butene-2, were formed, perhaps by disproportionation. Octane distilling mostly at 117–118° was a major product (12). Di-*sec*-butyl boiling at 116.5°[10] would be expected.

Summary

1. Di-*n*-butylmercury and di-*sec*-butylmercury were thermally decomposed within the range 350–450° under 3 mm. pressure and the products were given a rather complete analysis.

2. In addition to fracture of the carbon–mercury bonds, the carbon chains underwent fracture at a single point characteristic for each alkyl, at the middle carbon–carbon bond for the primary alkyl and at the terminal bond for the secondary alkyl.

(10) "International Critical Tables," McGraw-Hill Book Co., New York, 1926.

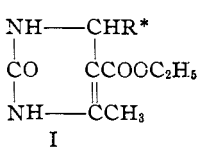
BARTLESVILLE, OKLAHOMA RECEIVED MARCH 16, 1933
PUBLISHED AUGUST 5, 1933

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

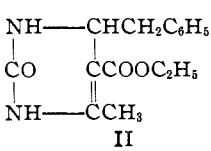
Researches on Pyrimidines. CXXXIV. The Reaction of Phenylacetaldehyde and Acetophenone with Urea

BY KARL FOLKERS[1] AND TREAT B. JOHNSON

In a recent paper from this Laboratory, improved experimental conditions were described for condensing an aldehyde and urea with a β-keto ester to form a tetrahydropyrimidine compound.[2] The various aldehydes investigated, of both the aromatic and aliphatic series, underwent condensation with ethyl acetoacetate and urea, for example, to form 2-keto-4-R-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidines as represented by the general formula I.



I



II

* R = the organic radical attached to the aldehyde group CHO (CH_3CHO, etc.).

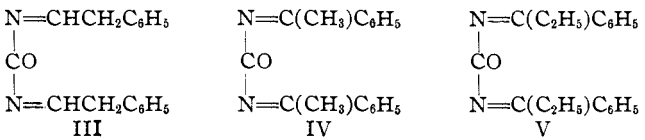
In order to complete a series of this type of pyrimidines for pharmacological study, we desired to obtain 2-keto-4-benzyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, II. Accordingly, urea, ethyl acetoacetate and phenylacetaldehyde were refluxed together according to the usual technique in ethanol solvent and in the presence of a few drops of hydrochloric acid as catalyst. Only one crystalline product was isolated. This was comparable in solubility, melting point, and also in yield and general properties to the tetrahydropyrimidines formed in our previous experiments with

(1) E. R. Squibb & Sons Research Fellow in Organic Chemistry.

(2) Folkers, Harwood and Johnson, THIS JOURNAL, **54**, 3751 (1932).

other aldehydes. The results obtained on analysis, however, indicated the empirical formula $C_{17}H_{16}ON_2$ instead of $C_{15}H_{18}O_3N_2$ (II), and suggested that the ethyl acetoacetate did not enter into the reaction. This suggestion was proved to be a fact by obtaining the same compound when an ethanol solution of urea, phenylacetaldehyde, and hydrochloric acid as catalyst, were digested for a corresponding time.

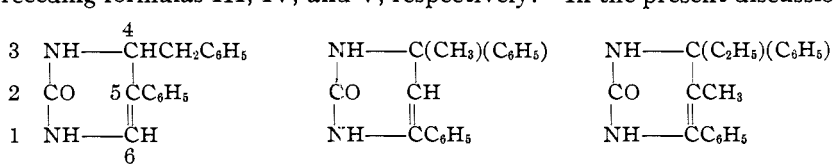
The empirical formula $C_{17}H_{16}ON_2$ is in agreement constitutionally with that of a compound formed by condensation of two molecules of phenylacetaldehyde with one of urea as expressed by formula III. So far as the



III IV V

writers are aware no representatives of this type of urea–aldehyde condensation product are known. Such unsaturated ureido combinations would be expected to possess high melting points and be susceptible to polymerization and easily broken down to the original aldehyde and urea by acid hydrolysis. However, a reaction between urea and acetophenone, which is isomeric with phenylacetaldehyde, leading to a urea–ketone condensation product of corresponding structure has been described by Scholtz.[3] This investigator has reported that acetophenone and urea, when heated at 170°, give a product to which he assigned the constitution of *s*-bis(α-methylbenzal)-urea as represented by formula IV. Scholtz also observed that propiophenone reacted with urea in an analogous manner giving the corresponding *s*-bis(α-ethylbenzal)-urea represented by formula V. No experimental data were presented by him in support of these constitutions. He commented in his paper, however, on the stability of his compounds and stated that the compound IV was not altered through long digestion in an alcohol solution of alkali or in boiling acetic acid solution. Long heating in hydrochloric acid solution was productive of some acetophenone.

In view of the remarkable stability of Scholtz's compound IV and the paucity of urea constructions of this type, it seemed to the authors that the pyrimidine formulas VI, VII and VIII probably more correctly represent the constitution of the three compounds under consideration than the preceding formulas III, IV, and V, respectively. In the present discussion



VI VII VIII

(3) Scholtz, *Arch. Pharm.*, **253**, 111 (1915).

of constitution the position of the double bond in the pyrimidine ring is quite arbitrary on account of the possibility of hydrogen migration in any reaction mechanism which might be formulated in the production of pyrimidines. The formulation of cyclic compounds exhibiting a tetrahydropyrimidine structure by condensation of an aldehyde or ketone with urea bears similarity (1) to the formation of 2,2,4-trimethyldihydroquinoline (acetone-anil) by condensation of acetone with aniline whose chemistry has been so well interpreted in the recent publication by Reddelien and Thurm,[4] (2) to Döbner and Miller's method of quinoline synthesis[5] and (3) to the formation of 2-phenylnaphthalene from phenylacetaldehyde by the action of sulfuric acid.[6]

In fact, the relationship with regard to the formation of 2-phenylnaphthalene is very strong if one visualizes the formation of this hydrocarbon as resulting from cyclization of previously formed aldol of phenylacetaldehyde. Volhard's use of equal volumes of concentrated sulfuric acid and glacial acetic acid as the medium was very drastic, and resulted in considerable resin formation. The authors found that an almost identical yield of pyrimidine VI was obtained if the urea and phenylacetaldehyde reacted in a glacial acetic acid solvent containing a few drops of sulfuric acid. An intermediate aldol formation could lead, by a subsequent reaction involving urea, to the pyrimidine VI.

It is of interest to note here that in the recent study of tetrahydropyrimidines,[2] phenylacetaldehyde was the only one of the substituted aliphatic aldehydes employed which reacted in this manner with urea. A salient fact seems to be, then, that there must be an active methylene (or methine) group adjacent to the carbonyl of the two molecules reacting with the urea. Accordingly, two molecules of ethyl acetoacetate might be expected to react under certain conditions with one molecule of urea to give ethyl 2-keto-4,6-dimethyl-5-carbethoxy-1,2,3,4-tetrahydropyrimidine-4-acetate, IX. However, when an ethanol solution of urea and ethyl aceto-

$$\overline{\text{NHCONHC(CH}_3\text{)(CH}_2\text{CO}_2\text{C}_2\text{H}_5\text{)C(CO}_2\text{C}_2\text{H}_5\text{)=CCH}_3} \quad \text{IX}$$

acetate was refluxed with a few drops of hydrochloric acid as catalyst, the only product isolated was ethyl β-carbamidocrotonate.[7] This ester is best prepared by the equimolecular condensation of urea with ethyl acetoacetate at 20–25°.[8] Scholtz[3] has reported that urea and ethyl acetoacetate interact at 170° to give β-dicarbamido-butyrylurea X. Thus far, the pyrimidine IX has not been detected as a product of reaction by interaction of urea with ethyl acetoacetate.

$$\text{CH}_3\text{C(NHCONH}_2\text{)}_2\text{CH}_2\text{CONHCONH}_2 \quad \text{X}$$

(4) Reddelien and Thurm, *Ber.*, **65**, 1511 (1932).

(5) For an excellent bibliography of the Döbner and Miller quinoline reaction see Hollins, "Synthesis of Nitrogen Ring Compounds," D. Van Nostrand and Company, New York, 1924, p. 251.

(6) Volhard, *Ann.*, **296**, 29 (1897); Auwers and Keil, *Ber.*, **36**, 3910 (1903).

(7) Behrend, *Ann.*, **229**, 5 (1885).

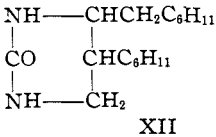
(8) J. J. Donleavy, unpublished results in This Laboratory.

Experimental Evidence in Favor of Pyrimidine Structure.—A support for the pyrimidine structure in these condensations is the fact that Scholtz[3] was unable to obtain a urea derivative XI by interaction of benzophenone with urea similar to the derivatives obtained from acetophenone and propiophenone. Furthermore, a *s*-bis(α-phenylbenzal)-urea XI, if formed, could not undergo ring closure as formulated for VI and VII.

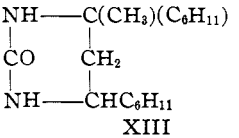
$$(C_6H_5)_2C{=}NCON{=}C(C_6H_5)_2 \quad \text{XI}$$

Absorption spectra measurements also support our conclusions regarding pyrimidine structure. Through the courtesy of Professor Emma P. Carr of Mount Holyoke College, the ultraviolet absorption spectra of the two compounds represented by formulas VI and VII, respectively, have been determined. Although these measurements will be published later by Professor Carr, it may now be said that the absorption curves bear close similarities to the absorption curves of phenyl-uracils[9] and certain tetrahydropyrimidines[10] which have been studied in the Mount Holyoke laboratory.

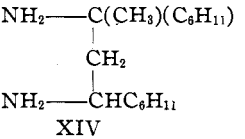
If these condensation products are to be represented by the acyclic structures III and IV, respectively, then eight moles of hydrogen should be required for their complete hydrogenation. On the other hand, if the pyrimidine formulas VI and VII, respectively, express their constitution then only seven moles of hydrogen would be consumed. Catalytic hydrogenation with the Adams platinum catalyst indicated that only seven moles were required for complete reduction, and the results of our analysis proved that the condensation products actually had added during the reduction process fourteen additional hydrogen atoms. These new hydrogenation products are represented by formulas XII and XIII as derived from the pyrimidines VI and VII, respectively. The ultraviolet absorption spectra of these two reduction products indicated that both compounds possessed completely saturated structures.[10]



XII



XIII



XIV

Hydrolysis of the hexahydropyrimidine XIII might be expected to give 1,3-diamino-1-methyl-1,3-dicyclohexylpropane XIV. However, after long digestion in an alcoholic sodium hydroxide solution 85.3% of this pyrimidine was recovered unaltered. This is in accord with the resistance of 2-keto-4-methyl-6-cyclohexylhexahydropyrimidine-5-carboxylic acid to hydrolysis with formation of β,β'-diamino-β-methyl-β'-cyclohexylisobutyric acid.[11]

(9) Evans, THIS JOURNAL, **54**, 641 (1932).
(10) Unpublished results of Professor Carr of Mount Holyoke College.
(11) Folkers and Johnson, THIS JOURNAL, **55**, 2886 (1933).

Experimental evidence unfavorable for an acyclic ureide structure was also furnished by fusing the compound XIII with phthalic anhydride. The ureide proved to be very resistant to the action of this reagent, for 82.6% of it was recovered unaltered. Many alkylureas,[12] and certain alkyl urethans[13] form alkyl phthalimides by this fusion.

If the Scholtz acyclic structure IV, as an expression of the constitution of the urea-acetophenone condensation product, were correct, then this substance might be expected to absorb selectively two moles of hydrogen on catalytic reduction to give the *s*-bis(α-methylbenzyl)-urea, XV. However, a mixture was obtained by stopping the reduction after absorption of two moles of hydrogen, which may be considered as further evidence against formula IV.

$$(CH_3)(C_6H_5)CHNHCONHCH(CH_3)(C_6H_5) \quad XV$$

It was stated at the beginning of this paper that the 4-benzyl-5-carbethoxypyrimidine derivative, II, was not obtained by the interaction of phenylacetaldehyde, urea and ethyl acetoacetate. When, however, phenylacetaldehyde reacted with ethyl β-carbamidocrotonate under similar experimental conditions, there was obtained chiefly the 4-benzyl-5-phenylpyrimidine derivative, VI and a small quantity of the desired 4-benzyl-5-carbethoxypyrimidine derivative, II. The mechanism and significance of the formation of both pyrimidines VI and II by the interaction of phenylacetaldehyde and ethyl β-carbamidocrotonate will be fully discussed in a later paper dealing exclusively with the mechanism of formation of tetrahydropyrimidines.

Experimental Part

2-Keto-4-benzyl-5-phenyl-1,2,3,4-tetrahydropyrimidine, VI.—Eight and three-tenths grams of freshly distilled phenylacetaldehyde, 4.2 g. of urea, 25 ml. of absolute ethanol and 5 drops (5-ml. pipet) of concentrated hydrochloric acid were refluxed for four hours. After allowing twenty-four hours for crystallization, the product was filtered and washed with 25 ml. of 50% ethanol. It melted at 212–214° (corr.) and the yield was 6.0 g. (65.6%). One crystallization from alcohol yielded 5.0 g. of pyrimidine of m. p. 213.5–215.5° (corr.). This experiment was repeated using 25 ml. of glacial acetic acid as solvent and 5 drops of concentrated sulfuric acid as catalyst. After heating for four hours on the steam-bath, the solution was poured into 300 ml. of water to precipitate the pyrimidine, which on crystallization from alcohol yielded 5.4 g. of m. p. 210–212° (corr.).

The same pyrimidine was obtained with ethyl acetoacetate included, although its presence was unnecessary: 24.2 g. of phenylacetaldehyde, 12.1 g. of urea, 39.4 g. of ethyl acetoacetate, 100 ml. of absolute ethanol and fifteen drops of concentrated hydrochloric acid were refluxed for seven and one-half hours. After twenty-four hours for crystallization, filtration and drying, 17.3 g. of product was obtained. A further three hours of refluxing and evaporation, etc., of filtrate yielded 2.0 g. more. The 19.3 g. (72.3% based on aldehyde) was dissolved in 650 ml. of ethanol under reflux and dis-

(12) Tingle and Brenton, THIS JOURNAL, **32**, 113 (1910).
(13) Manske, *ibid.*, **51**, 1202 (1929).

tilled to incipient crystallization. We obtained 14.2 g. of pyrimidine having the m. p. 214–216° (corr.). A second crystallization did not alter the melting point. The mixed melting point of the two products as obtained with and without the inclusion of ethyl acetoacetate was 213–215° (corr.).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.23; H, 6.10; N, 10.6. Found: (micro) C, 77.41; H, 6.23; N, 10.56; (macro) N, 10.42, 10.43.

2-Keto-4-benzyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, II.—Eight and six-tenths grams of ethyl β-carbamidocrotonate and 6.0 g. of phenylacetaldehyde were dissolved in 35 ml. of absolute ethanol, and after addition of twenty drops of concentrated sulfuric acid, the solution was refluxed for two hours. After standing for fifteen hours, filtering and washing, there was obtained 3.9 g. of pyrimidine VI of m. p. 205.5–212°. Recrystallization yielded 3.2 g. of pure pyrimidine VI of m. p. 212–214°.

The filtrate was poured into 300 ml. of water. The gum soon solidified, and, after crystallization from aqueous alcohol, there was obtained 1.0 g. of impure pyrimidine II. Five recrystallizations raised the melting point to 195–196° (corr.), and two more did not raise it further.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.65; H, 6.62; N, 10.22. Found: (micro) C, 65.81; H, 6.61; N, 10.15.

2-Keto-4-methyl-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine, VII.—The directions of Scholtz[3] were improved: 100 g. of urea and 100 g. of acetophenone were heated for nine hours at 170-190°. After cooling, the resin-like mass was refluxed with about 400 ml. of ethanol (two portions) until all dissolved but a white residue. This alcohol insoluble residue was filtered, leached with alcohol, filtered and dried to yield 18.2 g. It did not melt below 300° and gave a colored precipitate with ammoniacal copper sulfate solution characteristic of cyanuric acid.[14] The alcohol extracts when poured into a liter of water (to dissolve urea) gave a gummy mass which soon solidified. This solid was filtered, dissolved in hot ethanol, and again filtered to remove more cyanuric acid. Benzene was added and the solution distilled until all ethanol and water had been removed. The residue was poured into 500 ml. of petroleum ether to give a taffy-like mass which solidified overnight. This solid, after four crystallizations (dissolved in excess and distilled to incipient crystallization) from 95% alcohol, yielded 43.7 g. of the tetrahydropyrimidine of m. p. 179–180° (corr.), which was not raised by further ethanol crystallization. Scholtz gave m. p. 176°. The compound was further purified by dissolving in glacial acetic acid, filtering the very small amount of insoluble material, probably cyanuric acid and a final ethanol crystallization. It then melted at 179.5–180.5° (corr.).

Reaction of Urea and Ethyl Acetoacetate.—Twenty-six grams (0.2 mole) of ethyl acetoacetate, 6 g. (0.1 mole) of urea, 25 ml. of absolute ethanol, and eight drops of concentrated hydrochloric acid were refluxed for seven hours. After forty-eight hours urea crystallized from the solution. The filtrate was then poured into 400 ml. of water when crystals of ethyl β-carbamidocrotonate separated in a yield of 1.5 g. They melted at 164–165° (corr.) after one crystallization from aqueous ethanol. A mixed melting point with an authentic sample of the ester was 162–164°.

2-Keto-4-hexahydrobenzyl-5-cyclohexylhexahydropyrimidine, XII.—In 130 ml. of glacial acetic acid, 6.85 g. (0.025 mole) of pyrimidine VI was dissolved, and the solution shaken with 0.7 g. of the Adams platinum catalyst under three atmospheres hydrogen pressure.[15] During about twelve hours, 7 moles of hydrogen was absorbed, and

(14) Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, 1916, Vol. II, p. 84.

(15) "Organic Syntheses," John Wiley and Sons, Inc., New York, 1932, Coll. Vol. I, pp. 55, 452.

there was no more absorption in the following ten hours. After catalyst filtration, the filtrate was poured into 500 ml. of water to precipitate the reduced pyrimidine. After crystallizing three times by dissolving in excess ethanol and distilling to incipient crystallization, 4.6 g. of the hexahydropyrimidine XII was obtained of m. p. 267.5–269.5° (corr.).

Anal. Calcd. for $C_{17}H_{30}N_2O$: C, 73.31; H, 10.87; N, 10.07. Found: (micro) C, 73.30; H, 10.81; (macro) N, 9.88, 9.88.

2-Keto-4-methyl-4,6-dicyclohexylhexahydropyrimidine, XIII.—In 125 ml. of glacial acetic acid, 6.6 g. of pyrimidine VII was dissolved and the solution shaken with 0.7 g. of the platinum catalyst for twenty-eight hours under three atmospheres hydrogen pressure. As only about 80% of the hydrogen had been absorbed, 0.5 g. of fresh catalyst was added and the shaking continued eighteen hours longer (a total of 7 moles of hydrogen had been absorbed). After catalyst removal, the acetic acid was distilled under diminished pressure until only a small residue remained. This was poured into 300 ml. of water containing 50 ml. of concentrated ammonia solution. The filtered, washed precipitate, after two crystallizations from ethanol, yielded 4.8 g. of pyrimidine melting at 262–263° (corr.). Further crystallization did not raise the melting point.

Anal. Calcd. for $C_{17}H_{30}N_2O$: C, 73.31; H, 10.87; N, 10.07. Found: (micro) C, 73.46; H, 10.92; (macro) N, 10.05, 9.87.

When the hydrogenation of pyrimidine VII was interrupted after the absorption of two moles of hydrogen and the product isolated in the above described manner, the melting point range of 125–140° with indications of melting at 100° showed it to be a typical partial hydrogenation mixture.

Attempted Hydrolysis of Hexahydropyrimidine, XIII.—Seventy-five hundredths gram of pyrimidine XIII was dissolved in 75 ml. of 10% sodium hydroxide solution and 75 ml. of ethanol and the solution refluxed for eight and one-half hours. After dilution with water for precipitation, we recovered 0.64 g. (85.3%) of the original pyrimidine, of m. p. 262–263° (corr.).

Behavior of Hexahydropyrimidine XIII toward Phthalic Anhydride.—Seventy-five hundredths gram of pyrimidine XIII and 1.2 g. of phthalic anhydride were heated together for one-half hour at 250–300°. After cooling and leaching with sodium bicarbonate solution, the crude precipitate had m. p. 257–261°. After recrystallization from dilute alcohol, it yielded 0.62 g. (82.6%) of the recovered pyrimidine of m. p. 261.5–263° (corr.).

Summary

1. Acetophenone condenses with urea to form a tetrahydropyrimidine, namely, 2-keto-4-methyl-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine, and not *s*-bis(α-methylbenzal)-urea as described in the literature by Scholtz.

2. Phenylacetaldehyde and urea interact in the presence of hydrochloric acid as catalyst to form 2-keto-4-benzyl-5-phenyl-1,2,3,4-tetrahydropyrimidine. The same pyrimidine is also formed when ethyl acetoacetate is incorporated in the reaction mixture.

3. Phenylacetaldehyde, urea and ethyl β-carbamidocrotonate interact in the presence of sulfuric acid as catalyst to form 2-keto-4-benzyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine and 2-keto-4-benzyl-5-phenyl-1,2,3,4-tetrahydropyrimidine.

4. By application of catalytic hydrogenation the two keto-tetrahydro-

pyrimidines formed by condensation of acetophenone and phenylacetaldehyde with urea are reduced to the corresponding completely saturated cyclohexylhexahydropyrimidines, respectively.

NEW HAVEN, CONNECTICUT RECEIVED MARCH 22, 1933
PUBLISHED AUGUST 5, 1933

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Branched Chain Aliphatic Acids. Isomyristic, Isopalmitic and Isostearic Acids

BY CHARLES R. FORDYCE AND JOHN R. JOHNSON

The synthesis of higher aliphatic acids and their derivatives, of known constitution, is undertaken frequently for the purpose of establishing the structure of products isolated from natural sources. Since the conventional methods of extending carbon chains (involving the successive addition of increments of one or two carbons) are scarcely feasible for lengthening them by more than six atoms,[1] it is of advantage to employ a procedure in which a long chain can be added in a single operation. Two such methods have recently been developed: (a) the interaction of carbethoxy acyl chlorides, $CO_2Et\text{-}(CH_2)_n\text{-}COCl$, with sodium derivatives of substituted β-ketonic esters leading to ketonic acids of the type, $CO_2Et\text{-}(CH_2)_n\text{-}CH_2\text{-}CO\text{-}R$;[2] (b) the selective action of Grignard reagents upon aldehydic esters, $CO_2Et\text{-}(CH_2)_n\text{-}CHO$, to produce hydroxy acids such as $CO_2H\text{-}(CH_2)_n\text{-}CHOH\text{-}R$.[3] In both instances the unsubstituted acids can be obtained by subsequent reduction of the ketonic or hydroxy acid.

In planning the synthesis of branched chain aliphatic acids containing the systems $(CH_3)_2CH\text{-}(CH_2)_n\text{-}CO_2H$ and $CH_3\text{-}CH_2\text{-}CH(CH_3)\text{-}(CH_2)_n\text{-}CO_2H$, an effort was made to devise a simpler method for adding large increments of carbon atoms. The fact that ketones can be obtained by the selective action of Grignard reagents upon simple acid chlorides[4] suggested the use of the acid chlorides or acid chloride esters of dibasic acids to obtain ketonic acids of high molecular weight. Experiments using *n*-hexyl- and *n*-octylmagnesium bromides with sebacyl chloride gave the desired ketonic acids, 10-ketopalmitic and 10-ketostearic acids; although the yields in these reactions are relatively low (28 and 12% respectively),[5] this is mitigated by the fact that ten carbon atoms are added in one simple operation.

(1) Levene and Allen, *J. Biol. Chem.*, **27**, 433 (1916); Levene and Taylor, *ibid.*, **59**, 905 (1924).

(2) (a) Robinson and Robinson, *J. Chem. Soc.*, **127**, 175 (1925); (b) 2204 (1926); (c) Robinson, *ibid.*, 745 (1930).

(3) Noller and Adams, THIS JOURNAL, **48**, 1074 (1926). Numerous applications of this method are described in subsequent papers by Adams and his collaborators.

(4) *Cf.* Nilanidhi, Dawson and Johnson, unpublished investigations. In this work succinic anhydride was used to effect an addition of four carbon atoms, giving a γ-ketonic acid.

(5) These yields are similar to those obtained (10–25%) in the synthesis of hydroxystearic acids by the aldehydic ester method [Tomecko and Adams, THIS JOURNAL, **49**, 522 (1927)].