to give 42.0 g. of 11-ketoprogesterone, m.p. 167–171°. Infrared analysis and papergram analysis showed this material to be 11-ketoprogesterone of greater than 90% purity.

11β-Hydroxy-5-pregnene-3,20-dione 3,20-Bis-(ethylene ketal) (III).—Ten grams (24 millimoles) of 5-pregnene-3,11,-20-trione 3,20-bis-(ethylene ketal) (II) in 500 ml. of anhydrous ether was added to 10 g. of lithium aluminum hydride partially dissolved in 800 ml. of anhydrous ether. After stirring at 26° for 45 minutes and heating under reflux for one hour, water was added until a thick white precipitate was formed. The ether was decanted. The precipitate was washed with ether. Evaporation of the solvent gave crude III which after crystallization from 2-propanol weighed 6.5 g. (60.5% yield), m.p. 137–140°. Two recrystallizations from 2-propanol gave an analytical sample, m.p. 138–140°, $[\alpha]_D$ −23° (chloroform).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.71, 71.53; H, 9.03, 9.29.

11β-Hydroxy-4-pregnene-3,20-dione (11β-Hydroxyprogesterone) (IV). (a) **From Diketal III.**—Two grams (4.8 millimoles) of crude ketal III, m.p. 165–170°, was dissolved in 75 ml. of acetone and 25 ml. of water containing 1 ml. of concentrated sulfuric acid. After heating under reflux for 50 minutes the acid was neutralized and 75% of the acetone distilled under vacuum. Dilution of the residue with water gave 1.42 g. (89.9% yield) of crystals, m.p. 165–173°. Papergram analysis using a propylene glycol–toluene system[6] showed the presence of about 5–10% of 11α-hydroxyprogesterone. Several recrystallizations from acetone–ether gave 0.50 g., m.p. 186–188°, $[\alpha]_D$ +212° (acetone). Reichstein and Fuchs reported m.p. 187–188°, $[\alpha]^{17}_D$ +222.2 ± 4° (acetone).[4]

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.37. Found: C, 76.50, 76.44; H, 9.48, 9.07.

Oxidation of 11β-hydroxyprogesterone with chromic acid gave 98% yield of 11-ketoprogesterone, m.p. 171–174°, which when recrystallized melted 172.5–173°. This material was identical with a known sample of 11-ketoprogesterone.

(b) **From Diketal II.**—To a partial solution of 9 g. of lithium aluminum hydride in 2.8 l. of anhydrous ether there was added a solution of 50 g. (0.12 mole) of 5-pregnene-3,11,20-trione 3,20-bis-(ethylene ketal) (II), m.p. 170–176°, in 0.8 l. of benzene. After stirring at 26° for one hour and heating under reflux for one hour, a solution of 0.6 l. of concentrated hydrochloric acid and 0.6 l. of water was added to the cooled solution. The mixture was stirred at 26° for 16 hours. The crystals which formed were recovered by filtration. They weighed 17.0 g. (43.0% yield), m.p. 178–182°. After refrigeration of the ether solution for 8 hours a second crop of crystals, m.p. 182–185°, was obtained (8.0 g., 20.2% yield). The ether solution was concentrated to give an additional 11.2 g. (28.4% yield) of crystals, m.p. 174–177°. Recrystallization of this material from methylene dichloride–Skellysolve B gave 9.35 g., m.p. 178–181° (23.6% yield). The over-all yield of 11β-hydroxyprogesterone from II is therefore 86.8%.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FLORIDA STATE UNIVERSITY]

Sodium Hydride as a Condensing Agent with Acylaminomalonates in the Synthesis of Amino Acids[1,2]

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Sodium hydride in inert solvents has been employed in the synthesis of α-amino acids to effect the condensation between alkyl halides and diethyl formamidomalonate, diethyl acetamidomalonate and ethyl acetamidocyanoacetate. The use of toluene or benzene as solvent readily permits the removal of traces of water from the solvents, reagents, or apparatus by azeotropic distillation. This procedure has been found to be more convenient than the use of sodium ethoxide in absolute ethanol under conditions where high humidity is a problem. The liberation of hydrogen indicates whether the condensation has started and its progress. When dimethylformamide is used as the solvent, a solution of the sodium salt of diethyl formamidomalonate is readily obtained and permits the condensation with isopropyl bromide.

The use of specially dried ethanol in condensations between acyl derivatives of diethyl aminomalonate and primary or secondary halides in ethanolic sodium ethoxide has often been stressed.[3] Yields are drastically lowered or become nonexistent when traces of water are present in the reagents. Sodium in *t*-butyl alcohol can be used to advantage but when xylene or dioxane were used as solvents, tarry by-products and decreased yields resulted.[4] Sodium in refluxing toluene has been reported to effect the condensation between diethyl formamidomalonate and benzhydryl bromide in 25% yield accompanied by considerable coupling of the halide.[5]

Sodium hydride has been shown to have no effect on a wide variety of alkyl halides in an inert solvent even at elevated temperatures and after prolonged exposure.[6] It can also be used to effect a number of condensations with active methylenic compounds.[7]

In this paper is reported the use of sodium hydride in the condensation between various alkyl bromides or chlorides and diethylformamidomalonate (I), diethyl acetamidomalonate (II) and ethyl acetamidocyanoacetate (III). The reaction involves refluxing an equimolar mixture of the halide and amide with a slight excess of sodium hydride in a solvent such as toluene until the evolution of hydrogen has ceased, usually a few hours (Fig. 1).

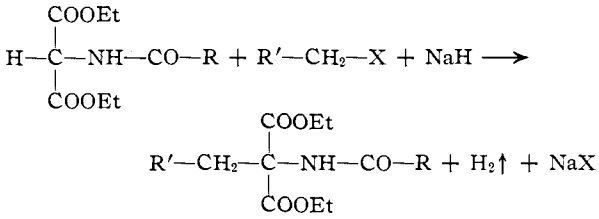

Fig. 1.

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(2) This work was supported in part by a research contract with the Office of Naval Research, Research Grant 2714 from U. S. Public Health Services, and a Parke, Davis and Company Research Grant.

(3) N. F. Albertson, THIS JOURNAL, **68**, 450 (1946); E. P. Painter, *ibid.*, **62**, 232 (1940); C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

(4) D. Goldsmith and M. Tishler, THIS JOURNAL, **68**, 144 (1946).

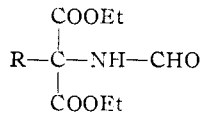
(5) Z. J. Vejdelek and M. Protiva, *Chem. Listy*, **45**, 44 (1951).

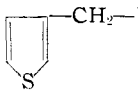
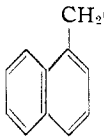
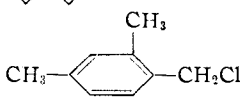
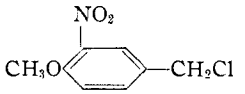
(6) S. J. Cristol, J. W. Ragsdale and J. S. Meek, THIS JOURNAL, **71**, 1863 (1949).

(7) V. J. Hansley and P. J. Carlisle, *Chem. Eng. News*, **23**, 1332 (1945); F. W. Swamer and C. R. Hauser, THIS JOURNAL, **72**, 1352 (1950); N. Green and L. B. LaForge, *ibid.*, **70**, 2287 (1948); G. H. Daub and W. S. Johnson, *ibid.*, **72**, 501 (1950).

TABLE I

CONDENSATION PRODUCTS OBTAINED FROM VARIOUS ORGANIC HALIDES AND DIETHYL FORMAMIDOMALONATE IN THE PRESENCE OF SODIUM HYDRIDE IN TOLUENE



Halide	Yield, %	M.p., °C.[a]	Formula	Analyses,[b] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$HC{\equiv}C{-}CH_2Br$	81.5[c]	74.4–75.0					
$H_2C{=}C(Cl){-}CH_2Cl$	83	70.0–71.2	$C_{11}H_{16}NO_5Cl$	47.6	47.8	5.8	5.5
$H_2C{=}C(Br){-}CH_2Br$	81	78.5–79.2[13]	$C_{11}H_{16}NO_5Br$				
	80[d]	99.0–100.0	$C_{13}H_{17}NO_5S$	52.2	52.6	5.7	5.8
	96	118–121.0	$C_{19}H_{21}NO_5$	66.5	66.3	6.2	5.9
	89	89–90	$C_{17}H_{23}NO_5$	63.5	63.8	7.2	7.2
	80	154.5–156.5	$C_{17}H_{20}N_2O_8$	52.2	52.5	5.5	5.3

[a] All melting points were determined in capillary tubes and are corrected. [b] All analyses were performed by Clark Microanalytical Laboratory, Urbana, Illinois. [c] Benzene, not toluene, used as the solvent. Reported[8] m.p. was 71–72° (uncor.). [d] Other solvents and yields were: benzene (80%) and dimethylformamide by procedure given for isopropyl bromide (93%). When II in toluene was condensed, the yield was 85%.

The liberation of hydrogen during the reaction afforded an elegant indication of whether the reaction was proceeding and when it had been completed. The procedure has been successfully used in the synthesis of amino acid analogs; Table I shows the intermediates obtained and used in these syntheses. Diethyl propargylformamidomalonate[8] and diethyl 3-thenylacetamidomalonate[9,10] were obtained here consistently in yields comparable to those obtained with sodium in absolute ethanol when it was successful and much better than many attempts in ethanol which failed.

The sodium hydride condensation procedure lends itself to a number of modifications which permit reactions with less reactive or more sensitive halides. When the reaction was slow in starting, as observed by the lack of hydrogen evolution during the first 15 minutes, the addition of catalytic amounts of an alcohol, usually *t*-butyl alcohol, accelerated the reaction. When the rate of reaction was slow in refluxing benzene, which was preferred as a solvent for sensitive compounds, toluene could be used, or even xylene, but the latter generally led to less pure products. Condensations of bromomethylthiophene with III gave an oil which did not crystallize but which could be hydrolyzed to the amino acid in approximately 50% over-all yield.

Neither isopropyl bromide nor cyclohexyl bromide could be condensed with I by any of these modifications, nor in the absence of solvent. A modification using dimethylformamide[11] gave the condensate between isopropyl bromide and I. When I was added to a suspension of sodium hydride in dimethylformamide, hydrogen was liberated and the sodium salt of I remained in solution. The filtered solution was refluxed for two hours with isopropyl bromide to give a 50% yield of diethyl isopropylformamidomalonate. This seems to be superior to other methods of condensation of the isopropyl group with I and II in the synthesis of valine.[12]

The condensate between freshly prepared, dry 2,3-dibromopropene and I using toluene and sodium hydride formed rapidly and had the same melting point as reported previously.[13] However,

(8) H. Gershon, J. S. Meek and K. Dittmer, THIS JOURNAL, **71**, 3573 (1949).

(9) R. G. Garst, E. Campaigne and H. G. Day, *J. Biol. Chem.*, **180**, 1013 (1949); E. Campaigne, *et al.*, THIS JOURNAL, **70**, 2611 (1948).

(10) It has been reported[9] that condensation of distilled 3-bromomethylthiophene with diethyl acetamidomalonate yielded a product melting at 90–91° while use of a crude reaction mixture, resulting from the treatment of a refluxing carbon tetrachloride solution of 3-methylthiophene with a mixture of benzoyl peroxide and N-bromosuccinimide, gave a product melting at 121–130°, which was acid-labile and on alkaline hydrolysis gave β-3-thienylalanine in an over-all yield of 39%. In our hands, the intermediate obtained with the use of distilled 3-bromomethylthiophene was smoothly converted to the amino acid hydrobromide by refluxing six hours with 10% hydrobromic acid.

(11) J. C. Sheehan and W. A. Bolhofer, THIS JOURNAL, **72**, 2786 (1950).

(12) R. O. Atkinson and P. A. A. Scott, *J. Chem. Soc.*, 1040 (1949).

(13) J. Capkova-Jirku, J. V. Kostir and M. Vondracek, *Chem. Listy* **44**, 114 (1950).

in one reaction which proceeded very sluggishly, the product was an oil which when distilled gave a product which had the analysis for the corresponding decarbethoxylated compound. This product was readily hydrolyzed in dilute hydobromic acid to the same amino acid obtained from the normal condensate but without the evolution of carbon dioxide. This type of reaction is not without precedent since similar decarbethoxylations were obtained when methyl methacrylate was condensed with II.[14,15]

The condensates listed in Table I were hydrolyzed to amino acids with 10% hydrochloric or hydrobromic acid. The physical and microbiological properties of new amino acids will be described at a later date.

Acknowledgments.—We wish to thank Drs. H. Walborsky and W. Herz of this department for their valuable assistance during this work, and Mr. K. R. Edlund, of Shell Development Company, Emeryville, California, for supplying a generous sample of 2,3-dichloropropene.

Experimental[16]

Diethyl (2-Bromo-2-propenyl)-formamidomalonate.—In a dry 500-ml. three-necked flask equipped with a mechanical stirrer and reflux condenser connected to a mercury bubble counter was placed a mixture of 44.0 g. (0.22 mole) of freshly prepared 2,3-dibromopropene, b.p. 74.0–74.5° (75 mm., and 5.3 g. (0.22 mole) of sodium hydride, to which was added a hot solution of 40.6 g. (0.2 mole) of I, m.p. 50–52°, in 75 ml. of toluene which had been boiled briefly to expel any traces of water. Evolution of hydrogen commenced immediately and had virtually ceased after 45 minutes of gentle refluxing. At this time the reaction mixture was allowed to cool and a few ml. of ethanol was added cautiously to decompose the excess sodium hydride. After addition of 75 ml. of water, the organic layer was separated with the aid of 50 ml. of ether, washed with water, and taken to dryness *in vacuo* to give a brown oil which solidified on cooling.

The product was recrystallized from ether–petroleum ether to give 37.0 g. of pale brown product, m.p. 76.5–78.0°. The mother liquors were distilled to give a major fraction at 144–149° (2 mm.), which on recrystallization gave 15.0 g. more colorless product, m.p. 72–76.5°. The total yield was 81%.

An analytical sample was obtained from ethanol–water and melted at 78.5–79.2°.[17]

Ethyl N-Formyl-2-amino-4-bromo-4-pentenoate.—By the same procedure as above, the condensation was accomplished between 44.0 g. (0.22 mole) of 2,3-dibromopropene[18] and 40.6 g. (0.20 mole) of I in the presence of 5.76 g. (0.24 mole) of sodium hydride, 0.5 ml. of *t*-butyl alcohol and 100 ml. of benzene. Hydrogen was evolved slowly during 14 hours refluxing to give a dark mixture which was worked up in the usual way to give a dark oil which could not be crystallized. The oil was distilled to give a major fraction weighing 35.9 g., b.p. 169–174° (3 mm.) which solidified on standing two weeks in the cold. It was recrystallized from ethanol–petroleum ether to give a first crop weighing 17.1 g., m.p. 60.5–63.0°, and a second crop weighing 11.2 g., m.p. 50–56°. Two further crystallizations gave an analytical sample melting at 62.5–63.5°.

Anal. Calcd. for $C_8H_{12}O_3NBr$: C, 38.42; H, 4.84; N, 5.60; Br, 31.95. Found: C, 38.28; H, 4.74; N, 5.69; Br, 31.79.

Diethyl (2-Propyl)-formamidomalonate.—A solution of the sodium derivative of I in dimethylformamide was prepared by adding 11.5 g. (0.056 mole) of I in small portions to 1.44 g. (0.06 mole) of sodium hydride in 25 g. of anhydrous dimethylformamide and filtering after about 30 minutes standing at room temperature, all under anhydrous conditions. There was then added 12.3 g. (0.10 mole) of anhydrous isopropyl bromide and the mixture refluxed gently for two hours.

The reaction mixture was reduced to a small volume *in vacuo* and diluted to 125 ml. with water. The oil which formed initially solidified on standing in the cold. It was filtered off and recrystallized from ether–petroleum ether to give 6.1 g. of tan crystals, m.p. 70–73°. The mother liquors yielded an additional 0.85 g., m.p. 67–69° to give a total yield which was 50%. An analytical sample (ether–petroleum ether) melted at 73.5–74.0°.

Anal. Calcd. for $C_{11}H_{19}NO_5$: N, 5.71. Found: N, 5.65.

β-3-Thienylalanine from III and 3-Bromomethylthiophene.—A mixture of 129.6 g. (1.32 moles) of freshly distilled 3-methylthiophene and 500 ml. of carbon tetrachloride held at gentle reflux in a three-necked flask equipped with a Hershberg stirrer was treated with small portions of an intimate mixture of 213.6 g. (1.20 moles) of N-bromosuccinimide and 8.0 g. of benzoyl peroxide over a period of 90 minutes. The mixture was cooled to 10° and filtered. Distillation yielded 151 g. of colorless product, b.p. 58–62.5° (3 mm.), which contained 96% of the amount of "active" halogen calculated for pure 3-bromomethylthiophene.

The condensation with III was performed in toluene in the usual manner and was complete in one hour. After addition of a small amount of ethanol, the solvents were removed *in vacuo* to give a brown oil, which was hydrolyzed by refluxing with 100 g. of 20% potassium hydroxide for 14 hours although the evolution of ammonia had virtually ceased after one hour.

The reaction mixture was cooled and made acidic with concentrated hydrochloric acid. After treatment with Darco and Super-Cel, it was taken to dryness *in vacuo*, water added and taken to dryness again, and the solid dried by the addition of absolute ethanol and a final removal of solvent at a low pressure. The mixture of salts was extracted with 250 ml. of absolute ethanol and the amino acid precipitated by neutralization with concentrated ammonium hydroxide. The yield of crude product was 50% of theoretical based on III and was microbiologically pure[19] after two recrystallizations.

TALLAHASSEE, FLORIDA

(14) J. Done and L. Fowden, *Biochem. J.*, **51**, 451 (1952).

(15) J. L. Fillman and N. F. Albertson, THIS JOURNAL, **74**, 4969 (1952).

(16) All melting points were determined in capillary tubes and are corrected.

(17) A reported[13] yield of 43%, m.p. 80.5°, was obtained by the use of ethanolic sodium ethoxide.

(18) Used as supplied by Columbia Organic Chemicals Co., Inc., Columbia, S. C., after drying over calcium chloride.

(19) K. Dittmer, THIS JOURNAL, **71**, 1205 (1949).