cases the products are easier to work up because of the absence of an acid catalyst.

The method is widely applicable. 2-Phenylindole, 2,3-dimethylindole, 2-methyl-3-ethylindole, 3,5-dimethylindole, 1,3-dimethylindole, 1,2,3-trimethylindole, 7-chloro-2,3-dimethylindole, 4,7-dichloro-2,3-dimethylindole and 3-ethyl-2-phenylindole have all been made in fair to good yields. The optimum reaction conditions have not been determined for most of these compounds. With some, reaction is complete after two to three hours in boiling ethylene glycol; others require refluxing 24 hr. or more. In some cases the reaction rate is accelerated by the higher temperature obtained in refluxing diethylene glycol. The polarity of the solvent is not critical; tetralin works about as well as the glycols.

No theory has been formulated about the mechanism of the reaction. Robinson and Robinson's widely accepted mechanism[4,5] for the Fischer synthesis involving an acid-catalyzed benzidine type rearrangement does not appear to be adequate, since the cyclization takes place even in the presence of small amounts of alkali.

Reaction conditions and yields are given in Table I. All reactions were carried out by refluxing a solution of the phenylhydrazone in the specified solvent. Products were isolated by steam distillation, reduced pressure distillation, or precipitation, and purified by recrystallization or distillation.

RESEARCH DEPARTMENT,
UNION CARBIDE CHEMICALS CO.
SOUTH CHARLESTON, W. VA.

(4) Robinson and Robinson, *J. Chem. Soc.*, **113**, 639 (1918).

(5) Robinson and Robinson, *J. Chem. Soc.*, **125**, 827 (1924).

Preparation and Reactions of Some Aralkyl Cyanoacetic Esters

PETE D. GARDNER AND RICHARD L. BRANDON

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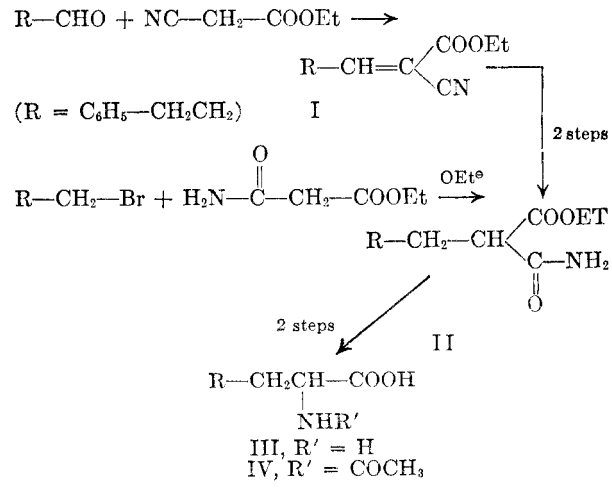
The occurrence in nature of cyclic structures possessing the acetamido function prompted an investigation of cyclization reactions of some aralkyl acids containing amine or acetamido functions.[1] The problem was twofold, that of synthesis of appropriate α-acetamido aralkyl acids and that of cyclizing such substances to the corresponding ketones without alteration of the substituent. Moreover, it was required that only those methods be considered which could be easily adapted to the use of variously substituted starting materials.

(1) One such cyclization using polyphosphoric acid has been reported. W. J. Horton and G. Thompson, *J. Am. Chem. Soc.*, 76, 1909 (1954).

α-Amino-δ-phenylvaleric acid (III) was prepared from hydrocinnamaldehyde by the sequence shown. Condensation of the aldehyde with ethyl cyanoacetate, by the general Knoevenagel[2] reaction using piperidine–acetic acid as a catalyst[3] gave I which was then converted by hydrogenation to ethyl α-cyano-δ-phenylvalerate. Hydrolysis of this cyano ester to α-carbethoxy-δ-phenylvaleramide (II) was effected by treatment with polyphosphoric acid.[4,5] The final conversion to the amine (III) was made by the Hofmann method.[6] Alternatively, II was prepared by the base-catalyzed condensation of 1-bromo-3-phenylpropane with ethyl malonamate.

Several attempts to cyclize the amino acid (III) or its acetyl derivative (IV) with polyphosphoric acid gave only recovered starting material. The carbethoxy amide (II) was equally resistant to cyclization by this reagent.

Another series of compounds of interest appeared to be obtainable by application of the above described sequence of reactions to *p*-hydroxybenzaldehyde. Thus, ethyl α-cyano-β-(*p*-hydroxyphenyl)-propionate (V, R = H) and the acetate (R = $COCH_3$) were prepared and the former converted to the amide (VI, R = H) *via* the imino ester hydrochloride. The use of polyphosphoric acid in this instance (R = H or $COCH_3$) was unsuccessful. Repeated attempts to prepare the corresponding amino acid from VI by the Hofmann method were unsuccessful. It has been reported that the corresponding methyl ether compound failed to undergo this reaction.[6] The failure of the Hofmann reaction as a general method appears to be a definite limitation in this approach to the α-amino acids.



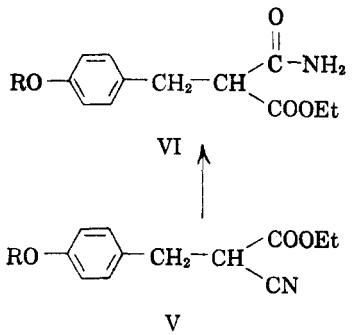
(2) J. Scheiber and F. Meisel, *Ber.*, **48**, 257 (1915).

(3) A. C. Cope, U. S. Patent 2,655,526; *Chem. Abstr.*, **48**, P11484 (1954).

(4) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **76**, 3039 (1954).

(5) C. R. Hauser and C. J. Eby, *J. Am. Chem. Soc.*, **79**, 725 (1957).

(6) See for example R. Gaudry, *Can. J. Research*, 23B, 234 (1954).



EXPERIMENTAL

Ethyl hydrocinnamylidenecyanoacetate (I). A mixture of 33.5 g. (0.25 mole) of hydrocinnamaldehyde and 28.2 g. (0.25 mole) of ethyl cyanoacetate was dissolved in 75 ml. of dry dioxane and the solution cooled to 0°. Piperidine (0.85 g.) was added dropwise and the solution cooled occasionally to maintain the temperature at 0°. After standing at room temperature for 5 hr., the solution was diluted with ether and washed successively with dilute hydrochloric acid, dilute potassium carbonate solution, and water. The ether solution was dried over calcium chloride and solvent evaporated under reduced pressure. The residue was distilled to give 21.5 g. (35%) of I as a light yellow liquid; b.p. 172–174° (dec.) (3.0 mm.). In a run allowing 8 hr. for reaction, the yield was 53%.

Anal. Calcd. for $C_{14}H_{15}O_2N$: C, 73.35; H, 6.59; N, 6.12. Found: C, 73.46; H, 6.44; N, 6.30.

Ethyl α-cyano-δ-phenylvalerate. A solution of 15.0 g. (0.065 mole) of I in pure dioxane was reduced with hydrogen at one atmosphere pressure over 5% palladium-charcoal. The crude product, after isolation in the usual manner, was dissolved in ether and washed successively with dilute hydrochloric acid, dilute potassium carbonate solution, and water. The dried solution was freed of solvent and distilled to yield 11.1 g. (74%) of faintly yellow liquid; b.p. 139–141° (0.5 mm.).

Anal. Calcd. for $C_{14}H_{17}O_2N$: C, 72.74; H, 7.44; N, 6.06. Found: C, 72.74; H, 7.43; N, 6.15.

α-Carbethoxy-δ-phenylvaleramide (II). (*a*) *From ethyl α-cyano-δ-phenylvalerate.* A mixture of 10.0 g. (0.045 mole) of ethyl α-cyano-δ-phenylvalerate and 100 g. of polyphosphoric acid was heated for 45 min. at 75°. Addition of a mixture of ice and water to the complex resulted in the formation of a heavy white precipitate. After drying in vacuum and recrystallization from ethyl acetate–petroleum ether (60–68°) there was obtained 5.1 g. (47%) of II, m.p. 114°. When the heating time was extended to 2 hr. and the temperature maintained at 100°, the yield was 83%.

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 67.40; H, 7.70; N, 5.62. Found: C, 67.69; H, 7.72; N, 5.90.

(*b*) *By aralkylation of ethyl malonamate.* A solution of 6.6 g. (0.05 mole) of ethyl malonamate[7] in 10 ml. of absolute ethanol was added to 1.1 g. (0.05 atom) of sodium dissolved in 20 ml. of ethanol. A solution of 10.0 g. (0.05 mole) of 1-bromo-3-phenypropane in 10 ml. of ethanol was added in one portion and the mixture stirred for 1.5 hr. at room temperature. A solution of 3.0 g. (0.05 mole) of acetic acid in 150 ml. of ether was added and the ether solution washed with water. Evaporation of solvent and recrystallization of the residue from ethyl acetate–petroleum ether (60–68°) gave 2.4 g. (19%) of II having the same m.p. as that observed for the preparation described in (a).

α-(3-Phenylpropyl)malonamic acid was obtained in 48% yield by hydrolysis of the ester in methanolic potassium hydroxide during 2 hr. at room temperature. Recrystallization from ethyl acetate-cyclohexane gave the pure acid, m.p. 129–131° (dec.).

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.12; H, 6.83. Found: C, 65.51; H, 7.03.

α-Amino-δ-phenylvaleric acid (III). A solution comprised of 1.8 ml. of bromine and 10 g. of potassium hydroxide in 100 ml. of water was cooled to −10° in an ice-methanol mixture. To this was added, with stirring, 5.0 g. (0.022 mole) of α-(3-phenylpropyl)malonamic acid. The mixture was stirred until the acid had completely dissolved (50 min.) and the resulting yellow solution was heated nearly to the boiling point and maintained at that temperature for 10 min. The solution was cooled to 0° and neutralized with dilute hydrochloric acid. Precipitation of the amino acid occurred near *p*H 7. Collection of the precipitate, followed by recrystallization from water, gave 3.2 g. (73%); m.p. 208–212° (dec.) (lit.[8] 203–206°).

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.38; H, 7.83. Found: C, 68.62; H, 7.72.

Of the many Hofmann reactions attempted with substituted malonamic acids, this was the only one which gave isolable amino acid. It was largely due to these failures that the study was discontinued.

α-Acetamido-δ-phenylvaleric acid (IV). The acetylation of III was effected by treating 5.0 g. (0.030 mole) of the amino acid with 10 ml. of acetic anhydride and three drops of pyridine and heating the resulting solution on a steam bath for 15 min. Isolation in the usual manner by hydrolysis and ether extraction gave the product as a viscous liquid. Crystallization from ethyl acetate–cyclohexane gave 2.5 g. (42%) of colorless IV, m.p. 144–146°.

Anal. Calcd. for $C_{13}H_{17}ON$: C, 66.35; H, 6.96; N, 5.95. Found: C, 66.62; H, 7.07; N, 5.95.

Attempts to cyclize either III or IV by the use of polyphosphoric acid were unsuccessful.

Ethyl α-cyano-β-(p-hydroxyphenyl)propionate (V). A mixture of 24.0 g. (0.20 mole) of *p*-hydroxybenzaldehyde, 22.6 g. (0.20 mole) of ethyl cyanoacetate and 1.2 g. of acetic acid was dissolved in 80 ml. of purified dioxane. To this was added 0.84 g. of piperidine and the solution was shaken with 1 g. of 5% palladium-charcoal under one atmosphere of hydrogen. After the theoretical quantity of hydrogen had been absorbed, the mixture was processed as described above. Material obtained in a previous run proved to be thermally unstable. This preparation was, therefore, freed of solvent and unreacted ethyl cyanoacetate by heating briefly under reduced pressure and used without further purification (39 g.).

Ethyl α-(p-hydroxybenzyl)malonamate (VI). The 39 g. preparation of V described above was mixed with 9.0 g. of ethanol and placed in a system equipped for the addition of hydrogen chloride. The solution was stirred and hydrogen chloride bubbled through with occasional cooling to maintain the temperature between 40° and 45°. After 1.25 hr. the solution became too viscous to permit stirring and crystalline material began to separate. The mixture was allowed to stand for 0.5 hr. at room temperature and then heated over a low flame until a brisk evolution of gas occurred. After gas evolution had ceased, dry ether was added and the mixture stirred until crystallization occurred. Recrystallization from benzene afforded 15.0 g. (35%) of light yellow solid, m.p. 127–129°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.76; H, 6.37; N, 5.91. Found: C, 60.71; H, 6.33; N, 6.05.

No amino acid could be obtained from the reaction of this substance under Hofmann conditions.

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TEXAS
AUSTIN, TEX.

(7) A. Pinner, *Ber.*, **28**, 479 (1895).

(8) J. von Braun and O. Kruber, *Ber.*, **45**, 389 (1912).