

ethyl ester  $\alpha$ -XIb was obtained as a gum. The picrate of  $\alpha$ -XIb, prepared by addition of the hydrochloride to an aqueous picric acid solution, was an oil as reported.<sup>10,12</sup> The chloroaurate, formed by addition of an aqueous solution of auric chloride to an aqueous solution of  $\alpha$ -XIb hydrochloride, melted at 121–122° after recrystallization from ethanol (lit., m.p. 122°, 122.5°<sup>10</sup>).

*Attempted epimerization of methyl tropane-2 $\beta$ -carboxylate ( $\beta$ -XIc).* A solution of 2.8 g. of ester  $\beta$ -XIc and 0.3 g. of sodium methoxide in 15 ml. of methanol was heated at reflux overnight. The solvent was removed *in vacuo*, and the residue was extracted with ether. The ether insoluble material containing sodium methoxide weighed 0.6 g. Upon distillation of the ether solution, 2.0 g. of ester, b.p. 125–128° (24 mm.), was obtained. The hydrochloride of this material was fractionally crystallized from acetone to give 1.2 g. of the starting ester salt. From the mother liquors was obtained 1.2 g. of an oily mixture of salts from which the epimeric ester  $\alpha$ -XIc could not be isolated.

*Hydrolysis of esters  $\alpha$ -IIIa,  $\beta$ -IIIa,  $\alpha$ -XIc, and  $\beta$ -XIc in aqueous solution at room temperature.* The data in Table II were obtained by the following procedure. All samples of esters were pure except the sample of  $\alpha$ -XIc which contained 10–20% of its epimer.

A drop (15.0–25.0 mg.) of ester was weighed in a vial and a drop of distilled water (pH 6.0) was added. The vial was stoppered and the clear solution was allowed to stand at room temperature for the prescribed period of time. The vial was then placed in a drying pistol charged with phosphorus pentoxide and the solution evaporated at room temperature under 0.5 mm. pressure. (In preliminary experiments using freshly prepared solutions of the esters, it was shown by observation of the weight loss of the contents of the vial at various intervals of time that practically all of the water was removed after 15 min. leaving a film of ester on the wall of the vial. After drying for an additional 1.5 hr. all of the ester was evaporated.) After 2 hr. the pistol was heated and the amino acid residue was dried to constant weight. Acids  $\alpha$ -IIIb,  $\beta$ -IIIb, and  $\beta$ -XIa were dried at 100° and acid  $\alpha$ -XIa, which sublimed at this temperature, was dried at 60°. The yields of acids given in Table II are based on the amount of amino acid remaining in the vial after drying to constant weight.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION,  
SMITH KLINE AND FRENCH LABORATORIES]

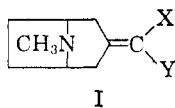
### 3-Substituted Tropane Derivatives. II. The Synthesis of 3 $\alpha$ - and 3 $\beta$ -Tropaneacetic Acids, 3-(3 $\alpha$ -Tropanyl)propionic Acid, and Related Compounds<sup>1</sup>

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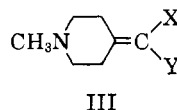
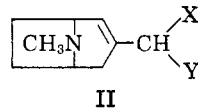
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3 $\alpha$ -Tropaneacetic and 3-(3 $\alpha$ -tropanyl)propionic acids, and related compounds, were prepared from the products of the condensation of tropinone with malononitrile or ethyl cyanoacetate. The ethyl ester of 3 $\beta$ -tropaneacetic acid was obtained from tropane-3 $\beta$ -carboxylic acid by the Arndt-Eistert method.

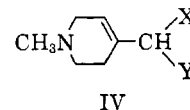
In addition to the isomeric tropane-3-carboxylic acids, described in the preceding paper,<sup>1</sup> we prepared higher homologs of these acids as intermediates for the synthesis of new 3-substituted tropane derivatives of potential pharmacological interest.<sup>2,3</sup> This article reports the synthesis of 3 $\alpha$ - and 3 $\beta$ -tropaneacetic acids (Vb and VIb), 3-(3 $\alpha$ -tropanyl)propionic acid (Vg), and related compounds.



- I  
a. X = CN, Y = CN  
b. X = CO<sub>2</sub>H, Y = H  
c. X = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, Y = H  
d. X = CN, Y = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>  
e. X = CN, Y = CO<sub>2</sub>H  
f. X = CN, Y = H

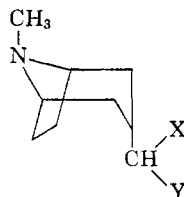


III

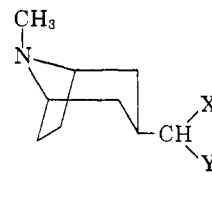


IV

- a. X = CN, Y = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>  
b. X = CN, Y = CN  
c. X = CO<sub>2</sub>H, Y = H



V



VI

- a. X = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, Y = CN  
b. X = CO<sub>2</sub>H, Y = H  
c. X = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, Y = H  
d. X = CH<sub>2</sub>OH, Y = H  
e. X = CH<sub>2</sub>Cl, Y = H  
f. X = CH<sub>2</sub>CN, Y = H  
g. X = CH<sub>2</sub>CO<sub>2</sub>H, Y = H  
h. X = CH<sub>2</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, Y = H

(1) Paper I of this series: C. L. Zirkle, T. A. Geissman, M. Bloom, P. N. Craig, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *J. Org. Chem.*, **27**, 1269 (1962).

(2) Paper III of this series: C. L. Zirkle, E. L. Anderson, P. N. Craig, F. R. Gerns, Z. K. Indik, and A. M. Pavloff, *J. Med. Pharm. Chem.*, **5**, 341 (1962).

(3) A preliminary account of part of this work has been presented elsewhere (C. L. Zirkle, P. N. Craig, T. A. Geissman, and M. Bloom, Congr. Handbook, Vol. II, 16th Intern. Conar. Pure and Appl. Chemistry, Paris, July 1957, p. 153).

In developing a route to 3 $\alpha$ -tropaneacetic acid, we studied the condensation of tropinone with active methylene compounds in the presence of ammonium acetate.<sup>4</sup> McElvain and Lyle,<sup>5</sup> in studying similar reactions of 1-methyl-4-piperidone, found that this amino ketone readily condensed with ethyl cyanoacetate or malononitrile to give the unsaturated cyano ester IIIa and dinitrile IIIb, respectively. The condensation products could be isolated from the reaction mixture in excellent yields as stable hydrochloride salts and the latter, by acid hydrolysis and decarboxylation, were converted smoothly to the unsaturated amino acid IVc. The free bases liberated from the salts of IIIa and IIIb, however, were not stable. The base from the hydrochloride of IIIa, shown to consist of an equilibrium mixture of isomers IIIa and IVa, slowly polymerized on standing; the free base of unsaturated dinitrile IIIb polymerized immediately after liberation from its salt.

In the present work we found that tropinone also condensed smoothly with malononitrile to give unsaturated dinitrile Ia, isolated as its hydrochloride, in excellent yield. The presence of a strong band at 6.21  $\mu$  in the infrared spectrum of the product indicated that it was the salt of the conjugated isomer Ia and not that of isomer IIa. Although the free base Ia, like its piperidine analog IIIb, was unstable, the hydrochloride of Ia could be readily hydrolyzed and decarboxylated in hydrochloric acid solution to afford, in good yield, a mixture of the salts of unsaturated acids Ib and IIb. Fischer esterification of the mixture of acids gave a mixture of esters Ic and IIc in which, according to infrared spectral data, the latter isomer predominated (see Experimental part). No attempts were made to separate the isomeric esters, but sharply melting salts of one isomer were readily obtained from the ester mixture. The absence of absorption peaks in the 6.1- $\mu$  and 220- $m\mu$  regions of the spectra of the ester hydrobromide and methiodide demonstrated that these were salts of the unconjugated ester IIc.

Catalytic hydrogenation of the mixture of unsaturated esters Ic and IIc occurred stereoselectively to yield predominantly the  $\alpha$  isomer of ethyl 3-tropaneacetate (Vc). The configuration of the ester was established by its conversion by Barbier-Wheland degradation to tropane-3 $\alpha$ -carboxylic acid.<sup>1</sup> Thus the reduction of esters Ic and IIc followed the same stereochemical course as that of the hydrogenation of methyl  $\Delta^2$ -tropidine-3-carboxylate.<sup>1</sup> By hydrolysis in aqueous or hydrochloric acid solutions ester Vc was converted to the corresponding acid Vb.

In contrast to 1-methyl-4-piperidone, tropinone

did not condense smoothly with ethyl cyanoacetate. The reaction mixture was complex, containing a considerable amount of polymeric material, and the unsaturated cyano ester Id could not be isolated as a crystalline salt. The condensation product was obtained in poor yield by distillation of the free base. According to infrared spectral data, the distilled base, like the corresponding product derived from 1-methyl-4-piperidone, was a mixture of isomeric unsaturated cyano esters, Id and IID.<sup>6</sup> Upon treatment with hydrogen bromide the base yielded a mixture of salts from which, by fractional crystallization, were isolated two hydrobromides, (A) m.p. 176-177° and (B) m.p. 188-189°. The infrared spectrum of salt (A) showed a strong band at 6.21  $\mu$  which was absent in the spectrum of (B), indicating that (A) was the hydrobromide of conjugated cyano ester Id and (B) was the hydrobromide of one of the diastereoisomers of unconjugated cyano ester IID.<sup>6</sup> These two isomeric esters were further characterized as their picrate salts, prepared directly from the hydrobromides. From the mother liquors of salts (A) and (B) was obtained a mixture of hydrobromides, m.p. 127-130°, which apparently consisted mainly of the salt of the second diastereoisomer of IID.<sup>6</sup> The mixture, as shown by spectral analysis, contained little or none of the conjugated ester salt (A), and it yielded a picrate which was different from that obtained from hydrobromide (B).

Better results in the condensation of tropinone with ethyl cyanoacetate were obtained when the reaction was carried out according to the simultaneous condensation-reduction procedure of Alexander and Cope<sup>7</sup> to yield directly the saturated cyano ester Va. However, the tropinone reaction required more strenuous conditions than those usually employed in condensation-reduction reactions of other ketones.<sup>7</sup> Whereas 1-methyl-4-piperidone reacted smoothly with ethyl cyanoacetate under mild conditions to yield ethyl (1-methyl-4-piperidyl)cyanoacetate, tropinone reacted at an appreciable rate only at 50-60° in the presence of a large amount of ammonium acetate.

In initial experiments, in which equimolar quantities of tropinone and ethyl cyanoacetate were used, complex mixtures were obtained from which cyano ester Va was isolated in variable

(6) Although the bridge-head carbon atoms of the tropane molecule are asymmetric, 3-substituted derivatives such as tropinone and the tropanols are optically inactive since they possess a plane of symmetry. However, most of the unsaturated 3-substituted derivatives I and II, including cyano ester Id, do not possess a plane of symmetry and therefore exist as *d* and *l* forms. In the molecule of unsaturated cyano ester IID, the carbon atom bearing the cyano and ester groups, as well as the unsaturated tropane ring, is asymmetric and consequently this ester exists as two diastereoisomers (two *dl* pairs).

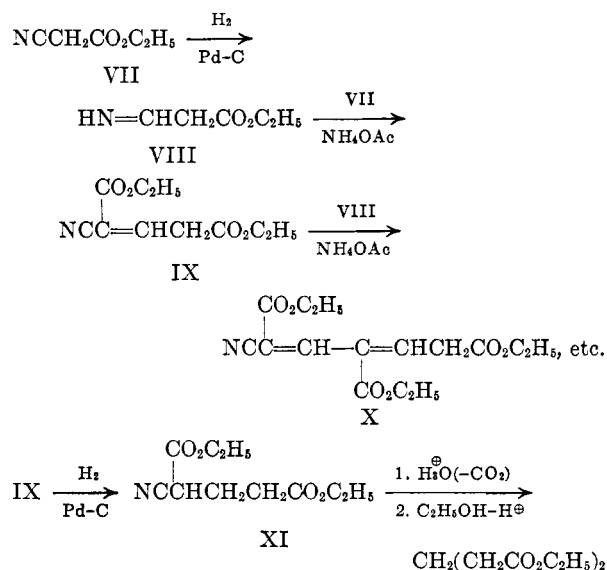
(7) E. R. Alexander and A. C. Cope, *J. Am. Chem. Soc.*, 66, 886 (1944).

(4) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, 63, 3452 (1941).

(5) S. M. McElvain and R. E. Lyle, Jr., *J. Am. Chem. Soc.*, 72, 384 (1950).

yields (20–50%). The product, in some instances, was contaminated by considerable amounts of unsaturated cyano esters Id and IId. Investigation of the reaction revealed that ethyl cyanoacetate itself, under the conditions necessary for its reaction with tropinone, readily consumed hydrogen and was converted mainly to a mixture of high-boiling neutral materials distilling over a very wide temperature range. Infrared and ultraviolet spectral analysis of various fractions indicated the presence of considerable amounts of unsaturated compounds. Although no attempts were made to isolate and characterize components of the mixture, a clue to one of the processes involved in the transformation of ethyl cyanoacetate was found in the following way. The total reaction mixture from the condensation-reduction of tropinone and ethyl cyanoacetate was hydrolyzed with hydrochloric acid, and the resulting mixture of acids was esterified with ethanol. Upon fractional distillation of the neutral fraction from the esterification mixture diethyl glutarate was isolated.

A probable explanation of these results is that ethyl cyanoacetate underwent reduction to imine VIII which, in the presence of ammonium acetate, condensed with active methylene species to form IX, X, etc. Hydrogenation of the cyano diester



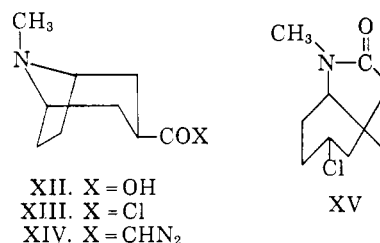
IX would lead to the corresponding saturated ester XI which, as indicated in the reaction scheme, would be the source of diethyl glutarate.

With knowledge of the side reactions of ethyl cyanoacetate occurring in the condensation-reduction reaction, it was possible to select reaction conditions for a satisfactory synthesis of the tropane cyano ester Va. When three mole equivalents of ethyl cyanoacetate were used and the reaction was allowed to proceed until hydrogen absorption ceased, the cyano ester Va, after removal of the neutral by-products, was obtained in 64% yield.

Upon acid hydrolysis and decarboxylation of Va and esterification of the resulting amino acid, ethyl (3 $\alpha$ -tropanyl)acetate (Vc), identical with the hydrogenation product of unsaturated esters Ic and IIc, was obtained.

Tropinone also did not condense smoothly with cyanoacetic acid under conditions in which cyclohexanone readily reacts to form cyclohexylidene-cyanoacetic acid.<sup>8</sup> During the reaction the intermediate unsaturated cyano acid Ie (and/or IIe) decarboxylated to form a mixture of isomeric nitriles If and IIf which, according to spectral data on the base and its salts, consisted chiefly of the conjugated isomer If.

The  $\beta$  isomer of ethyl 3-tropaneacetate (VIc) was synthesized from tropane-3 $\beta$ -carboxylic acid (XII)<sup>1</sup> by the Arndt-Eistert method.



Treatment of the hydrochloride of XII with thionyl chloride gave the salt of acid chloride XIII. Under these conditions the chloro lactam XV might form since a number of tertiary amino acid chlorides cyclize with *N*-dealkylation to form lactams.<sup>9,10</sup> Furthermore, a compound closely related to XIII, 1-methyl-4-piperidine carbonyl chloride, has been reported<sup>10</sup> to form 3-(2-chloroethyl)-2-pyrrolidone. That the chief product was XIII was shown by its conversion to the anilide of XII. However, other evidence suggested that a small amount of lactam XV was present in the reaction mixture (see Experiment part).

The acid chloride salt XIII was carried through the usual Arndt-Eistert procedure without isolation of the diazo ketone XIV. The ester obtained in this way, however, was found to be quite impure. Although it distilled over a narrow temperature range and yielded a sharply melting picrate of ethyl (3 $\beta$ -tropanyl)acetate (VIc), it formed, upon treatment with phenyllithium, not only the expected product, 1,1-diphenyl-2-(3 $\beta$ -tropanyl)ethanol, but also a considerable amount of the lower homolog, diphenyl-3 $\beta$ -tropanylcarbinol.<sup>2</sup> Thus the ester product was a mixture of VIc and either the methyl or ethyl ester of the starting acid XII.

Finally, the  $\alpha$ -isomer of 3-(3-tropanyl)propionic acid (Vg) and its ethyl ester Vh were easily ob-

(8) A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, *Org. Syntheses*, **31**, 25 (1951).

(9) J. H. Gardner, N. R. Easton, and J. R. Stevens, *J. Am. Chem. Soc.*, **70**, 2906 (1948).

(10) R. L. Clarke, A. Mooradian, P. Lucas, and T. J. Slauson, *J. Am. Chem. Soc.*, **71**, 2821 (1949).

tained in good yield from ethyl (3 $\alpha$ -tropanyl)-acetate (Vc) *via* intermediates Vd-Vf. This route, although longer, was more satisfactory than the Arndt-Eistert procedure applied to acid Vb which, as in the case described above, gave an impure ester product.

#### EXPERIMENTAL<sup>11,12</sup>

**3-Dicyanomethylenetropane hydrochloride (Ia).** A mixture of 12.0 g. (0.156 mole) of freshly distilled malononitrile and 240 ml. of benzene was stirred and refluxed under a water separator. During a 10-min. period a solution of 42.0 g. (0.30 mole) of tropinone and 18 g. (0.3 mole) of acetic acid in 60 ml. of benzene was added. After an additional 5-min. reflux period the dark red mixture was cooled in an ice bath, and excess hydrogen chloride gas was introduced. The hydrochloride of I separated as a bright yellow precipitate which was collected and thoroughly triturated with ether. The mixture of product and ammonium chloride weighed 76 g. (theory = 75.6 g.). After repeated recrystallization from ethanol-ether the salt melted at 195-198°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>·HCl: C, 59.06; H, 6.31; N, 18.79. Found: C, 58.37; H, 6.33; N, 18.83.

The infrared spectrum of Ia showed peaks at 4.46  $\mu$  (CN) and 6.21  $\mu$  (conj. C=C).

The *picrate*, prepared by adding the hydrochloride to a saturated aqueous solution of picric acid, melted at 195-205°. Two recrystallizations of the salt from aqueous acetone caused little change in the melting range (197-207°).

*Anal.* Calcd. for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>·C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>: C, 49.04; H, 3.87; N, 20.19. Found: C, 49.08; H, 4.02; N, 20.20.

Treatment of the hydrochloride of I with alkali gave a thick oil which solidified on standing. The solid base showed little or no infrared absorption at 4.46 and 6.2  $\mu$  and formed a hygroscopic mixture of hydrochlorides from which a pure salt could not be isolated.

**Mixture of ethyl [3-( $\Delta^2$ -tropidene)]acetate (IIc) and 3-carbethoxymethylenetropane (Ic).** A solution of 50.0 g. of crude 3-dicyanomethylenetropane hydrochloride (containing ammonium chloride) in 300 ml. of concd. hydrochloric acid was refluxed for 12 hr. The solution was evaporated to dryness *in vacuo* and water retained by the residue was removed azeotropically with benzene. Dry ethanol (250 ml.) was added to the residue, the solution was saturated with hydrogen chloride and the mixture was stored for 3 days at room temperature. The ethanol was removed *in vacuo*, the gummy residue was dissolved in water, the solution was saturated with potassium carbonate, and the mixture was extracted thoroughly with ether. From the dried ether extracts was obtained 31.7 g. (76%) of ester, b.p. 85-93° (0.3 mm.),  $n^{20}_D$  1.4835-1.4842.

The infrared spectrum (natural film) of the product exhibited a peak at 5.75  $\mu$  (unconj. C=O), a shoulder at 5.82 (conj. C=O), and a weak band at 6.10  $\mu$  (conj. C=C), indicating that the material was a mixture of esters IIc and Ic in which the former predominated.

Treatment of the ester mixture with hydrogen bromide in ether gave a mixture of salts from which, upon recrystallization from ethyl acetate-acetone, the *hydrobromide of ethyl [3-( $\Delta^2$ -tropidene)]acetate* (IIc), m.p. 150-151°, was obtained;

(11) Microanalyses were performed by Mrs. Doris Rolston and co-workers of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories, and spectral data were obtained by Dr. Walter E. Thompson and co-workers of the same section.

(12) We are indebted to Dr. George H. Connitt of the Organic Chemistry Section, Smith Kline and French Laboratories, for the large-scale preparations of esters Va and Vc.

the infrared spectrum of the salt (mineral oil mull) showed no absorption in the 6.1- $\mu$  region.

*Anal.* Calcd. for C<sub>12</sub>H<sub>19</sub>NO<sub>2</sub>·HBr: C, 49.66; H, 6.95. Found: C, 49.34; H, 7.44.

The *picrate of ester IIc*, prepared by addition of the hydrobromide to an ethanol solution of picric acid, melted at 141-142° after recrystallization from ethanol.

*Anal.* Calcd. for C<sub>12</sub>H<sub>19</sub>NO<sub>2</sub>·C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>: C, 49.31; H, 5.06; N, 12.78. Found: C, 49.40; H, 5.42; N, 12.71.

The *methiodide of ester IIc*, recrystallized from ethanol, melted at 221-223°; its infrared spectrum (mineral oil mull) showed no absorption in the 6.1- $\mu$  region.

*Anal.* Calcd. for C<sub>13</sub>H<sub>22</sub>INO<sub>2</sub>: C, 44.46; H, 6.31. Found: C, 44.25; H, 6.75.

**Ethyl (3 $\alpha$ -tropanyl)acetate (Vc).** A. A solution of the mixture of unsaturated esters IIc and Ic (15.1 g.; 0.072 mole) in 75 ml. of alcohol was hydrogenated over Raney nickel at room temperature and an initial pressure of 60 p.s.i. The product, 13.5 g. (89%), was a colorless oil, b.p. 80-84° (0.3 mm.),  $n^{20}_D$  1.4760-1.4766. Its infrared spectrum showed characteristic carbonyl absorption at 5.75  $\mu$ .

The *picrate*, recrystallized from alcohol, melted at 141-142°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>21</sub>NO<sub>2</sub>·C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>: C, 49.09; H, 5.49; N, 12.72. Found: C, 49.33; H, 5.77; N, 12.70.

The *methobromide* melted at 257-258° after recrystallization from alcohol-ether.

*Anal.* Calcd. for C<sub>13</sub>H<sub>24</sub>BrNO<sub>2</sub>: C, 50.98; H, 7.90; N, 4.57. Found: C, 51.12; H, 7.93; N, 4.62.

B. Hydrolysis and decarboxylation of ethyl (3 $\alpha$ -tropanyl)-cyanoacetate (Va) and esterification of the resulting acid, according to the procedures described above for the preparation of the mixture of unsaturated esters IIc and Ic, gave in 74% yield an ester identical with that obtained by method A.

**3 $\alpha$ -Tropaneacetic acid (Vb).** A. A solution of 1.0 g. of ester Vc in 10 ml. of water was heated at reflux for 3 hr. Upon evaporation of the water and recrystallization of the residue from butanone, the amino acid was obtained as colorless crystals, m.p. 195-196°. The analytical sample was dried at 100° *in vacuo* and then allowed to equilibrate with air.

*Anal.* Calcd. for C<sub>10</sub>H<sub>17</sub>NO<sub>2</sub>·H<sub>2</sub>O: C, 59.68; H, 9.52. Found: C, 59.61; H, 9.78.

B. A solution of 8.5 g. (0.04 mole) of ester Vc in 50 ml. of 6 N hydrochloric acid was heated at reflux for 20 hr. Upon evaporation of the solution to dryness and recrystallization of the residue from methanol-ether, 7.9 g. (90%) of colorless crystals of the amino acid hydrochloride, m.p. 172-174°, was obtained.

*Anal.* Calcd. for C<sub>10</sub>H<sub>17</sub>NO<sub>2</sub>·HCl: C, 54.66; H, 8.26. Found: C, 54.72; H, 8.09.

**Degradation of ethyl (3 $\alpha$ -tropanyl)acetate (Vc) to methyl 3 $\alpha$ -tropanecarboxylate.** Ethyl (3 $\alpha$ -tropanyl)acetate was converted to 3 $\alpha$ -(2,2-diphenylvinyl)tropane<sup>2</sup> *via* 1,1-diphenyl-2-(3 $\alpha$ -tropanyl)ethanol.<sup>2</sup> The diphenyl olefin was oxidized with chromic acid according to the procedure of Hoehn and Mason.<sup>13</sup> After destruction of excess chromic acid, the reaction mixture was diluted with water and steam distilled to remove benzophenone. The residual solution was made strongly alkaline with concd. ammonium hydroxide, and the mixture was allowed to stand overnight. Solid material which separated was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. Water remaining in the residue of crude tropanecarboxylic acid was removed azeotropically with benzene. Esterification of the crude acid with methanol by the Fischer method gave an ester identical in all respects with an authentic sample of methyl 3 $\alpha$ -tropanecarboxylate.<sup>1</sup>

**Mixture of 3-( $\alpha$ -carbethoxyl- $\alpha$ -cyano)methylene tropane (Id) and ethyl [3-( $\Delta^2$ -tropidine)]cyanoacetate (IIId).** A mixture of

(13) W. M. Hoehn and H. L. Mason, *J. Am. Chem. Soc.*, 60, 1493 (1938).

30.6 g. (0.22 mole) of tropinone, 64.5 g. (0.44 mole) of ethyl cyanoacetate, 10.2 ml. of acetic acid, and 100 ml. of benzene was heated at reflux under a water separator. After 1 hr., 6.4 ml. of aqueous layer was collected in the separator (the theoretical amount of water was 4 ml.). The cooled reaction mixture was extracted with dilute hydrochloric acid, the acid solution was neutralized with 40% sodium hydroxide and saturated with potassium carbonate, and the resulting mixture was extracted thoroughly with ether. From the dried ether extracts was obtained 38 g. of dark oil, containing a large amount of polymeric material, which upon distillation yielded 13.4 g. (26%) of product, b.p. 105–120° (0.5 mm.). Redistillation of the material gave a yellow oil, b.p. 105–120° (0.3–0.7 mm.),  $n_D^{20}$  1.5039, which rapidly changed to a dark red liquid showing green fluorescence.

The infrared spectrum (natural film) of the product exhibited peaks at 4.43  $\mu$  (unconj. CN), 4.49  $\mu$  (conj. CN), 5.75  $\mu$  (ester), and 6.3  $\mu$  (conj. C=C), indicating that the cyano ester was a mixture of isomers Id and IId. The spectrum (mineral oil mull) of the hydrochloride of ethyl (1-methyl-4-piperidylidene)cianoacetate<sup>5</sup> showed bands at 4.47, 5.75, and 6.2  $\mu$ .

Attempts to isolate solid mineral acid salts of the cyano esters from the condensation reaction mixture were unsuccessful, but the distilled product yielded a mixture of crystalline hydrobromide salts. One salt (B), insoluble in hot acetone, melted at 188–189° after recrystallization from ethanol. The absence of a band in the 6.2- $\mu$  region of its spectrum (mineral oil mull) indicated that this salt was the hydrobromide of one of the diastereoisomers of unconjugated cyano ester IId. Addition of salt B to a saturated solution of picric acid in ethanol gave a picrate which, after recrystallization from acetone, melted at 178–179°.

*Anal.* Calcd. for  $C_{13}H_{18}N_2O_2 \cdot C_6H_3N_3O_7$ : C, 49.24; 4.57; N, 15.11. Found: C, 49.21; H, 4.32; N, 15.32.

From the acetone filtrate of salt B was obtained a second hydrobromide (A) which, after recrystallization first from acetone and then from ethanol, melted at 176–177°. The presence of a strong band at 6.21  $\mu$  in the spectrum of salt A (mineral oil mull) indicated that it was the hydrobromide of conjugated cyano ester Id.

*Anal.* Calcd. for  $C_{13}H_{18}N_2O_2 \cdot HBr$ : C, 49.53; H, 6.08. Found: C, 49.22; H, 6.09.

The picrate of Id, prepared from the hydrobromide and recrystallized from ethanol–acetone, melted at 199–200°.

*Anal.* Calcd. for  $C_{13}H_{18}N_2O_2 \cdot C_6H_3N_3O_7$ : C, 49.24; H, 4.57. Found: C, 49.20; H, 4.59.

From the acetone mother liquor from hydrobromide A was obtained a mixture of salts which melted at 127–130° after two recrystallizations from ethyl acetate–acetone. According to the spectrum of the mixture (mineral oil mull) (no band at 6.2  $\mu$ ), it was chiefly a mixture of hydrobromide B and the salt of the other diastereoisomer of unconjugated cyano ester IId in which the latter predominated.

*Anal.* Calcd. for  $C_{13}H_{18}N_2O_2 \cdot HBr$ : C, 49.53; 6.08. Found: C, 49.48; H, 6.34.

From the mixture of hydrobromides, m.p. 127–130°, was obtained a picrate which, after several recrystallizations from ethanol–acetone, melted at 177–178°.

*Anal.* Calcd. for  $C_{13}H_{18}N_2O_2 \cdot C_6H_3N_3O_7$ : C, 49.24; 4.57; N, 15.11. Found: C, 49.15; H, 4.99; N, 14.99.

A mixture of this picrate and that obtained from hydrobromide B (m.p. 178–179°) melted at 166–173°.

To determine whether the unsaturated cyano esters decomposed to an appreciable extent during their isolation, the total acid-soluble fraction from a second run of the condensation-reduction reaction was immediately converted to the mixture of unsaturated esters IIc and Ic by the methods described above for their preparation from the dinitrile Ia. The yield of the mixture of IIc and Ic was only 16% which is consistent with the 26% yield of isolated unsaturated cyano esters.

*Ethyl (3 $\alpha$ -tropanyl)cianoacetate (Va).* A mixture of 13.9 g. (0.10 mole) of tropinone, 12.4 g. (0.11 mole) of ethyl cyanoacetate, 2.4 g. of ammonium acetate, 10.8 g. (0.18 mole) of acetic acid, 20 ml. of dry ethanol, and 0.4 g. of Hartung's palladium-charcoal catalyst<sup>14</sup> was shaken under hydrogen at an initial pressure of 60 p.s.i. No hydrogen absorption occurred within 1 hr. either at room temperature or at 35°. After the temperature was raised to 50–60° approximately the theoretical amount of hydrogen was absorbed within 3 hr. The solution, after removal of the catalyst, was evaporated *in vacuo*. The amber oil remaining was dissolved in dilute hydrochloric acid, and the solution was neutralized and saturated with potassium carbonate and the resulting mixture was extracted thoroughly with ether. Distillation of the residue from the dried ether extracts gave 10.4 g. (44%) of pale yellow oil b.p. 114–118° (0.3 mm.),  $n_D^{20}$  1.4942.

The *picrate*, after three recrystallizations from alcohol–acetone, melted at 179–180°.

*Anal.* Calcd. for  $C_{13}H_{20}N_2O_2 \cdot C_6H_3N_3O_7$ : C, 49.03; H, 4.98; N, 15.05. Found: C, 49.08; H, 5.32; N, 15.10.

In other runs of the condensation-reduction, carried out under essentially the same conditions described above, yields varied from 20–50% and the products, as shown by infrared spectral analysis, contained considerable amounts of unsaturated cyano ester Id.

Consistent yields and a better quality product were obtained when the reaction was carried out in the following way. A mixture of 13.9 g. (0.10 mole) of tropinone, 33.9 g. (0.30 mole) of ethyl cyanoacetate, 1.9 g. of ammonium acetate, 25 ml. of acetic acid, 25 ml. of dry ethanol, and 0.7 g. palladium-charcoal catalyst was hydrogenated at 50–60° and an initial pressure of 60 p.s.i. until hydrogen uptake ceased. During the 6-hr. reaction period 2.2 mole eq. of hydrogen was absorbed. Upon working up the reaction mixture in the way described above, 15.3 g. (64%) of cyano ester was obtained; b.p. 128–137° (0.6–0.7 mm.),  $n_D^{20}$  1.4840.

*Ethyl (1-methyl-4-piperidyl)cianoacetate.* The condensation reduction of 1-methyl-4-piperidone (11.3 g.; 0.10 mole) was conducted under the first set of conditions described above. Hydrogenation proceeded smoothly at 36–38° and was complete (95% of theory) after 2.5 hr. The product, 17.2 g. (82%), was a pale yellow oil, b.p. 123–127° (1.7 mm.),  $n_D^{20}$  1.4651.

The *picrate*, recrystallized from ethanol, melted at 174–175°.

*Anal.* Calcd. for  $C_{11}H_{18}N_2O_2 \cdot C_6H_3N_3O_7$ : C, 46.47; H, 4.83. Found: C, 46.29; H, 4.83.

*Hydrogenation of ethyl cyanoacetate in the presence of ammonium acetate.* A mixture of 51.5 g. (0.45 mole) of ethyl cyanoacetate, 7.6 g. of ammonium acetate, 100 ml. of acetic acid, 85 ml. of dry ethanol, and 1.9 g. of palladium-charcoal catalyst<sup>14</sup> was hydrogenated at 50–55° under an initial pressure of 60 p.s.i. Hydrogen uptake ceased after about 10 hr.; 0.7 mole of hydrogen was absorbed. The reaction mixture, after removal of catalyst and ethanol, was taken up in ether, and the solution was washed first with several portions of dilute hydrochloric acid, then with 10% sodium hydroxide and finally with water. From the dried ether solution was obtained 33 g. of neutral yellow oil which distilled over a range of 90–235° (0.6–1.0 mm.). The infrared spectra of various fractions showed strong absorption throughout the 5.7–6.2- $\mu$  region, with peaks at 5.75 and 6.05  $\mu$ . The ultraviolet spectrum of a fraction boiling at 90–99° (0.6 mm.) showed a peak at 242  $m\mu$  and that of a fraction boiling 230–235° (mm.) showed a peak of 320  $m\mu$ . Intermediate fractions exhibited a peak at 275  $m\mu$  in addition to these peaks.

*Isolation of diethyl glutarate from the products of hydrolysis of the total mixture resulting from the condensation-reduction of*

(14) Footnote 7 in ref. 7.

*tropinone with ethyl cyanoacetate.* The reaction mixtures from several large-scale condensation-reduction experiments were pooled, and the solvent was removed *in vacuo*. The residue was dissolved in concd. hydrochloric acid, and the solution was evaporated to dryness. The mixture remaining was added to a large volume of concd. hydrochloric acid and the resulting solution was heated at reflux overnight. The hydrolysis solution was evaporated, and the residual mixture, after thorough drying, was esterified with ethanol by the Fischer method. After removal of the ethanol *in vacuo*, the esterification mixture was partitioned between ether and water to separate neutral material from the hydrochlorides of ethyl (3 $\alpha$ -tropanyl)acetate (Vc) and other basic materials. The ether extract was washed with sodium bicarbonate solution and dried over sodium sulfate. After removal of ether, the residual neutral material was fractionated through a  $\frac{3}{4}$  in.  $\times$  5 ft. spinning band column to give, among other fractions, 10 g. of colorless liquid distilling at 128–136° (29 mm.). Upon refractionation of the liquid, 5.4 g. of diethyl glutarate was obtained; b.p. 129–130° (29 mm.) [lit.,<sup>15</sup> b.p. 103–104° (7 mm.)];  $n_D^{20}$  1.4248 (lit.,<sup>15</sup>  $n_D^{20}$  1.4241). The infrared spectrum of the ester product was identical with that of diethyl glutarate, and the product formed a dihydrazide, m.p. 178–179° (lit.,<sup>16</sup> m.p. 176°), identical with a sample prepared from authentic ester.

*3-Cyanomethylenetropane (If).* A mixture of 30.0 g. (0.216 mole) of tropinone, 20.4 g. (0.24 mole) of cyanoacetic acid, 0.9 g. of ammonium acetate, and 30 ml. of benzene was heated at reflux (bath temp. 150–155°) under a water separator. After about 30 min. the solid material gradually liquified, carbon dioxide was rapidly evolved, and water collected in the separator. The mixture was heated until no more water separated (1 hr.). The reaction mixture was extracted with dilute hydrochloric acid, the acid extracts were neutralized with sodium hydroxide and saturated with potassium carbonate, and the resulting mixture was extracted thoroughly with ether. From the dried ether extracts was obtained 8.7 g. (25%) of yellow oil, b.p. 67–77° (0.1 mm.),  $n_D^{20}$  1.5212–1.5222.

The infrared spectra of the base (natural film) and its methiodide and hydriodide salts (mineral oil mulls) showed strong absorption peaks at 4.45  $\mu$  (CN) and 6.10  $\mu$  (conj. C=C). The ultraviolet spectrum of the hydriodide (water solution) exhibited a maximum at 222 m $\mu$  ( $\epsilon$  18,100).

The *methiodide*, recrystallized from ethanol, melted at 217–218°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>17</sub>IN<sub>2</sub>: C, 43.43; H, 5.63. Found: C, 43.09; H, 5.82.

The *hydriodide*, after recrystallization from acetonitrile-ether, melted at 201°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>·HI: C, 41.40; H, 5.21. Found: C, 41.55; H, 5.21.

The *picrate*, prepared from both the base and the hydriodide salt, melted at 173–174° after recrystallization from ethanol-water.

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>·C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>: C, 49.11; H, 4.38. Found: C, 49.02; H, 4.35.

*Ethyl (3 $\beta$ -tropanyl)acetate (VIc).* A mixture of 15.5 g. (0.075 mole) of 3 $\beta$ -tropanecarboxylic acid hydrochloride,<sup>1</sup> 23.3 g. (0.2 mole) of thionyl chloride, and 175 ml. of chloroform was heated at reflux for 2.5 hr. The solution was evaporated to dryness *in vacuo*, benzene was added to the residue, and the solvent was evaporated *in vacuo* to remove traces of thionyl chloride. The crude amino acid chloride hydrochloride was a tan solid. A sample (1.0 g., 0.0045 mole) was added to excess aniline and the mixture was heated on a steam bath for a few minutes. The cooled solution was stirred with ether, and the insoluble product was collected

on a filter. Upon recrystallization of the solid from ethanol, 0.83 g. (66%) of 3 $\beta$ -tropanecarboxanilide hydrochloride was obtained as colorless crystals, m.p. 258°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O·HCl: C, 64.16; H, 7.54; N, 9.98. Found: C, 64.02; H, 7.64; N, 10.07.

The remainder of the crude acid chloride hydrochloride (ca. 0.07 mole), suspended in 250 ml. of methylene chloride was added over a 10–15-min. period to a solution of diazomethane in methylene chloride maintained at –10°. (The diazomethane solution was prepared in the usual way by adding 112 g. (0.72 mole) of *N*-methyl-*N*-nitroso-*N'*-nitroguanidine to a stirred mixture of 240 ml. of 50% potassium hydroxide solution and 1200 ml. of methylene chloride.) The mixture was kept at –10° for 1 hr. and then was allowed to stand at room temperature for 2 hr. Some solid material was removed by filtration, and the filtrate was evaporated to give 13.2 g. of crude diazoketone as a thick orange-brown oil. The oil was dissolved in 115 ml. of dry ethanol, silver oxide (prepared from 3 g. of silver nitrate) was added and the mixture was heated at 55–60° until evolution of nitrogen ceased (30 min.). Inorganic material was removed by filtration and the filtrate was evaporated to yield 10.7 g. of brown semisolid material. The latter was added to a saturated solution of potassium carbonate and the mixture, which contained a considerable amount of brown gum, was extracted with ether. From the dried ether extracts was obtained 5.1 g. of oil which was distilled *in vacuo*. The distillate was collected in 3 fractions: (1) 2.7 g., b.p. 62–64° (0.1–0.15 mm.),  $n_D^{20}$  1.4740; (2) 0.42 g., b.p. 69–99° (0.15 mm.),  $n_D^{20}$  1.4800; (3) 0.65 g., b.p. 99–105° (0.15 mm.),  $n_D^{20}$  1.4998.

The infrared spectrum of fraction (1) showed a carbonyl band at 5.75  $\mu$  and the material readily formed a crystalline picrate, m.p. 158–160°. After two recrystallizations from acetone-ethanol the *picrate* of ethyl (3 $\beta$ -tropanyl)acetate had a constant m.p. of 161–162°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>21</sub>NO<sub>2</sub>·C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>: C, 49.09; H, 5.49; N, 12.72. Found: C, 49.29; H, 5.82; N, 12.83.

Treatment of fraction (1) with phenyllithium<sup>2</sup> gave a mixture of 1,1-diphenyl-2-(3 $\beta$ -tropanyl)ethanol and diphenyl-3 $\beta$ -tropanylcarbinol,<sup>2</sup> indicating that fraction (1) was a mixture of ethyl (3 $\beta$ -tropanyl)acetate and either methyl or ethyl 3 $\beta$ -tropanecarboxylate.

Fraction (3) gave a positive Beilstein test for halogen and its infrared spectrum (natural film) exhibited a strong band at 5.86  $\mu$  and a weaker one at 5.75  $\mu$ . These data indicated that fraction (3) was a mixture of ester VIc and a second carbonyl-containing component in which the latter predominated. To remove the amino ester the mixture was allowed to stand overnight in a large excess of methyl iodide. The methyl iodide was evaporated and the residue was extracted with ether to separate the neutral material from insoluble quaternary salt. Short-path distillation of the ether soluble fraction at 0.025 mm. (bath temp. 75°) gave a hygroscopic, colorless oil. The oil gave a positive Beilstein test and its spectrum exhibited a broad band at 2.85–2.95  $\mu$  (water) and a single, strong carbonyl band at 5.86  $\mu$ . Due to the presence of water in the sample, analysis gave inconclusive results. However, the data cited above suggest that the oil was the *chloro lactam* XV.

*Anal.* Calcd. for C<sub>10</sub>H<sub>16</sub>ClNO· $\frac{1}{2}$ H<sub>2</sub>O: C, 56.99; H, 8.13; N, 6.65. Found: C, 56.19; H, 7.75; N, 6.77.

*2-(3 $\alpha$ -Tropanyl)ethanol (Vd).* To a stirred mixture of 30.0 g. (0.79 mole) of lithium aluminum hydride and 2 l. of ether was added a solution of 164 g. (0.78 mole) of ethyl (3 $\alpha$ -tropanyl)acetate (Vc) in 500 ml. of ether at such a rate that steady reflux of solvent was maintained. The reaction mixture was heated at reflux for 3 hr., cooled in an ice bath, and hydrolyzed by addition of 72 ml. (4.0 moles) of water. The resulting mixture was filtered, and the inorganic solid was washed thoroughly with ether. From the combined filtrates, dried over magnesium sulfate, was obtained 123 g. (94%) of colorless solid, m.p. 56–59°. After two recrystal-

(15) I. Heilbron and H. M. Bunbury, eds., "Dictionary of Organic Compounds," Vol. 2, Oxford University Press, New York, 1953, p. 606.

(16) R. F. Paschke and D. H. Wheeler, *J. Am. Oil Chemists' Soc.*, **26**, 637 (1949).

lizations from benzene-petroleum ether (b.p. 30–60°) the product melted at 63–64°.

*Anal.* Calcd. for  $C_{10}H_{19}NO$ : C, 70.96; H, 11.31; N, 8.28. Found: C, 70.73; H, 11.12; N, 8.39.

The *picrate*, recrystallized from acetone-ether, melted at 125–126°.

*Anal.* Calcd. for  $C_{10}H_{19}NO \cdot C_6H_3N_3O_7$ : C, 48.24; H, 5.57; N, 14.07. Found: C, 48.16; H, 5.82; N, 13.79.

*3 $\alpha$ -(2-Chloroethyl)tropane* (Ve). A solution of 39.0 g. (0.23 mole) of 2-(3 $\alpha$ -tropanyl)ethanol in 150 ml. of chloroform was saturated with hydrogen chloride. To the mixture with stirring was gradually added 33 ml. of thionyl chloride. The resulting clear solution was heated at reflux for 1 hr. and then evaporated to dryness *in vacuo*. The residual tan solid was dissolved in a minimum volume of water, the solution was made strongly basic with sodium hydroxide, and the alkaline mixture was extracted with four portions of ether. From the ether extracts, dried over potassium carbonate, was obtained 39.5 g. (92%) of chloro amine as a colorless liquid, b.p. 75–80° (0.6–0.8 mm.).

The *hydrochloride*, recrystallized from ethanol-ether, melted at 167–168°.

*Anal.* Calcd. for  $C_{10}H_{19}NCl$ : C, 53.57; H, 8.54; N, 6.25. Found: C, 53.73; H, 8.40; N, 6.18.

The *picrate*, recrystallized from water, melted at 159–160°.

*Anal.* Calcd. for  $C_{10}H_{19}NCl \cdot C_6H_3N_3O_7$ : C, 46.10; H, 5.08. Found: C, 46.25; H, 4.93.

*3-(3 $\alpha$ -Tropanyl)propionitrile* (Vf). A solution of 47.0 g. (0.25 mole) of 3 $\alpha$ -(2-chloroethyl)tropane, 48.5 g. (0.75 mole) of potassium cyanide, and 0.1 g. of sodium iodide in 250 ml. of alcohol-water (3:1) was heated at reflux for 17 hr. The reaction mixture was evaporated *in vacuo*, the residue was dissolved in water, the solution was made strongly alkaline with sodium hydroxide, and the mixture was ex-

tracted with several portions of ether. From the dried ether extracts was obtained 38.8 g. (87%) of almost colorless oil, b.p. 114–116° (0.3 mm.),  $n_D^{20}$  1.4960.

The *picrate*, recrystallized from acetone-ether, melted at 150–151°.

*Anal.* Calcd. for  $C_{11}H_{18}N_2 \cdot C_6H_3N_3O_7$ : C, 50.12; H, 5.20; N, 17.19. Found: C, 49.99; H, 4.96; N, 17.15.

*Ethyl 3-(3 $\alpha$ -tropanyl)propionate* (Vh). A solution of 25 g. (0.14 mole) of nitrile Vf in 100 ml. of concd. hydrochloric acid was heated at reflux for 7 hr. The cooled mixture was filtered to remove ammonium chloride (3.1 g.), and the filtrate was evaporated to dryness. The residue, from which traces of water were removed by azeotropic distillation with benzene, was dissolved in 300 ml. of dry ethanol, 5 ml. of concd. sulfuric acid was added, and the solution was heated at reflux for 6 hr. Upon working up the mixture in the usual way, 25.0 g. (80%) of ester was obtained as a colorless oil, b.p. 97–100° (0.4 mm.),  $n_D^{20}$  1.4771.

*Anal.* Calcd. for  $C_{13}H_{23}NO_2$ : C, 69.29; H, 10.27; N, 6.22. Found: C, 68.76; H, 10.09; N, 6.13.

The *picrate*, recrystallized from 2-propanol, melted at 108–109°.

*Anal.* Calcd. for  $C_{13}H_{23}NO_2 \cdot C_6H_3N_3O_7$ : C, 50.21; H, 5.77. Found: C, 50.21; H, 5.48.

*3-(3 $\alpha$ -Tropanyl)propionic acid hydrochloride* (Vg). A solution of 4.7 g. of ester Vh in 25 ml. of concd. hydrochloric acid was heated at reflux for 3 hr. Upon evaporation of the solution *in vacuo* and recrystallization of the residue from methanol-ether, 3.1 g. of amino acid hydrochloride was obtained as colorless crystals, m.p. 194–195°.

*Anal.* Calcd. for  $C_{11}H_{19}NO_2 \cdot HCl$ : C, 56.52; H, 8.63; N, 5.99. Found: C, 56.36; H, 8.25; N, 5.94.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEFENSE ACADEMY]

## Solvent-Catalyzed Michael Reaction of Derivatives of Malonic and Cyanoacetic Acids with Acrylic Acid Derivatives in Liquid Ammonia

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Acrylonitrile or ethyl acrylate can react with ethyl malonate and cyanoacetamide and their monoalkyl derivatives in liquid ammonia to yield the corresponding Michael condensation products without the use of catalysts. This Michael reaction is characterized by a catalytic action of the solvent, presumably *via* formation of the carbanion of the active methylene compound. An attempted reaction with acrylamide was unsuccessful under the same conditions. Nineteen new compounds have been prepared in the course of the present work.

In our previous paper,<sup>1</sup> a new modification of the Michael reaction was reported, wherein derivatives of acetamidomalonic or acetamidocyanoacetic acid were condensed with acrylonitrile, ethyl acrylate, and acrylamide in liquid ammonia without additional catalysts. The reaction was probably due to the basic character of liquid ammonia in contrast with the common organic solvents usually employed.

The present study was concerned with an extension of the new modification to the esters and amides of malonic and cyanoacetic acids and to their monoalkyl derivatives.<sup>2</sup> We have found that

acrylonitrile can condense with ethyl malonate, cyanoacetamide, and their monoalkyl derivatives in liquid ammonia to form mono- and dicyano-ethylation products in which the hydrogens of the methinyl or methylene groups have reacted. Even with limited amounts of acrylonitrile both ethyl malonate and cyanoacetamide gave exclusively dicyanoethylation products. With the less reactive ethyl acrylate as the acceptor, ethyl malonate formed only a low yield of monocarbethoxyethyla-

(1) K. Shimo and S. Wakamatsu, *J. Org. Chem.*, **26**, 3788 (1961).

(2) Among these, the ester of cyanoacetic acid and its monoalkyl derivatives were quite unstable in liquid ammonia and were spontaneously converted to the corresponding amides, so they have not been used as starting materials in the present work.