved in 50 cc. of methanol for twenty minutes. None of the extracts gave a positive indole test.

After addition of 50 cc. of water, the methanol was removed under reduced pressure. The basic solution was extracted with ether, and the extract discarded. The solution was then acidified with dilute hydrochloric acid and the oil which separated was extracted with three 100-cc. portions of ether. The combined extracts were shaken with 100 cc. of half-saturated sodium bicarbonate solution, the latter separated, carefully acidified, and extracted with three 100-cc. portions of ether. After drying, the extract was concentrated to 3.2 g. (38%) of solid of m. p. 215° (dec.). Recrystallization from benzene by addition of hexane raised the m. p. to 220–221° (dec.).

Anal. Calcd. for $C_{11}H_9O_2NCl_2$: C, 51.16; H, 3.52; N, 5.43; neut. equiv., 258. Found: C, 50.81; H, 3.33; N, 5.42, 5.36; neut. equiv., 262, 260.

Substituted Phenylhydrazones of β-Formylpropionic Acid.—The phenylhydrazones of β-formylpropionic acid were prepared from the acid[14] with the phenylhydrazines

(10) Hewitt, *J. Chem. Soc.*, **59**, 209 (1891).

(11) Kögl and Kostermans, *Z. physiol. Chem.*, **238**, 215 (1935).

(12) Sah, Lei and Shen, *Sci. Repts. Natl. Tsing Hua Univ.*, [A] **2**, 7 (1933); *C. A.*, **27**, 4222 (1933).

(13) Chattaway and Pearse, *J. Chem. Soc.*, **107**, 33 (1915).

(14) Langheld, *Ber.*, **42**, 2371 (1909).

described above, in about 60% yield. The m. p.'s and N contents of those not found in the literature are presented in Table I.

TABLE I

PHENYLHYDRAZONES OF β-FORMYLPROPIONIC ACID

Substituents of phenylhydrazine	M. p., °C. cor., dec.	Nitrogen, % Calcd.	Found
2-Nitro	155–156	17.7	17.4 17.4
2-Chloro	180–185.5	12.4	12.3 12.2
2,4-Dichloro	181–182	10.7	10.4 10.6

4,5-Dihydro-2-(*o*-nitrophenyl)-3(2)-pyridazone.—One gram (0.0042 mole) of the *o*-nitrophenylhydrazone of β-formylpropionic acid was dissolved in concentrated sulfuric acid. After twenty-four hours at room temperature, the solution was poured into a large amount of water. The aqueous solution was extracted with ether, and the ether extract dried with Drierite. The ether was allowed to evaporate and the residue crystallized from hot benzene. There was obtained 0.5 g. (54%) of crystals of m. p. 99–102°. Several recrystallizations from ethanol with addition of water raised the m. p. to 101.5–102°. The compound was not soluble in 5% hydrochloric acid solution, nor immediately soluble in cold 5% sodium hydroxide solution. It dissolved slowly in cold, rapidly in hot, sodium hydroxide solution to give a deep red-brown solution. The color of the solution changed to yellow upon acidification. Analysis indicated this compound to be the pyridazone.

Anal. Calcd. for $C_{10}H_9O_3N_3$: N, 19.2. Found: N, 19.4, 19.2.

Acknowledgments.—Dr. S. W. Loo, now of the Botany Department of the University of Peking, was very helpful in the testing of the compounds. We are indebted to General Mills for a generous supply of technical grade glutamic acid.

Summary

The preparation of a series of substituted 2-methyl-3-indoleacetic acids and of a series of substituted phenylhydrazones of β-formylpropionic acid has been described.

AMES, IOWA RECEIVED[15] APRIL 8, 1948

(15) Original manuscript received July 10, 1947.

[CONTRIBUTION FROM PHILLIPS PETROLEUM COMPANY, RESEARCH DEPARTMENT]

Relative Rates of Propylation of Monoalkylbenzenes

BY FRANCIS E. CONDON

Repeated observations by many workers that monoalkylation of benzene is accompanied by considerable polyalkylation have indicated that aromatic alkylation, like halogenation[1] and nitration,[2] is faster for an alkylbenzene than for benzene.[3] As indicated by Francis and Reid,[4] the rate of alkylation of a monoalkylbenzene relative to that of benzene can be evaluated from the composition of the reaction mixture. Although they favored the view that the rates are equal, some of their calculations showed that, under some conditions, benzene appeared to be twice as readily ethylated as ethylbenzene.[5] They pointed out, however, that this may not represent the true relative reactivities of benzene and ethylbenzene because the reaction mixture was not homogeneous and because of the possibility of simultaneous dealkylation of polyethylbenzenes.

In the work reported herein, the rates of propylation of toluene, ethylbenzene, cumene and *t*-butylbenzene relative to the rate of propylation of benzene were determined, in competition-type experiments, in homogeneous reaction mixtures and under conditions which were shown to be ineffective for dealkylation of the polyisopropylbenzenes produced. In one series of runs, boron fluoride etherate, which is completely miscible with these hydrocarbons, was used as a catalyst. In other runs, aluminum chloride was the catalyst and nitromethane was the solvent.[6]

(1) de la Mare and Robertson, *J. Chem. Soc.*, 279 (1943).

(2) Ingold, Lapworth, Rothstein and Ward, *ibid.*, 1959 (1931).

(3) See, for example, Fieser and Fieser, "Organic Chemistry," D. C. Heath and Co., Boston, 1945, p. 535; Price, in "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, 1946, p. 5.

(4) Francis and Reid, *Ind. Eng. Chem.*, **38**, 1194 (1946).

(5) Coincidentally, relative rates calculated from the data of Slanina, Sowa and Nieuwland, THIS JOURNAL, **57**, 1547 (1935), indicate that benzene is apparently about twice as readily propylated as cumene.

I. Experimental Part

Materials.—Commercial C. P. benzene and toluene were distilled, discarding the first and last ten per cents., approximately.

Ethylbenzene, *p*-cymene (both Eastman Kodak Co. White Label) and *t*-butylbenzene (from hydrogen fluoride alkylation of benzene with isobutylene) were distilled in a Podbielniak Hypercal column with Heligrid packing[7]; only middle fractions of constant boiling point were used.

Nitromethane from the Commercial Solvents Corporation was distilled from an ordinary Claisen flask and the first and last ten per cents., approximately, were discarded.

Boron fluoride etherate was obtained from Eastman Kodak Company. The formula $BF_3 \cdot (C_2H_5)_2O$ was assumed.

Reagent quality anhydrous aluminum chloride was used.

The propylene was a high-purity product of Phillips Petroleum Company.

Alkylation Procedure.—Alkylation was carried out in a 500-cc. flask provided with a mercury-sealed Hershberg stirrer,[8] an inlet tube for propylene, a thermometer, and a reflux condenser, the top of which communicated through a Drierite-filled drying tube with a water-bubbler that indicated any escape of propylene. The flask was charged with a mixture of 100–150 g. of aromatic hydrocarbons and boron fluoride etherate or nitromethane and aluminum chloride. The stirrer was started and the

(6) Schmerling, paper presented before the Petroleum Division, ACS Meeting, New York, September, 1947.

(7) Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **13**, 639 (1941).

(8) Hershberg, *ibid.*, **8**, 313 (1936).