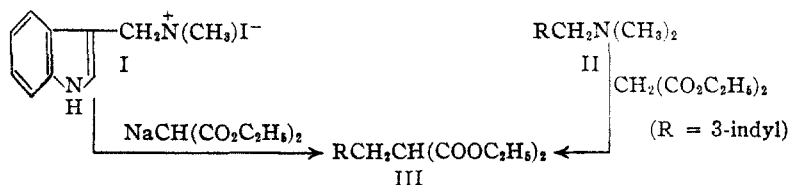


[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC., RAHWAY, NEW JERSEY, AND THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Application of a New Alkylation Reaction to the Synthesis of Tryptophan

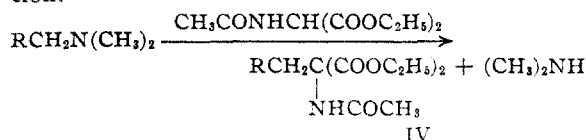
BY E. E. HOWE, A. J. ZAMBITO, H. R. SNYDER¹ AND M. TISHLER

During an extended investigation of carbon alkylation with quaternary ammonium salts, in particular with gramine methiodide (skatyltrimethylammonium iodide) (I),² it was observed by one of us (H.R.S.) that gramine (II) condenses with malonic ester to yield ethyl α -carbethoxy- β -(3-indole)-propionate (III) in much the same way as the methiodide condenses with sodio malonic ester.



This observation prompted us to study the condensation of gramine with acetaminomalonic ester in the hope of developing a more economical route to ethyl α -acetamino- α -carbethoxy- β -(3-indole)-propionate (IV)—a key intermediate in the recently published *dl*-tryptophan synthesis.³

Although Mannich bases (β -dialkylaminoketones) have been condensed with β -keto esters in the presence of sodium ethoxide in ethanol,⁴ we found that unsatisfactory yields of the ester IV were obtained from gramine and acetaminomalonic ester with the same condensing agent. Better yields were obtained when the reactants were heated at 165° or when solutions of the reactants in pyridine or dioxane were heated to boiling. The presence of a small amount of a basic catalyst such as sodium methylate, sodium carbonate or sodium hydroxide was beneficial. The best results (90%) were obtained when the reactants in an inert solvent (such as toluene or xylene) were refluxed in the presence of a small amount of powdered sodium hydroxide. Under these conditions, dimethylamine was evolved and the reaction was completed in five hours. The crystalline product was readily obtained in a state of high purity by cooling the filtered solution.



(1) University of Illinois, Urbana, Illinois.

(2) For some of the results of this work, see Snyder, Smith and Stewart, *This Journal*, **66**, 200 (1944).

(3) (a) Snyder and Smith, *ibid.*, **66**, 350 (1944); (b) Albertson, Archer and Suter, *ibid.*, **66**, 500 (1944). In both papers the ester IV is obtained by the condensation of a gramine alkiodide with the sodium derivative of acetamino-malonic ester.

(4) Mannich, Koch and Borkowsky, *Ber.*, **70**, 355 (1937).

With this modification for preparing the ester IV and with subsequent operations according to the experimental procedure of Snyder and Smith^{3a} the over-all yield of *dl*-tryptophan from indole is 66% as compared to the reported 45%.⁵

The alkylation of acetaminomalonic ester to the ester IV was also accomplished with 3-diethylaminomethyl-indole and with 3-(*N*-piperidylaminomethyl)-indole. It was also found that phthalimidomalonic ester readily condenses with gramine to give skatylphthalimidomalonic ester. Attempts to condense diketopiperazine and hydantoin with gramine under similar conditions were without success.

Whether the reaction between skatylalkyl amines and malonic ester derivatives depends on the same type of mechanism as is involved in the reaction of Mannich bases (or their methiodides) with active methylene compounds⁶ has not been investigated. In this connection it is of interest to point out the following facts: (1) Gramine is not stable when heated alone (above 131°), in pyridine or in xylene containing powdered sodium hydroxide. In these instances dimethylamine is evolved. (2) The reaction mixture of gramine and acetaminomalonic ester (especially in pyridine) is extremely sensitive to air. On exposure to air the reaction mixture darkens and an intractable mixture is obtained. (3) When a mixture of gramine and piperidine is heated dimethylamine is evolved and 3-(*N*-piperidylmethyl)-indole is formed.

Experimental

Ethyl- α -acetamino- α -carbethoxy- β -(3-indole)-propionate, IV. (a) Reaction of Gramine and Ethyl Acetaminomalonate

(1) **Solvent—Toluene or Xylene.**—To a boiling mixture of 1200 cc. of toluene (or xylene) and 17 g. of powdered sodium hydroxide contained in a 5-liter three-necked flask fitted with a mechanical stirrer, a condenser and a nitrogen inlet tube, were added 250 g. (1.43 moles) of gramine and 311 g. (1.43 moles) of ethyl acetaminomalonate. While a stream of nitrogen was passed through the reaction mixture refluxing and rapid stirring were continued for five hours. The evolution of dimethylamine, which was very rapid at the beginning, almost ceased at the end of the heating period.

The reaction mixture was filtered through a preheated funnel and the filtrate was allowed to cool at room temperature. After chilling at 5° for several hours the product

(5) The communication of Albertson, Archer and Suter^{3b} does not include experimental procedures; their reported yield of tryptophan from indole was 35%.

(6) For a discussion of this reaction see Blicke, "The Mannich Reaction" in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, pp. 320-322.

was filtered and washed with cold toluene followed by petroleum ether. The dried product (wt. 446 g., 90% yield) melted at 158–159° and was converted without further purification to *dl*-tryptophan in essentially the same yield as reported by Snyder and Smith.^{3a}

Substitution of anhydrous sodium carbonate for sodium hydroxide in this reaction reduced the yield to 77.5%.

(2) **Solvent—Pyridine.**—A mixture of 19.7 g. of gramine, 24.5 g. of ethyl acetaminomalonate and 100 cc. of pyridine was refluxed for two hours in an atmosphere of nitrogen. The mixture was treated with Darco, filtered, concentrated to 50 cc. and diluted with 20 cc. of warm water. After storage at 5° for six hours an additional 80 cc. of water was added and the mixture was kept at 5° for eighteen hours. The product melted at 157–158° and weighed 18 g. (47.5%). The presence of 3 g. of powdered sodium hydroxide in the same size run increased the yield of product to 21.3 g. (54.6%). With smaller size runs (one-tenth size) yields as high as 73% were obtained.

When air was bubbled through the mixture during the reaction a deep red color was formed, the intensity of which increased with time. After such treatment none of the desired product could be isolated.

(3) **No Solvent.**—To 24.5 g. of molten ethyl acetaminomalonate at 150° was added 19.7 g. of gramine portionwise over a period of five to ten minutes. The temperature was raised during the addition to 165° and maintained there for ten minutes. The red oily product was cooled to 70°, dissolved in 70 cc. of alcohol and the solution was diluted with 50 cc. of warm water. After storage at 5° for eighteen hours the mixture was filtered, yielding 21.0 g. (54%) of product, m. p. 157–158°.

Gramine is unstable on heating above its melting point (131°); the decomposition is accompanied by the evolution of dimethylamine.

(b) **Condensation of Skatyl-diethylamine with Ethyl Acetaminomalonate.**—A mixture of 36.8 g. of ethyl acetaminomalonate, 34.4 g. of skatyl-diethylamine,⁷ 150 cc. of

(7) Skatyl-diethylamine was prepared from indole, formaldehyde and diethylamine by the method of Kuhn and Stein, *Ber.*, **70**, 567 (1937), in 98% yield. Our product (analytically pure) melts at 105°, rather than at 165° as recorded by Kuhn and Stein.

toluene and 2 g. of powdered sodium hydroxide treated in the manner described in section (1) gave 50.6 g. (85.5%) of product melting at 156–158°.

(c) **Condensation with β -(*N*-piperidylmethyl)-indole.**—When ethyl acetaminomalonate and β -(*N*-piperidylmethyl)-indole⁸ were treated as in section (1), skatyl-aminomalonate ester was obtained in 64% yield; m. p., 157–158°.

Ethyl Skatylphthalimidomalonate.—A mixture of 3.5 g. of ethyl phthalimidomalonate, 2 g. of gramine, 0.3 g. of powdered sodium hydroxide and 15 cc. of toluene was refluxed for five hours. The evolution of dimethylamine appeared more sluggish than with ethyl acetaminomalonate. The filtered reaction mixture was kept cold for eighteen hours and filtered. The crude material (m. p. 120–145°) when recrystallized from ethanol gave 0.5 g. of light green crystals, m. p. 175–176°.

Anal. Calcd. for $C_{24}H_{22}N_2O_6$: C, 66.50; H, 5.07. Found: C, 66.77; H, 4.99.

Acknowledgment.—The authors are indebted to Drs. R. T. Major and J. R. Stevens for their interest and valuable suggestions and to Mr. R. Boos and his associates for microanalyses.

Summary

Ethyl α -acetamino- α -carboethoxy- β -(3-indole)-propionate is made in excellent yields by direct condensation of gramine and ethyl acetaminomalonate, making possible the preparation of *dl*-tryptophan in 66% yields from indole. The condensation of other skatyl-dialkylamines with ethyl acetaminomalonate is described.

(8) β -(*N*-piperidylmethyl)-indole was prepared by refluxing a mixture of gramine and piperidine for three hours; yield, over 90%; m. p., 158–159°. *Anal.* Calcd. for: $C_{14}H_{18}N$: C, 78.50; H, 8.43; N, 13.10. Found: C, 78.35; H, 8.49; N, 12.93. We first obtained it by attempting to condense gramine and acetaminomalonate ester in the presence of piperidine.

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

Preparation of Alkoxyacetaldehydes

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References to the preparation of alkoxyacetaldehydes have frequently appeared in the literature, but none has provided an entirely satisfactory laboratory method. The original method used was to treat halogen acetals with sodium alcoholates followed by acid hydrolysis of the alkoxyacetals.² Yields were low. Since β -alkoxyethyl alcohols have become commercially available, several methods for the preparation of alkoxyacetaldehydes have been proposed which depend upon either dehydrogenation³ or oxidation⁴ of these alcohols. Dehydrogenation was re-

ported to give yields of 8–10% based on the starting materials while oxidation using chromic acid gave yields of 16.7 and 10% for methoxyacetaldehyde and ethoxyacetaldehyde.^{4b} Redemann and Icke obtained a 30–35% yield of ethoxyacetaldehyde from cellosolve over a copper chromite catalyst at 310–330°.^{3d} Somewhat higher yields are claimed in patented processes of a similar nature.

Lead tetraacetate and periodic acid will oxidize compounds having two hydroxyl groups attached to adjacent carbon atoms, and the oxidations are characterized by cleavage of the carbon-carbon bond to form carbonyl compounds.^{5,6} Although this type of oxidation has been known for some time and the reactions used to prepare benzyloxy-

(1) From the M.A. thesis of S. S. Nesbitt, August, 1944. At present on active duty in the U. S. N. R.

(2) Rotbart, *Ann. chim.*, [11] **1**, 439 (1934), a review.

(3) (a) Drake, Duvall, Jacobs, Thompson and Sonnichsen, *THIS JOURNAL*, **60**, 73 (1938); (b) Drake, U. S. Patent 2,170,854 (1939); (c) Gresham, U. S. Patent 2,286,034 (1942); (d) Redemann and Icke, *J. Org. Chem.*, **8**, 159 (1943).

(4) (a) Malm, Nadeau and Diesel, U. S. Patent 2,000,604 (1935); (b) Hurd and Abernethy, *THIS JOURNAL*, **63**, 1966 (1941).

(5) Criegee, *Ber.*, **64**, 260 (1931).

(6) Malaprade, *Bull. soc. chim.*, [4] **43**, 683 (1928); *Compt. rend.*, **186**, 382 (1928).