Experimental

Fifteen-Minute Esterification.—An aqueous standard solution containing 0.005 mole of sodium hydroxide was titrated with freshly prepared methanolic hydrogen chloride solution. The same volume required (8.00 ml. for example) of methanolic HCl was then added to a solution of 0.01 mole of the benzoylbenzoic acid in question in enough absolute methanol to bring the total volume to 25 ml. The same flask was used in each experiment. This solution was placed in a bath at 55.5° (this temperature was maintained by boiling acetone) and held at this temperature for 15 min. The contents were then transferred to a flask containing 6 ml. of 1 *N* aqueous sodium acetate with the aid of a 3-ml. methanol wash. The solvent was then removed in a rotary evaporator, and the product was taken into ether–benzene. After two or three extractions with aqueous sodium bicarbonate (from which extract the unesterified acid was recovered) and a washing with saturated sodium chloride solution, the ether–benzene layer was dried by filtration through a bed of anhydrous magnesium sulfate. The solvents were quantitatively removed under reduced pressure and the amount of ester formed was determined by weighing. The composition of the esters was determined by comparing the ratio of the appropriate methoxy methyl peaks in the n.m.r. spectrum.[6] The τ- values for these groups in methylene chloride are as follows: I_n, 6.59; I_p, 6.97; II_n, 6.52; II_p, 6.80; III_n, 6.55; III_p, 6.96; IV_n, 6.76; IV_p, 7.02; V_n, 6.61; V_p, 7.02; VI_n, 6.56; VI_p, 7.03; VII_n, 6.57; VII_p, 7.08; $VIII_n$, 6.70; $VIII_p$, 7.07.

The use of sodium acetate for neutralization, rather than potassium carbonate, was adopted after blank experiments with known amounts of normal and pseudo esters. For example, a mixture made up of 39.5% I_n and 60.5% I_p gave analytical figures for 41.5% I_n and 58.5% I_p. Considering the lability of I_p in the presence of methanol and the errors inherent in all of the measurements, this gives an idea of the accuracy involved. For some other, less readily rearranged esters, less change occurred during the work-up procedure.

All of the values reported in Table I are the average of at least two determinations, the individual results of which checked to 1–1.5%.

Equilibrium Values (Column 4, Table I.)—A solution of 0.01 mole of the *o*-benzoylbenzoic acid in 25 ml. of 0.5 *N* methanolic HCl was held at reflux for 5 hr. Equilibrium was attained in all cases, but those of acids X and XI (see footnotes *i* and *j*, Table I). The proportion of esters formed was determined by n.m.r. analysis as described above.

Structure of Acids in Methanol.—The per cent of acid in the keto acid form was determined by comparing the extinction coefficient of the acid in the 325–340-mμ range with that of the corresponding normal methyl ester. We assume that the ϵ value of the keto acid is the same as that of the normal ester. Because of the errors involved, the values obtained may not be too accurate, but the trend is clearly seen. The values earlier reported[3] were carried out by comparison of extinction coefficients in the 250-mμ region in which both normal and pseudo esters absorb. We believe the present determinations in the 325–340-mμ range (log ϵ 2.0–2.5), in which there is almost no absorption by the pseudo form, are more valid.

Benzylidenepyruvic Acids. V. *m*-Nitrobenzylidenepyruvic Acid and Its Enol–Lactone Tautomer*

EMMA DIETZ STECHER,[1] ANITA WALDMAN, AND DIANE FABINY

Department of Chemistry, Barnard College, New York, New York 10027

Received November 13, 1964

Acid-catalyzed condensation of *m*-nitrobenzaldehyde with pyruvic acid produces chiefly a stable enol–lactone, 2,4-dihydroxy-4-(*m*-nitrophenyl)crotonic acid γ-lactone (IV), which is a weak acid, as well as two minor products of multiple condensations. Base-catalyzed condensation forms only *m*-nitrobenzylidenepyruvic acid (I), a strong acid. Reactions of I with bromine and with phenylhydrazine are described, as well as pK' measurements of all acidic compounds.

In a recent publication[2] we reported the preparation of *o*-nitrobenzylidenepyruvic acid and its enol–lactone tautomer. Some differences are noted in the *m*-nitro series. *m*-Nitrobenzaldehyde condenses slowly with pyruvic acid using sodium carbonate as the catalyst in 50% methanol solution, to form yellow sodium *m*-nitrobenzylidenepyruvate.[4] On employing potassium hydroxide in methanol, which is the best method for other members of the series,[3] much decomposition resulted, and, indeed, with *o*-nitrobenzaldehyde, the only product of any base-catalyzed condensation was indigo.

On acidification of sodium *m*-nitro benzylidenepyruvate with hydrochloric acid, a characteristic acid–salt complex[3] often formed; so a reverse procedure of adding the salt solution to warm, dilute mineral acid was used. A more convenient method was that of acidifying in a separatory funnel in the presence of ether and adding ethyl acetate to increase the solubility of the acid product. The acid I was easily converted to its methyl ester II using hydrogen chloride in methanol or diazomethane in ether. The keto acid structure of I was confirmed by its conversion in alkaline hydrogen peroxide solution to known *trans*-*m*-nitrocinnamic acid (III), which with diazomethane gave the known methyl ester of correct melting point. The pK' of the acid I in 50% methanol (2.7)[5] and the rapid hydrolysis rate of the methyl ester[3a] are consistent with the α-keto acid and ester structures.

Acid-catalyzed condensation of *o*-nitrobenzaldehyde with 2 equiv. of pyruvic acid at 35° gave the enol–lactone in 60–80% yield.[2] Parallel experiments with *m*-nitrobenzaldehyde resulted in rather poor yields of mixtures difficult to separate. Using either hydrogen chloride or methanesulfonic acid as catalysts, the expected enol–lactone IV crystallized out and could be

* To Professor Louis F. Fieser.

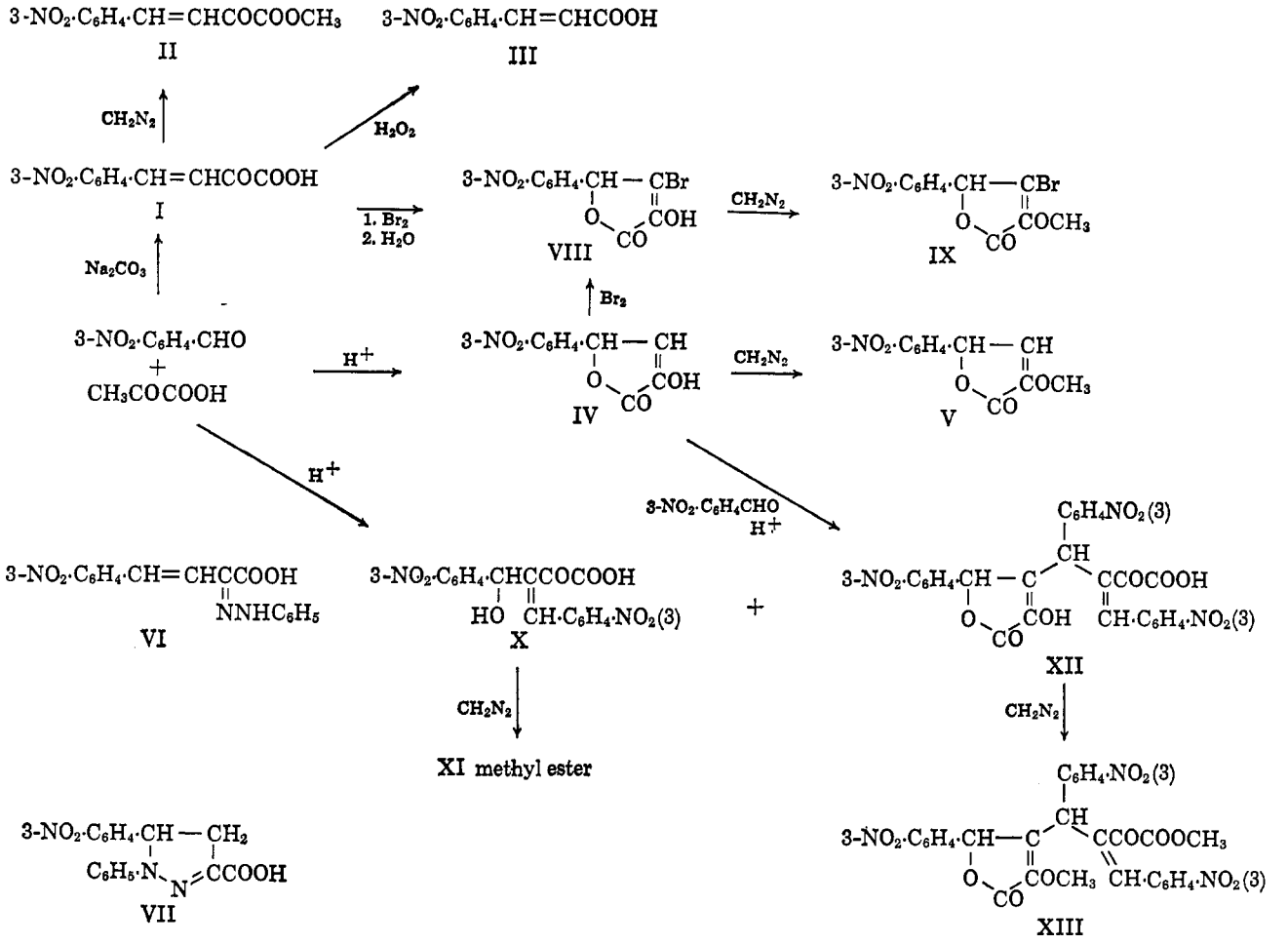
(1) Acknowledgment is made to the National Science Foundation for Undergraduate Research Participation Summer Grants which supported this research.

(2) IV: E. D. Stecher and E. Gelblum, *J. Org. Chem.*, **26**, 2693 (1961). For Papers III and II, see ref. 3a and b.

(3) (a) E. D. Stecher, F. Dunn, and E. Gelblum, *J. Am. Chem. Soc.*, **79**, 4748 (1957); (b) E. D. Stecher and A. Clements, *ibid.*, **76**, 503 (1954).

(4) R. Ciusa [*Gazz. chim. ital.*, **49**, 168 (1919)] reported using aqueous sodium carbonate as condensing agent.

(5) The determination of pK' in 50% (v./v.) methanol–0.2 *N* lithium chloride is described in ref. 2a. Present values were also derived from pH titration, but using a recording Titrigraph TTT-1C. Calculations were based on the expression $pK' = pH(obsd.) - \log([X^-]/[HX]) + A\sqrt{I}/(1 + \sqrt{I})$. In the Debye–Hückel term, $A = 0.76$, a constant for 50% (v./v.) methanol solutions, and I is the ionic strength. In most cases this term was equal to 0.02–0.04 pK unit at the midpoint for acid solutions ranging from 0.004–0.0002 *N*. In this way pK' for benzoic acid was found to be 5.18 ± 0.03. We are indebted to Dr. Edward J. King for suggesting this treatment of the data. See his "Acid-Base Equilibria," Pergamon Press, Oxford, 1965, Chapters 1 and 4.



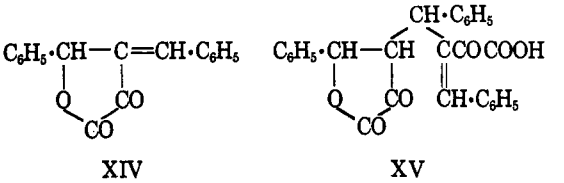
filtered off directly in 23–51% yield. As Table I shows, the keto acid was a minor product along with two interesting acidic compounds of higher molecular weight (X and XII), products of multiple condensation. All of these crystallized only erratically and incompletely from the filtrate, and their satisfactory recovery was achieved only after an extraction procedure was developed using sodium bisulfite solution and a series of buffers.

After filtering off the lactone, the viscous filtrate was dissolved in ether and extracted with bisulfite solution, removing unchanged *m*-nitrobenzaldehyde and *m*-nitrobenzylidene pyruvic acid (I). These were transferred to ether by acidification and dilution and then separated from each other by extraction of the keto acid with pH 6.9 phosphate buffer. The main ether solution was extracted further with pH 7.2 and 7.5 buffers removing XII and finally by 1% sodium bicarbonate and 1% sodium carbonate solutions removing X. The extracts were worked up to obtain crystalline products. Column chromatography on a variety of adsorbents was unsuccessful because of strong retention and then decomposition of samples on the columns.

Table I summarizes the per cent yields of crystalline products isolated by this procedure. It will be noted that hydrogen chloride as catalyst gave a lower yield of lactone IV (23–35%) than methanesulfonic acid. In three identical experiments lower temperatures with a 1:1 ratio of aldehyde and pyruvic acid yielded 22.6–29.2% of lactone. Higher temperatures increased the small yield of keto acid somewhat.

The weakly acidic enol–lactone structure of IV is supported by the pK' of 7.4 in 50% methanol. The infrared and n.m.r. data are consistent with this structure and with that of the ether V formed with diazomethane.

The structures of the minor products X and XII were a mystery until pH titration indicated equivalent weights of 372 and 575, respectively. This suggested multiple aldol condensation of the reagents and indeed Erlenmeyer,[6] obtained two products of high molecular weight from the condensation of excess benzaldehyde (unsubstituted) with pyruvic acid, catalyzed by hydrogen chloride. He assigned structures XIV and XV based on his analytical and chemical evidence, but prepared no methyl derivatives.



XIV XV

Our assignment of a mono keto acid–monoenol–lactone structure to XII (220–230° dec.) is based on correct elementary analysis of this compound and of a sharply melting (246–247°) dimethyl product formed with diazomethane, which is no longer soluble in sodium bicarbonate solution. The Erlenmeyer structure XV could not form a dimethyl product without previous

(6) E. Erlenmeyer, Jr., *Ber.*, **32**, 1450 (1899); **34**, 817 (1901).

TABLE I
PRODUCTS OF ACID-CATALYZED CONDENSATIONS

Catalyst	Moles of acid to aldehyde	Conditions, temp., °C. (time, hr.)	Yield of crystalline products, % Recovered aldehyde	Lactone IV	Keto acid I	X	XII
CH_3SO_3H	2:1	45–50 (23)	4.8	43–51	8.6	0.5	3.1
CH_3SO_3H[a]	1:2	45 (72)	19.7	44.0	14.1	3.0	11.4
HCl	2:1	42–47 (93)	6.0	25.5–35	11.6	0.5	6.4
HCl[b]	1:1	34–36 (72)	0.5–3.0	22.6–29.2	0.3–1.1	1.6–3.4	0.8–3.2

[a] For details see method C. Yields are not corrected for recovered aldehyde. [b] Range of per cent yield in three large-scale condensations of 17.6 g. of pyruvic acid and 30.0 g. of *m*-nitrobenzaldehyde.

enolization. The titration curve indicates that XII has one fairly strong acid group ($pK' = 4.9$ in 50% methanol) and a possible second weak acid group consistent with the enol structure. It is extracted from ether solution by pH 7.2 phosphate buffer with a yellow color. The original colorless compound is easily recovered on acidification of this extract. The infrared spectrum in THF of XII and of its dimethyl derivative included three carbonyl peaks.

To the colorless compound, m.p. 174–176°, we have assigned structure X, that of a hydroxy keto acid, rather than the lactone structure XIV of Erlenmeyer. This is based on correct elementary analysis of this compound and of a monoester formed with diazomethane XI. Erlenmeyer's structure could not form an ester without first adding a molecule of water. The compound is extracted rapidly from ether by 1% sodium carbonate solution (but not by pH 7.5 phosphate buffer) forming a yellow basic solution. It titrates rapidly as a typical weak acid ($pK' = 6.4$ in 50% methanol). Both X and XII are weaker acids than might be predicted from their α-keto acid structures (the pK' of I = 2.7 in 50% methanol). Also unlike I, they are not extracted from ether by sodium bisulfite solution and they react very slowly with 2,4-dinitrophenylhydrazine solution, further indications of less reactive or hindered carbonyl groups. The infrared spectrum in THF of X and of its methyl ester includes three carbonyl peaks. The n.m.r. spectra of X, XII, and their methylated products were unsatisfactory because of low solubility in a variety of solvents, and apparent overlapping of peaks.

As Table I shows, acid-catalyzed condensation using 2 equiv. of aldehyde and 1 equiv. of pyruvic acid resulted in a four- to sixfold increase in the yield of the multiple condensation products (X and XII). In one additional experiment, the simple enol–lactone IV was heated for 24 hr. at 45° with an equal weight of aldehyde and a catalytic amount of methanesulfonic acid. Of the 70% of converted lactone, 36.7% changed to keto acid I and 9.5% to impure XII. The latter was probably formed by the condensation of two molecules of the keto form of the lactone with the carbonyl group of one molecule of aldehyde. This indicates that lactone (IV) may be a precursor of XII and also that acid catalyzes the conversion of lactone to its keto acid tautomer.

Bromination of the keto acid I in dry chloroform solution gave a colorless dibromide, which on heating with water readily lost hydrogen bromide to form the α-bromo enol–lactone VIII. This product was identical with that formed by direct bromination of lactone IV. The pK' of 5.5 for the lactone in 50% methanol indicates that the bromine atom increases the acid strength of the enol 100-fold. The bromo lactone (VIII) treated with diazomethane formed the bromoenol ether IX. Infrared spectra in tetrahydrofuran included lactone carbonyl bands at 5.60 for the free enol and 5.70 μ for the ether. A characteristic second weak band at 5.90 μ in the enol spectrum may be due to some keto lactone present in solution. These reactions parallel those observed in the *o*-nitro series.

Treatment of the keto acid I with phenylhydrazine gave the expected phenylhydrazone VI accompanied by considerable isomeric pyrazoline VII formed by ring closure. Titration in 50% aqueous methanol was rapid, showing typical carboxyl groups in solution ($pK' = 4.2$ for the phenylhydrazone VI and 5.0 for the pyrazoline VII). These results parallel those in the *o*-nitro series, except that pyrazoline formation during preparation was not observed there.

Experimental[7]

Sodium 3-Nitrobenzylidenepyruvate.—*m*-Nitrobenzaldehyde (15.0 g., 0.01 mole) and redistilled pyruvic acid (8.8 g., 0.01 mole) were dissolved in 120 ml. of methanol. A solution of 11.0 g. (0.1 mole) of sodium carbonate in 120 ml. of water was added and the mixture was kept under reflux at 70–75° for 90 min. After cooling to room temperature, the red solution was extracted with ether to remove unchanged aldehyde, reheated and evacuated to drive off traces of ether, and chilled. The yield of yellow crystals washed with methanol, then ether, was 12.1 g. of 89% purity. A second crop of 2.7 g. was obtained after concentrating in a rotating vacuum evaporator, total yield 61%.

To purify the salt, it was recrystallized from 50% methanol solution (7.75 g. in 70 ml.). The filtered product was dried at 60° for 30 min. and weighed 5.7 g. (74%). Its purity (93%) was determined by comparison of the absorbancy with that of a pure sample of the acid I, both in 2×10^{-5} *M* solutions in 0.1 *M* phosphate buffer at pH 7.5. The expected absorbancy is 0.530 at 281 mμ (ϵ 26,500), λ_{max}^{Nujol} 5.95 (C=O) and 6.20 μ (COO^-).

3-Nitrobenzylidenepyruvic Acid (I).[8] By Precipitation.—A reverse procedure was used to avoid formation of the less soluble acid–salt complex. A solution prepared from 8.35 g. of sodium salt (89% pure) in 120 ml. water was added dropwise to a stirred solution of 50 ml. of 2.5 *N* hydrochloric acid at 50°, and the mixture was stirred and cooled slowly. The recovered pale yellow acid, dried *in vacuo*, weighed 6.0 g. (93% based on 100% pure salt), m.p. 145–147°. To recrystallize it, 6 g. was dissolved in 150 ml. of benzene and 10 ml. of acetone, and the volume was reduced *in vacuo* to 50 ml. (yield 4.25 g.; melting point of dry sample, 149–150°).

By Extraction.—A solution of 10.0 g. (0.04 mole) of sodium *m*-nitrobenzylidenepyruvate (89% pure) in 225 ml. of water was added to a separatory funnel containing 350 ml. of ether and 50 ml. of ethyl acetate to increase solubility, and 15 ml. of dilute hydrochloric acid was added in four portions, shaking well each

(7) Melting points were determined with total immersion thermometers, with samples inserted 10° below the melting point. Ultraviolet spectra were measured on a Beckman DU or a Cary recording spectrophotometer, usually on 4×10^{-5} *M* solutions. Infrared spectra were measured on a Baird or a Beckman IR-5 instrument; n.m.r. spectra were taken on a Varian A60 using tetramethylsilane as internal standard and acetonitrile or dimethyl sulfoxide as solvent. Analytical samples were dried for several hours at 3 mm. and 35 or 55°. Microanalyses were by Microtech, Skokie, Ill.

time to redissolve precipitated solid. The pale yellow water layer was extracted again with ether. The ether layers were washed twice with saturated sodium chloride solution, dried, and filtered rapidly because of a tendency to precipitate. The solution was concentrated on a rotating vacuum evaporator, and 50 ml. of benzene was added several times to remove hydrate water as the azeotrope. The acid was finally crystallized from 50 ml. of benzene containing 5 ml. of acetone, yield 7.29 g. in two crops, 93% cor., m.p. 144–147°.

The keto acid structure is supported by the pK' of 2.49 in 50% methanol–0.2 N lithium chloride.[8] A more recent value for this pK' in 50% methanol without lithium chloride is 2.7; $\lambda_{max}^{CH_3OH}$ 273 mμ (ϵ 22,500), $\lambda_{max}^{pH\ 7.5}$ 281 mμ (ϵ 26,500), λ_{max}^{KBr} carbonyl bands at 5.83 and 5.98 μ, and $\lambda_{max}^{CHCl_3}$ 5.63 (acid C=O) and 5.94 μ (C=O).

A bright yellow hydrate separated from a water solution: immediate m.p. 111–112° (Ciusa 111°),[4] after 30 min. in air m.p. 144°; λ_{max}^{KBr} 2.81, 5.82, and 5.96 μ.

Anal. Calcd. for monohydrate, $C_{10}H_7O_5N\cdot H_2O$: C, 50.20; H, 3.79; N, 5.86. Found: C, 50.43; H, 3.74; N, 5.92.

Methyl 3-Nitrobenzylidenepyruvate (II).[8] With Diazomethane.—A solution of 1.6 g. of acid in 200 ml. of warm ether was treated with an excess of diazomethane in 175 ml. of ether. A fine yellow precipitate soon appeared, and after 20 min. at room temperature 1.1 g., m.p. 168–169°, was filtered off.

With Methanol–3% Hydrogen Chloride.—The same ester (determined by mixture melting point and infrared spectrum) was obtained when 1 g. of acid was boiled with 10 ml. of the reagent for 5 min. Yellow crystals separated immediately (0.8 g.) and on recrystallization from benzene–petroleum ether the melting point was 169–170°. This and the acid rapidly formed an orange 2,4-dinitrophenylhydrazone.[9] The ester is hydrolyzed very rapidly in weak base from which the original acid is recovered (hydrolysis constant, $k^1 = 3.97 \times 10^{-3}$ sec.$^{-1}$ at 24.8° in 11.8% methanol at pH 7.72[2a]): $\lambda_{max}^{CH_3OH}$ 213 mμ (ϵ 10,500), 270 (15,750), and 295 (15,870); $\lambda_{min}^{CH_3OH}$ 231 mμ (ϵ 9200) and 280 mμ (ϵ 15,250); and λ_{max}^{KBr} 5.78 (ester C=O) and 5.94 μ (C=O).

trans-**3-Nitrocinnamic Acid (III).**—To 0.44 g. of I or its salt, dissolved in 20 ml. of 1% sodium carbonate solution was added 20 ml. of 3% aqueous hydrogen peroxide. The yellow color disappeared instantly, and after 5 min. the product was acidified, yield 0.3 g. (79%), m.p. 204–205° (lit.[10] m.p. 200–201°).

Methyl *trans*-3-Nitrocinnamate.—This was prepared in ether solution using diazomethane. It separated in pure condition from the concentrated solution, m.p. 124–125° (lit.[11] m.p. 123–124°).

Acid-Catalyzed Condensation.—The chief product was the lactone IV, which was filtered off directly in crystalline form. The ether solution of the filtrate was subjected to an elaborate extraction procedure which permitted the satisfactory recovery of the various products shown in Table I. This method of fractionation was based on model experiments on pure compounds.

A. With Methanesulfonic Acid.—A mixture of 7.5 g. (0.05 mole) of 3-nitrobenzaldehyde and 8.8 g. (0.1 mole) of pyruvic acid was warmed until dissolved, and 0.96 g. (0.01 mole) of methanesulfonic acid was added. The mixture was left for 23 hr. in a bath at 45–50° and was seeded with lactone IV if crystals had not appeared after 8 hr. The grainy product was filtered through a sintered-glass funnel removing a viscous orange oil. The solid was washed repeatedly with small portions of ether, leaving 4.60 g. of compact crystals of impure lactone, m.p. 143–149°.

A second crop resulted after some purification as follows. The filtrate was dissolved in a total of 200 ml. of ether in a separatory funnel, and all extracts were passed through a second funnel containing 150 ml. of ether. Water extracts removed unchanged pyruvic acid and the catalyst and were discarded. After several 25-ml. extracts of saturated sodium bisulfite solution (removing aldehyde and keto acid I, but not X or XII) the ether solution containing the residue was washed, dried, and vacuum evaporated to an oil. Using acetone–petroleum ether (b.p. 30–60°) the second crop of lactone (1.0 g.) was obtained. The total crude yield was 51%.

To decompose the bisulfite extracts, they were pooled, diluted with an equal volume of water, acidified with 50 ml. of concentrated hydrochloric acid, and warmed to 45°, and air was pulled through for 15 min. with a water pump. The partly precipitated carbonyl compounds were then transferred in six small portions to 150 ml. of ether in a separatory funnel, adding water or acid as needed to complete transfer and produce a clear aqueous layer. The ether solution of recovered aldehyde and keto acid I was evaporated somewhat and extracted several times with 0.1 M phosphate buffer of pH 6.9. The ether solution containing the residue was washed, dried, and evaporated to recover *m*-nitrobenzaldehyde (0.36 g., 4.8%). The buffer extract was acidified and extracted with ether, which was worked up to recover keto acid I (0.95 g., 8.6%), usually quite pure. When crystallization was difficult, boiling for 5 min. with methanol containing 3% hydrogen chloride precipitated the less soluble keto ester in good yield.

The above filtrate from the second crop of lactone IV was taken up in 200 ml. of ether (usually two or more preparations were combined at this point) and extracted successively with several 30-ml. extracts of 0.1 M pH 6.9 and 7.5 phosphate buffer, then with 1% sodium bicarbonate, and finally with 1% sodium carbonate solutions. All extracts were passed through a second funnel containing 150 ml. of ether. If much XII was present, its insoluble alkali salts precipitated, causing emulsions. These were washed through with more buffer or filtered out and acidified separately. If acidic products tended to precipitate, ether solutions were diluted with ethyl acetate. All extracts of a given pH were acidified and extracted with ether. The separate ether solutions were washed, dried, evaporated, and, if necessary, taken up in acetone–petroleum ether and refrigerated overnight to obtain crystals. Crops were combined for recrystallization in terms of melting point. In this way pH 6.9 and 7.5 buffer fractionation permitted recovery of pure, shiny needles of XII directly from the concentrated ether solution (0.45 g., 3.1%). Sodium bicarbonate and sodium carbonate extracts were worked up to obtain impure X (0.1 g., 0.5%, m.p. 165–172°). A crystalline residue insoluble in 5% sodium carbonate solution was recovered in about 1% yield. On recrystallization from acetone–petroleum ether, it separated very slowly, m.p. 185.5–187.5° dec., λ_{max}^{THF} 5.54 and 5.81 μ. Its structure was not investigated.

Anal. Found: C, 55.00, 54.85; H, 3.17, 3.40; N, 8.16, 7.93.

B. With Hydrogen Chloride.—Conditions were varied in an effort to increase the yield of the minor products X and XII so that their structures could be determined. The reaction mixture was saturated with hydrogen chloride by bubbling in the dry gas for 15 min. It was stoppered and placed in a bath. Table I summarizes the results of the fractionation procedure already described.

C. With Excess Aldehyde.—To improve the yield of X and of XII, 4.4 g. (0.05 mole) of pyruvic acid and 15.0 g. (0.1 mole) of *m*-nitrobenzaldehyde were warmed to dissolve, and 0.96 g. (0.01 mole) of methanesulfonic acid was added. After 3 days at 45° the product was filtered, and the filtrate was fractionated with sodium bisulfite solution and with buffers as described in method A. Products isolated were 4.83 g. of lactone IV, 2.12 g. of keto acid, 2.95 g. of recovered aldehyde, 1.65 g. of XII, 0.56 g. of X, and 0.3 g. of base-insoluble residue. Per cent yields are summarized in Table I and are not corrected for recovered aldehyde.

D. Lactone with Aldehyde.—In one experiment, 1.7 g. of lactone IV was warmed with 3.4 g of *m*-nitrobenzaldehyde and 0.75 g. of methanesulfonic acid. After 25 hr. at 45–48° the nearly solid mass was digested with nine 10-ml. portions of 1:1 ether–petroleum ether. The decanted extracts were evaporated (3.5 g.), dissolved in ether, and fractionated as before, recovering 2.04 g. of *m*-nitrobenzaldehyde and 0.17 g. (14.2% cor.) of keto acid I. The solid residue was stirred with 50 ml. of boiling ethyl acetate, leaving 0.5 g. (30%) of unchanged lactone IV (m.p. 150–153°). The filtrate yielded on fractionation, 0.27 g. (22.5% corr.) of keto acid I and 0.15 g. (9.5% based on 1.2 g. of converted lactone) of somewhat impure XII, formed by condensation of 2

(8) Analytical figures were given in ref. 2a where a reaction constant, ρ, was determined for the dissociation of a series of benzylidenepyruvic acids, and another for the hydrolysis of the corresponding esters in basic medium.

(9) For the ferric chloride test, a drop of aqueous ferric chloride solution was added to a methanol solution of a few crystals of the compound. Enols gave a soluble colored complex, keto acids sometimes a less soluble colored salt. The 2,4-dinitrophenylhydrazine test consisted of heating a methanol solution of the compound with reagent for 1 min., then chilling. Immediate precipitation of a voluminous orange product constituted a positive test. Lactone IV and keto acids X and XII gave only traces of precipitate under these conditions. The reagent was prepared in ethanol–phosphoric acid: L. F. Fieser, "Organic Experiments," D. C. Heath and Co., Boston, Mass., 1964, p. 94.

(10) A. Kailan, *Monatsh.*, **28**, 1171 (1907).

(11) J. J. Sudborough and L. L. Lloyd, *J. Chem. Soc.*, **73**, 85 (1898).

equiv. of lactone with 1 equiv. of aldehyde. All products were identified by purification and mixture melting points with authentic samples.

2,4-Dihydroxy-4-(*m*-nitrophenyl)crotonic Acid γ-Lactone IV.—This was the main product of acid-catalyzed reaction of pyruvic acid with *m*-nitrobenzaldehyde and was filtered off in 30–50% yield from the reaction mixture. The crude lactone, m.p. 143–149° (sometimes lower), was recrystallized from acetone–petroleum ether or ethyl acetate–petroleum ether. The off-white, grainy crystals melted constantly at 154–156°. The ferric chloride color is orange,[9] and the pK' in 50% methanol is 7.4; $\lambda_{max}^{CH_3OH}$ <215 mμ (ε >11,125) and 262 mμ (ε 9500); $\lambda_{min}^{CH_3OH}$ 231 mμ (ε 6750); and λ_{max}^{THF} 5.63 (lactone C=O), 5.96 (weak C=O) (due to a little keto form?), and next band 6.06 μ; n.m.r. (in CH_3CN) doublets (J = 2 c.p.s.) corresponding to single hydrogen atoms at τ 3.61 and 3.98 (β- and γ-H atoms).

Anal. Calcd. for $C_{10}H_7NO_5$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.19; H, 3.19; N, 6.94.

4-Hydroxy-2-methoxy-4-(3-nitrophenyl)crotonic Acid γ-Lactone V.—A solution of 0.5 g. of IV in 7 ml. of methanol and 20 ml. of ether was treated with an excess of diazomethane in ether solution. After standing for 30 min. the solution was concentrated, and 0.42 g. (78%) of crystals was recovered in two crops, m.p. 121–124°. On recrystallization from acetone–petroleum ether the melting point was constant at 125.5–126.6° and the ferric chloride test was negative; $\lambda_{max}^{CH_3OH}$ <215 mμ (ε 15,250), shoulder 224 (13,000), and 258 (8000); $\lambda_{min}^{CH_3OH}$ 249 mμ (ε 7500); and λ_{max}^{THF} 5.60 (lactone C=O), next band 6.04 μ; n.m.r. (in CH_3CN) doublets (J = 2 c.p.s.) corresponding to single hydrogen atoms at τ 3.92 and 3.55 (β- and γ-H atoms), singlet at τ 6.20 (3H, CH_3 group).

Anal. Calcd. for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.96. Found: C, 55.73; H, 3.79; N, 6.09.

4-Hydroxy-3-(*m*-nitrobenzylidene)-4-(*m*-nitrophenyl)-2-oxobutyric Acid X.—As Table I shows, this compound was isolated in 0.5–3.4% yield from acid-catalyzed condensations of *m*-nitrobenzaldehyde and pyruvic acid. The recovery procedure has already been described. The crude product (m.p. 166–168°) was twice recrystallized from acetone–petroleum ether to constant m.p. 174–176°. Sodium carbonate solution (1%) extracted it readily from ether solution with a yellow color. The pK' in 50% methanol is 6.4 and the ferric chloride color is red; $\lambda_{max}^{CH_3OH}$ 210 mμ (ε 22,250) and 262 mμ (ε 17,750); $\lambda_{min}^{CH_3OH}$ 232 mμ (ε 12,900); λ_{max}^{KBr} 2.87 fairly sharp (OH), 5.61–5.65 (double peak), and 5.99 μ (weak); λ_{max}^{THF} 3.03 (OH), 5.63, and 5.86 μ (weak).

Anal. Calcd. for hydroxy acid, $C_{17}H_{12}N_2O_8$: C, 54.84; H, 3.25; N, 7.53; equiv. wt., 372. Calcd. for lactone structure resembling XIV, $C_{17}H_{10}N_2O_7$: C, 57.63; H, 2.84; N, 7.91. Found: C, 54.93, 55.05; H, 3.61, 3.43; N, 7.56, 7.76; equiv. wt. (found by titration), 359.

Methyl 4-Hydroxy-3-(*m*-nitrobenzylidene)-4-(*m*-nitrophenyl)-2-oxobutyrate XI.—To a solution of 0.5 g. of lactone IV in 3 ml. of acetone, was added 50 ml. of anhydrous ether. The volume was reduced to 20 ml. and an excess of diazomethane in ether was added. After standing for 25 min., it was extracted with 2% sodium carbonate solution. The dried ether solution was concentrated and the product (0.4 g., m.p. 165–168°) was recrystallized three times from acetone–petroleum ether (m.p. 170–171°, m.m.p. 159–160° with X): $\lambda_{max}^{CH_3OH}$ <215 mμ (ε 48,500) and 234–254 mμ (ε 35,500); λ_{max}^{KBr} 2.87 sharp (OH), 5.61–5.65, and 5.98 μ (weak); and λ_{max}^{THF} 3.03 (sharp), 5.64 (acid C=O), 5.81 weak (C=O), and 5.96 μ weak (conj. C=C?).

Anal. Calcd. for $C_{18}H_{14}N_2O_8$: C, 55.98; H, 3.65; N, 7.26. Found: C, 56.21, 56.35; H, 3.85, 3.81; N, 7.40, 7.37.

2,5-Dihydro-4-hydroxy-β-(*m*-nitrobenzylidene)-γ,2-bis(*m*-nitrophenyl)-α,5-dioxo-3-furanbutyric Acid XII.—As Table I shows, this was isolated in 3–11% yield from acid-catalyzed condensations of *m*-nitrobenzaldehyde and pyruvic acid. In the recovery procedure already described it is extracted from ether by 7.2–7.5% phosphate buffer forming a yellow solution, but not by sodium bisulfite. It crystallized very slowly from supersaturated solution in ether, as highly charged, silky needles with a complex melting point. It formed a clear glass at *ca.* 100–120° and melted again with browning and gas evolution at 220–230°. It was recrystallized twice for analysis by a method which avoided heating above 40°. After dissolving in a minimum volume of acetone (0.5 g. in 3 ml.), 25 ml. of anhydrous ether was added. The solution was evaporated to about 10 ml. and the product (0.4 g.) crystallized slowly overnight. The ferric chloride color is red. The pK' in 50% aqueous methanol is 4.9, with a possible second weaker acid group obscured by the first so that its pK' could not be calculated. This supports a half enol–lactone, half keto acid structure rather than a dienol or diketo acid form: $\lambda_{max}^{CH_3OH}$ <215 mμ (ε 32,750) and 253 mμ (ε 28,900); $\lambda_{min}^{CH_3OH}$ 230 mμ (ε 20,750); λ_{max}^{KBr} 571 and 5.90 μ (weak); and λ_{max}^{THF} 5.63, 5.83, and 5.89 μ (shoulder).

Anal. Calcd. for $C_{27}H_{17}N_3O_{12}$: C, 55.01; H, 2.98; N, 7.30; equiv. wt. (based on one acid group), 575. Found: C, 55.42, 55.31; H, 3.38, 3.37; N, 7.56, 7.30; equiv. wt. (by titration), 588.

Methyl 2,5-Dihydro-4-methoxy-β-(*m*-nitrobenzylidene)-γ,2-bis(*m*-nitrophenyl)-α,5-dioxo-3-furanebutyrate XIII.—To a solution of 0.5 g. of XII in 3 ml. of THF or of acetone, was added 20 ml. of anhydrous ether. After evaporation to 10 ml. an excess of diazomethane in ether was added and an immediate precipitate of pure, powdery crystals separated (0.4 g., m.p. 245–246°). Recrystallization from acetone–petroleum ether raised the melting point to 246–247° dec. This compound was much more stable to heat than XII. The ferric chloride test was negative, $\lambda_{max}^{CH_3CN}$ 253 mμ (ε 26,250), $\lambda_{min}^{CH_3CN}$ 244 mμ (ε 25,000), λ_{max}^{KBr} 5.64–5.68 (double) and 5.94 μ (weaker); and λ_{max}^{THF} 5.63 and 6.02 μ (weaker).

Anal. Calcd. for monoester, $C_{28}H_{19}N_3O_{12}$: C, 57.04; H, 3.25; N, 7.13. Calcd. for lactone ether–ester, $C_{29}H_{21}N_3O_{12}$: C, 57.69; H, 3.51; N, 6.96. Found: C, 57.64, 57.77; H, 3.67, 3.72; N, 7.24, 7.26.

3,4-Dibromo-4-(*m*-nitrophenyl)-2-oxobutyric Acid.—To a stirred solution of 4.0 g. (0.018 mole) of finely ground *m*-nitrobenzylidenepyruvic acid (I) dissolved in 330 ml. of chloroform (dried over calcium chloride) was added dropwise 4.6 ml. (0.021 mole) of a 25% (v./v.) solution of bromine in chloroform at 25°. After standing for 1 hr., the solvent was removed from the still deeply colored solution on a rotating vacuum evaporator at 25°. Higher temperatures during evaporation caused debromination and gave intractable oily dibromide products which were found to contain original acid I. The crystalline dibromide separated very slowly from benzene–petroleum ether, yield 4.2 g. in several crops (69%), m.p. 64–68° (Ciusa[4] reported 64°). Yields in other preparations ranged from 52–85%.

3-Bromo-2,4-dihydroxy-4-(*m*-nitrophenyl)crotonic Acid γ-Lactone VIII. From the Dibromide.—Unrecrystallized solid dibromide (1.2 g., 0.003 mole) was stirred rapidly with 30 ml. of water at 65–75° for 10 min. On chilling, flaky crystals separated from the solution and the oil solidified, yield 0.70 g. (74%), m.p. 120–130° (after drying for 1 hr. at 55°). A second crop of 0.11 g. was collected after slow evaporation of the filtrate. On recrystallization from benzene–petroleum ether and twice from 75% aqueous methanol, the fluffy white crystals were dried at 60° for 30 min. and melted constantly at 167–168°. When two samples of oily dibromide which had failed to crystallize were heated with water, mixed solid products were obtained. In both cases solution in methanol and boiling for 3 min. with methanol containing 3% dry hydrogen chloride gave bromine-free keto ester II, identified by mixture melting point. The $FeCl_3$ color is purple and the pK' in 50% methanol is 5.5, $\lambda_{max}^{CH_3OH}$ 250–251 mμ (ε 14,000) and λ_{max}^{THF} 5.60 (lactone C=O) and 5.90 μ (weak C=O). The n.m.r. spectrum in acetonitrile includes a singlet at τ 3.97 (1 H), assignable to the benzyl proton.

Anal. Calcd. for $C_{10}H_6BrNO_5$; C, 40.02; H, 2.01; Br, 26.63. Found: C, 40.05; H, 2.11; Br, 26.42.

By Bromination of Lactone IV.—A solution of 0.22 g. (0.001 mole) of lactone IV in 85 ml. of dry chloroform was stirred and treated slowly with 0.32 ml. (0.0015 mole) of 25% (v./v.) bromine in chloroform solution. Absorption was rapid and after standing 30 min. the solvent was removed completely at 40° and 15 mm. On recrystallization from 50% methanol, a fluffy precipitate formed, yield 0.2 g., m.p. 165–167° (dried at 60° for 1 hr.). There was no depression on mixture melting point with the β-bromo lactone (VIII) of m.p. 167–168°, and the infrared spectra were identical.

3-Bromo-2-hydroxy-2-methoxy-4-(*m*-nitrophenyl)crotonic Acid γ-Lactone IX.—A solution of 1.0 g. (0.033 mole) of the β-bromolactone VIII in ether was treated with an excess of diazomethane in 75 ml. of ether. After 30 min. the solution was evaporated and then chilled. The fluffy crystals separated in two crops, 0.95 g. (87%), m.p. 106–109°. On recrystallization twice from acetone–petroleum ether, the melting point was 110–110.8°. The ferric chloride test was negative, $\lambda_{max}^{CH_3OH}$ 251–253 mμ (ε 11,425) and λ_{max}^{Nujol} 5.79 μ (bromo lactone C=O).

Anal. Calcd. for $C_{11}H_8BrNO_5$: C, 42.06; H, 2.56; Br, 25.44; N, 4.46. Found: C, 42.42; H, 2.78; Br, 25.62; N, 4.66.

***m*-Nitrobenzylidenepyruvic Acid Phenylhydrazone VI.**—This deep orange product was always accompanied by 30% of the tautomeric bright yellow pyrazolinecarboxylic acid (VII), even when the usual solvent, 50% acetic acid, was replaced by 50% methanol. Separation was accomplished by a tedious fractional crystallization, which was easily followed because of the marked difference in color of the two products.

A solution of 2.4 g. of sodium *m*-nitrobenzylidenepyruvate of 90% purity (0.009 mole) was dissolved in 25 ml. of 50% acetic acid at 60°, and 2.0 ml. (0.02 mole) of phenylhydrazine was added dropwise. Heating was continued for 15 min., during which time the original oil became granular. The orange solid was washed with 50% acetic acid, then with water, and air dried (weight of crude mixture of VI and VII, 2.8 g., 90%). The phenylhydrazone was less soluble in methanol and the pyrazoline was less soluble in ether. The product was conveniently purified and fractionated by dissolving in 150 ml. of ether, washing with 2% hydrochloric acid and with water, drying, and concentrating to crystallization at room temperature. Usually two crops of fairly pure pyrazoline (0.75 g.) were recovered in this way. The residual filtrate was then taken to dryness and the crude phenylhydrazone (1.62 g.) was recrystallized twice from methanol. The compact red-orange crystals melted at 180–181° dec. (melting point tube inserted in the bath 5° below the melting point). The carboxylic acid rather than an inner salt structure[12] was supported by the S-shaped pH titration curve and the pK' value of 4.2 in 50% methanol solution; $\lambda_{max}^{CH_3OH}$ 217 mμ, (ε 18,600), 266 (22,000), and 383 (30,000); $\lambda_{min}^{CH_3OH}$ 236 mμ (ε 13,750) and 320 (5500); and λ_{max}^{THF} 5.93 μ.

Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 62.05; H, 4.48; N, 13.84.

5-*m*-Nitrophenyl-1-phenyl-$\Delta^{2,3}$-pyrazoline-3-carboxylic Acid VII.—The crude yellow pyrazoline which separated from ether solution in the previous preparation was recrystallized from acetone, m.p. 161–162°. The carboxylic acid structure is indicated by the pK' of 5.0 in 50% methanol and by the normal S-shaped titration curve. An intense purple color lasting for 2 days was obtained in the Knorr pyrazoline test[12]; the phenylhydrazone (VI) gave a pale orange color, a negative test; $\lambda_{max}^{CH_3OH}$ >215 mμ (ε 16,150), 264 (26,100), and 384 (20,750); $\lambda_{min}^{CH_3OH}$ 233 mμ (ε 15,250) and 322 mμ (ε 5,750); and λ_{max}^{THF} 5.75 and 5.85 μ.

Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.57; H, 4.31; N, 13.75.

(12) L. Knorr, *Ber.*, **26**, 100 (1893). A few crystals are dissolved in 90% sulfuric acid and a drop of 1% aqueous ferric chloride solution is added. An intense purple color lasting for more than 24 hr. is a positive test.

Ring Openings of Substituted Cyclobutanes Induced by Grignard Reagents. II. 2,2,4,4-Tetramethyl-3-dimethylaminocyclobutanone*

LEONARD WEINTRAUB, ARMIN WILSON, DAVID L. GOLDHAMER, AND DONALD P. HOLLIS[1]

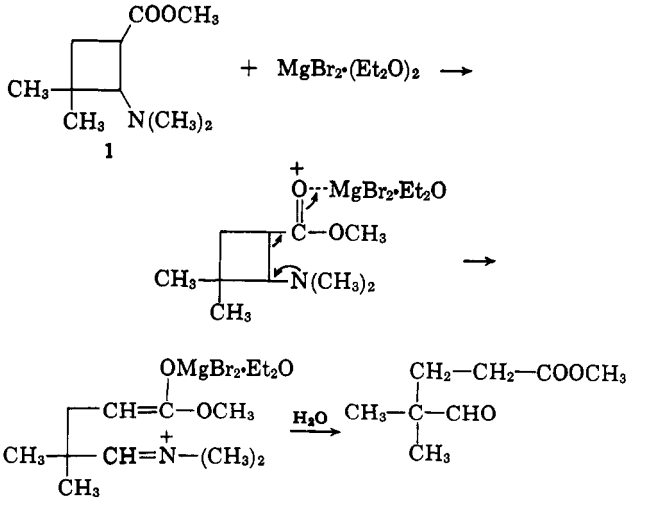
The Bristol-Myers Company, Products Division, Hillside, New Jersey, and Varian Associates, Palo Alto, California

Received November 10, 1964

The reaction of 2,2,4,4-tetramethyl-3-dimethylaminocyclobutanone has been studied with (1) the Grignard reagent, (2) phenyllithium, and (3) magnesium bromide. In some instances the ring is opened in a manner analogous to the cyclobutanes studied previously, methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate and tetramethyl-1,3-cyclobutanedione. The extent of ring cleavage brought about by the various reagents is related to the nature of the specific reagent and the structure of a particular ring.

We have recently shown that aryl Grignard reagents react with methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (1) to cleave completely the cyclobutane ring and produce only open-chain ketones of the type $ArCH(NMe_2)C(Me_2)CH_2CH_2COAr$.[2] With cycloalkyl and alkyl Grignard reagents higher than ethyl, a second open-chain ketone of the type $Me_2NCH_2C(Me_2)CH_2CH_2COR$ was obtained. The reaction of phenylmagnesium bromide with **1** produced 1,5-diphenyl-4,4-dimethyl-5-dimethylaminopentanone-1 in 90% yield. However, phenyllithium gave only the normal carbonyl addition product, diphenyl(2-dimethylamino-3,3-dimethyl)cyclobutylcarbinol.

The reaction of **1** with magnesium bromide etherate was also studied. This reagent effected a 15% conversion of **1** into methyl 4,4-dimethylglutaraldehydate. This reaction must have occurred as shown. First a complex is formed between the carbonyl oxygen and the magnesium bromide. This complex then withdraws the electrons from the α–β bond with the assistance of the unshared pair on the nitrogen atom. Grignard reagents may also open the cyclobutane ring by forming a similar electron-withdrawing complex. However, these reagents can function as nucleophiles as well as electrophiles. They could therefore open the ring by direct nucleophilic attack at the β-carbon. This attack would be facilitated by complex formation between the reagent and the amino nitrogen.



A study of the reactions of Grignard reagents, phenyllithium and magnesium bromide etherate, with other β-aminocarbonyl compounds in the cyclobutane series would be worthwhile. This study has now been ex-

* To Professor Louis F. Fieser.

(1) Johns Hopkins School of Medicine, Department of Physiological Chemistry, Baltimore, Md.

(2) L. Weintraub, A. Wilson, D. L. Goldhamer, and D. P. Hollis, *J. Am. Chem. Soc.*, **86**, 4880 (1964).