τ ($CDCl_3$) 6.73. On admixture with IIIb, the melting point was depressed more than 25°.

Anal. Calcd. for $C_{13}H_{21}NOS_2$: C, 57.52; H, 7.80; N, 5.16; S, 23.63. Found[22,23]: C, 57.5; H, 7.9; N, 5.1; S, 23.6.

***trans*-Decalin-9-carboxamide (IIIc).**—A mixture consisting of 285 mg. (1.05 mmoles) of *trans*-thioketal IIIb, m.p. 161–162°, 3.0 g. of Raney nickel and 20 ml. of absolute ethanol was refluxed for a period of 12.5 hr.[24] The mixture was cooled, Raney nickel was removed by centrifugation and washed thoroughly with hot absolute ethanol, and the combined reaction solution and washings were evaporated to dryness. An ether solution of the residual oil was centrifuged to remove turbidity and evaporated to dryness, affording 178 mg. (94%) of crude *trans*-amide IIIc, m.p. 115–121°, with an infrared spectrum which differed from that of the *cis* isomer. Repeated recrystallization from ethyl acetate–cyclohexane yielded 89 mg. (47%) of colorless prisms, m.p. 127–128° (reported[25] 125–126°); $\lambda_{\max}^{CHCl_3}$ 2.82 μ, 2.92, 5.97, 6.31.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found[22]: C, 72.5; H, 10.3; N, 7.3.

***cis*-Decalin-9-carboxamide (IIc).**—Reaction conditions were similar to those used with the *trans*-thioketal IIIb. Reaction of 84 mg. (0.31 mmole) of *cis*-thioketal IIb, m.p. 161–162°, with 1.0 g. of Raney nickel in 5 ml. of absolute ethanol yielded 48 mg. (86%) of a crystalline residue, m.p. 128.5–130°, devoid of infrared absorptions characteristic of the *trans* isomer. After several recrystallizations from cyclohexane, 32 mg. (57%) of analytically pure *cis*-amide IIc was obtained as colorless prisms, m.p. 131–132°; $\lambda_{\max}^{CHCl_3}$ 2.82 μ, 2.92, 6.01, 6.32.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found[22]: C, 72.7; H, 10.3; N, 7.6.

***trans*-Decalin-9-carboxylic Acid (IIId).**—To 49 mg. (0.27 mmole) of *trans*-amide IIIc, m.p. 128–129°, in 0.5 ml. of concd. sulfuric acid was added dropwise 0.5 ml. of a solution of 1 g. of sodium nitrite in 5 ml. of water.[26] After addition was complete the solution was heated on a steam bath for 5 min., cooled, diluted with 20 ml. of water, and extracted with three 75-ml. portions of ether. The ether extracts were washed with water, dried with sodium sulfate, and evaporated to dryness to afford 44 mg. (90%) of a pale yellow crystalline residue, m.p. 133–136°, which lacked infrared absorption at 11.26 μ characteristic of the *cis* isomer. After recrystallization from aqueous ethanol, 28 mg. (58%) pure *trans*-acid IIId was obtained as white platelets, m.p. 136.5–137° (reported[11] 135°); $\lambda_{\max}^{CHCl_3}$ 3.4 μ (sh), 3.7 (broad), 5.90, 10.28. On admixture with an authentic sample,[11] there was no melting point depression. The infrared spectrum of a chloroform solution was rich in detail, identical in all respects with that of the authentic sample, and quite different in the 7–12-μ region from that of the *cis* isomer.

***cis*-Decalin-9-carboxylic Acid (IId).**—The *cis*-acid IId was prepared in the manner described above for the *trans* isomer. From 30 mg. (0.17 mmole) of *cis*-amide IIc, m.p. 129–130.5°, was obtained 32 mg. (100%) of crude solid IId devoid of the 10.28 μ infrared band characteristic of IIId. One recrystallization from aqueous ethanol yielded 15 mg. (50%) of white plates, m.p. 117–121°, and further recrystallization raised the m.p. to 123–124° (reported[11] 122°); $\lambda_{\max}^{CHCl_3}$ 3.3 μ (broad), 3.8 μ (broad), 5.90. A mixture melting point with an authentic sample[11] was undepressed, although when mixed with the *trans* acid IIId the melting point was depressed more than 20°. The solution infrared spectrum was identical with that of the authentic sample.

Acknowledgment.—We are indebted to the Graduate School of Indiana University and to the National Science Foundation for grants in support of this study, and to Professors Marvin Carmack and V. J. Shiner, Jr., for many stimulating discussions.

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[24] F. Sondheimer and D. Rosenthal, *J. Am. Chem. Soc.*, **80**, 3995 (1958).

[25] W. Dauben, R. Tweit, and R. MacLean, *J. Am. Chem. Soc.*, **77**, 48 (1955).

[26] W. Dauben and E. Hoerger, *J. Am. Chem. Soc.*, **73**, 1504 (1951).

Production of a Fused-Ring System by an Intramolecular Michael Condensation

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The unsaturated diketone IV has been prepared from the succinoylation product (VIII) of *m*-cresyl methyl ether. Wolff-Kishner reduction gave the acid X; this was converted into the methyl ketone XI which was in turn transformed into the ketal XII, then submitted to the Birch reduction followed by acid hydrolysis. The resulting unsaturated diketone IV was treated under basic conditions in order to effect an intramolecular Michael condensation. The major product was shown to be the ketol XV arising from the *cis*-fused diketone XIV.

Friedmann and Robinson[1] have studied in a preliminary manner an ingenious scheme for synthesizing the steroid nucleus containing an 11-keto group. The approach consisted of a Michael condensation of an appropriate donor species with the bicyclic ketone I, followed by an intramolecular aldol reaction to produce the tricyclic intermediate II, and finally an intramolecular Michael condensation to complete ring D. The product was a complex mixture, and although no evidence has been advanced for the structure or stereochemisty of this product, it was presumed to contain the steroidal compound III.

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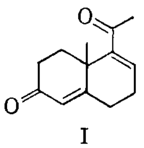
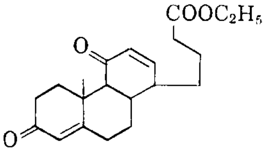
[1] C. A. Friedmann and R. Robinson, *Chem. Ind.*, **777**, 1117 (1951).



I



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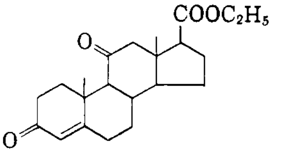
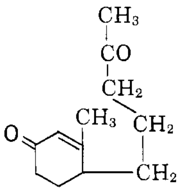
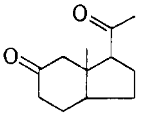


III

The last stage of this synthetic sequence, *i.e.*, II → III, is of special interest, particularly from the stereochemical point of view, and the aim of this present work was to test the feasibility of this stage in a model system. We therefore undertook the preparation of the unsaturated diketone IV in order to determine if it would undergo the intramolecular Michael reaction to yield V which represents the C/D portion of 11-keto progesterone.

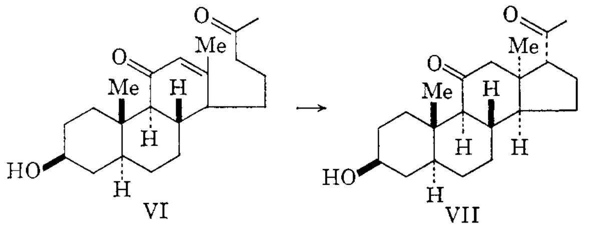


IV



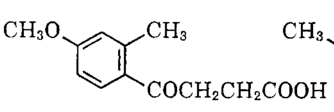
V

In connection with another objective Barton, Campos-Neves, and Scott[2] have now provided an answer to the question through their investigation of the cyclization of the tricyclic substance VI, which afforded the 13-iso structure VII (with the unnatural C/D *cis* configuration). Since our study (which was in essence completed before the Barton disclosure) provides confirmatory although somewhat different results, we are recording our observations herewith.

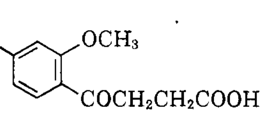


VI VII

For the preparation of the unsaturated diketone IV, it was planned to start with the keto acid VIII. On examining the literature, we discovered that the Friedel-Crafts succinoylation of *m*-cresyl methyl ether had already been described several times[3] as giving a crystalline keto acid, melting points ranging from 131° to 138°. The structure VIII was assigned to this product, but no evidence had been given to exclude the isomeric structure IX which would result from substitution *para* to the methyl instead of the methoxyl group. The latter structure was arbitrarily assigned to a minor product, m.p. 124–126°, isolated in 4% yield by Dutta and Bagchi.[3d] In our hands the succinoylation of *m*-cresyl methyl ether in nitrobenzene–tetrachloroethane solution afforded in 70% yield a mixture of two products in the ratio of about 2:1. The predominant product after purification melted at 130–133° and evidently corresponded to that previously regarded as VIII. The other isomer after purification melted at 121–123.5° and was undoubtedly the same as that described by Dutta and Bagchi.

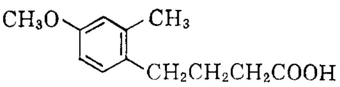


VIII

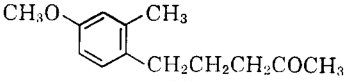


IX

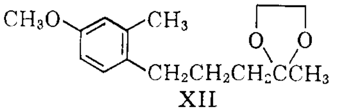
The structures of the keto acids were proved by oxidation with sodium hypobromite. The 133° isomer afforded 2-methyl-4-methoxybenzoic acid, m.p. 174.5–175° (reported,[4] 176°), and the 123° acid was thus converted into 4-methyl-2-methoxybenzoic acid, m.p. 103–104° (reported,[4] 103°). The latter product was compared in mixed melting point experiments with authentic material produced by the Reimer-Tiemann reaction of *m*-cresol followed by methylation and oxidation by silver oxide. It was thus shown that the previously assumed structures were correct.



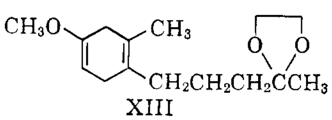
X



XI



XII



XIII

The keto acid VIII was treated by the Huang-Minlon modification of the Wolff-Kishner reaction[5] to give in 86% yield the previously known[3c] reduction product, m.p. 91.5–93°. The formerly presumed structure of this substance thus was proved to be γ-(2-methyl-4-methoxyphenyl)butyric acid X. This acid was converted, by the di-*t*-butyl

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[2] D. H. R. Barton, A. S. Campos-Neves, and A. I. Scott, *J. Chem. Soc.*, 2698 (1957).

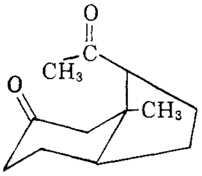
[3] (a) W. H. Bentley, H. D. Gardner, C. Weizmann, and C. V. Temperly, *J. Chem. Soc.*, 1624 (1907). (b) K. W. Rosenmund and D. Shapiro, *Arch. Pharm.*, **272**, 313 (1934). (c) R. D. Desai and M. A. Wali, *Proc. Indian Acad. Sci.*, **6A**, 144 (1937). (d) D. K. Dutta and P. Bagchi, *Sci. and Culture* (Calcutta), **17**, 137 (1951).

[4] C. Schall, *Ber.*, **12**, 816 (1879).

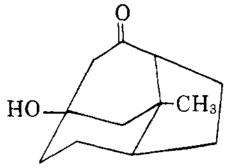
[5] Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

malonate synthesis,[6] into the corresponding methyl ketone XI in 87% yield. Treatment of this oily product with ethylene glycol in the presence of acid afforded the oily ketal XII in 94% yield. The ketal was then reduced with lithium and alcohol in ammonia[7] and, without isolation, the resulting enol ether was submitted to acid hydrolysis. The oily product, isolated in 80% yield, was evidently a mixture containing a large proportion of the desired unsaturated diketone IV as shown by the ultraviolet spectrum, $\lambda_{\max}^{95\%\ C_2H_5OH}$ 235 mμ (ε 11,700). The most likely major contaminant was the β,γ-unsaturated isomer which, however, was considered to be as useful as the α,β-tautomer in the next stage.

The intramolecular Michael condensation was carried out in *t*-butyl alcohol solution containing 10% potassium *t*-butoxide, and the course of the reaction was followed by ultraviolet spectroscopy. The absorption maximum at 235 mμ disappeared within a few minutes and after thirty minutes a crystalline product, m.p. 106.5–108°, was isolated in 75% yield.



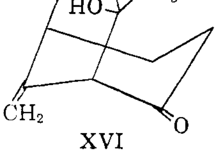
XIV



XV

Compositional analysis and molecular weight determinations were in accord with the structure V; however, the infrared spectrum of the 108° substance exhibited strong absorption at 2.98 μ, indicating the presence of a hydroxyl group. This conclusion was confirmed by conversion of the 108° compound into a crystalline mono-3,5-dinitrobenzoate. The 108° compound also exhibited ketonic absorption at 5.9 μ in the infrared spectrum, and its ready conversion into a crystalline monooxime confirmed the ketol structure.

Molecular models show that there is only one reasonable structure for this ketol, namely XV which is derived from the *cis*-fused hydrindane system XIV by an intramolecular aldolization. It is to be noted that the *trans*-fused product could not undergo an intramolecular aldol condensation.



XVI

The alternative bridged ring structure XVI may be excluded by the infrared spectrum which shows no appreciable absorption in the 11-μ region characteristic of a terminal methylene group, and by the NMR spectrum which shows no vinyl proton absorption.

The failure of the substance VII to form a bridged ring ketol of the type XV may be due to a destabilization of such a structure (in the case of VII) by the 1,3-diaxial interaction between the C-19 methyl and C-21 methylene groups.

The failure of the unsaturated diketones IV and VI to yield *trans*-fused products shows that this method of forming a steroidal ring D has a serious stereochemical drawback, and it may be concluded that the product of Friedmann and Robinson most probably contained little, if any, of the natural product.

Experimental

Succinoylation of *m*-Cresyl Methyl Ether.—This procedure was adapted from that for the succinoylation of benzene.[8] A solution of 87 g. of *m*-cresyl methyl ether and 75 g. of succinic anhydride in 800 ml. of tetrachloroethane and 200 ml. of nitrobenzene was cooled to 0° in an ice–salt bath; then 200 g. of anhydrous aluminum chloride was added with stirring over a period of 1 hr., during which time the temperature was not allowed to rise above 5°. After the addition was complete, the mixture was allowed to stand for 2 days at 12°, and then poured onto ice and 250 ml. of hydrochloric acid. The organic layer was separated and extracted repeatedly with dilute ammonium hydroxide solution. Acidification of the alkaline extracts with hydrochloric acid gave a light gray crystalline mixture which was recrystallized from 4 l. of water (Norit). The colorless product thus obtained amounted to 110 g., m.p. 104.5–120.5°. A combination of mechanical separation and repeated recrystallizations from acetone showed this mixture to contain two products, one needles, m.p. 130–133°, and the other prisms, m.p. 121–123.5°, in a ratio of about 2:1, respectively. The higher melting isomer has been previously described as melting at 131–132°,[3a] 133°,[3b] and 135°.[3d]

The 133° isomer was oxidized according to the procedure for the preparation of β,β-dimethylglutaric acid from menthone.[9] The product obtained after three recrystallizations from benzene melted at 174.5–175° (reported for 2-methyl-4-methoxybenzoic acid,[4] m.p. 176°).

Similarly the 123° isomer yielded a crude oily oxidation product which upon recrystallization from benzene was obtained as needles, m.p. 103–104° (reported,[4] 103°), undepressed on admixture with authentic 2-methoxy-4-methylbenzoic acid.

Succinoylation by the procedure of Desai and Wali[3c] appeared to give a higher proportion of the higher melting isomer VIII. Thus from 250 g. of *m*-cresyl methyl ether and 200 g. of succinic anhydride, there was obtained after recrystallization 270 g. (60% yield) of material, m.p. 133.5–136°, which was employed in the next stage of the synthesis.

γ-(2-Methyl-4-methoxyphenyl)-butyric Acid (X).—The following procedure is an adaptation of that described for the reduction of β-(4-methoxy-1-naphthoyl)propionic acid.[10] A mixture of 200 g. of the aforementioned keto acid VIII, m.p. 133.5–136°, 900 ml. of diethylene glycol, 168 g. of 85% potassium hydroxide, and 90 ml. of 95% hydrazine hydrate was boiled under reflux (atmosphere of nitrogen) for 1.5 hr., then allowed to distill until the temperature of the solution

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(6) G. S. Fonken and W. S. Johnson, *J. Am. Chem. Soc.*, **74**, 831 (1952).

(7) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

(8) L. F. Somerville and C. F. H. Allen, *Org. Syntheses*, Coll. Vol. II, 81 (1943).

(9) W. T. Smith and G. L. McLeod, *Org. Syntheses*, **31**, 40 (1951).

(10) R. Hirschmann and W. S. Johnson, *J. Am. Chem. Soc.*, **73**, 326 (1951).

reached 205°. Heating was continued for an additional 2 hr. (internal temperature 205–215°), then the dark mixture was cooled, diluted with 200 ml. of water, and then 250 ml. of dimethyl sulfate was added slowly with stirring while the temperature was maintained below 30°. Sodium hydroxide was added from time to time in order to maintain the reaction mixture alkaline. After all of the dimethyl sulfate was added, the mixture was heated under reflux for 1 hr. The solution was cooled and added slowly with stirring to a mixture of excess hydrochloric acid and ice. The crystalline acid which separated was dried and recrystallized from petroleum ether (b.p. 60–68°) to give 171 g. (85.5% yield), m.p. 91.5–93° (reported,[3c] 92°).

5-(2-Methyl-4-methoxyphenyl)pentanone-2 (XI).—A mixture of 52.0 g. of the aforementioned acid X, m.p. 91–93°, 125 ml. of anhydrous benzene and 23 ml. of thionyl chloride (Eastman Kodak Co., White Label grade) was heated under reflux for 1.5 hr.; then the solvent was removed under reduced pressure. A 50-ml. portion of benzene was added to the dark residue and the solvent removed again under reduced pressure. This treatment was repeated once more in order to insure complete removal of excess thionyl chloride.

According to a previously described procedure,[6] 136 g. of di-*t*-butyl malonate in 600 ml. of anhydrous benzene was converted to the sodio derivative by refluxing for approximately 3 hr. with 16 g. of sodium hydride. The mixture was cooled to about 60°, and a solution of the crude acid chloride (see above) in 100 ml. of anhydrous benzene was added with stirring over a period of about 5 min. The mixture was heated under reflux with stirring for 1 hr. and then allowed to cool. After standing overnight the viscous orange-brown solution was treated with excess of cold 1:1 aqueous hydrochloric acid. The organic layer was washed with water, then concentrated under reduced pressure. The residual oil was dissolved in 20 g. of acetic acid and 20 g. of monochloroacetic acid and heated at 140–150° for 4 hr. During the early part of the heating period vigorous evolution of gas (isobutylene and carbon dioxide) was observed. The dark reaction mixture was diluted with benzene, then washed with water, 5% sodium hydroxide solution, again with water, and dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the solvent was fractionally distilled through a short Vigreux column, and the ketone was thus obtained as a colorless liquid, b.p. 122–125° (0.7–0.8 mm.), $n^{25}\text{D}$ 1.5165. The yield was 44.8 g. (87%).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.6; H, 8.75.

The **2,4-dinitrophenylhydrazone** was obtained as orange crystals from absolute ethanol–ethyl acetate, m.p. 99.5–101.5°.

Anal. Calcd. for $C_{19}H_{22}O_5N_4$: C, 59.06; H, 5.74. Found: C, 59.4; H, 5.8.

2-Ethylenedioxy-5-(2-methyl-4-methoxyphenyl)pentane (XII).—According to the usual procedure[11] a mixture of 20.6 g. of the aforementioned ketone XI, 62 ml. of ethylene glycol, and 1 g. of *p*-toluenesulfonic acid in 1.5 l. of benzene was allowed to reflux in a system containing a water separator. After 5 hr. there was no evidence of further reaction, and the mixture was cooled, then washed with 5% sodium hydroxide solution, followed by water, and finally dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was fractionally distilled through a short Vigreux column. The portion boiling at 140–143° (1 mm.) amounted to 23.4 g. (94% yield), $n^{25}\text{D}$ 1.5122.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.1; H, 8.7.

3-Methyl-4-(4-ketopentyl)-2-cyclohexenone (IV).—According to the Wilds procedure[7] a total of 20.8 g. of lithium wire was added with stirring over a period of about 10 min. to a solution of 25.0 g. of the aforementioned ketal XII in 75 ml. of anhydrous ether and 2.5 l. of anhydrous ammonia. After the addition was complete, the dark blue mixture was stirred for 20 min., then absolute ethanol was added drop by drop until the blue color disappeared. This stage required approximately 2 hr. About 1 lb. of ether was added, and the mixture evaporated slowly to dryness over a steam bath. The grayish-white residue was treated with ether and ice water. The aqueous layer was extracted with ether and the combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained upon removal of the solvent under reduced pressure was dissolved in 75 ml. of 0.2 *N* hydrochloric acid in 1:1 aqueous ethanol, and the solution was heated under reflux for 1 hr. The mixture was cooled, diluted with water, and the aqueous layer extracted with ether. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained upon removal of the solvent under reduced pressure was distilled through a short Vigreux column to yield 15.5 g. of colorless liquid, b.p. 132–143° (0.8–0.9 mm.), $n^{25}\text{D}$ 1.4930–1.5000, $\lambda_{\max}^{95\%\ C_2H_5OH}$ 235 mμ (ε 11,700). Further distillation did not effect any apparent separation of this mixture which was used directly in the next experiment.

1-Methyl-tricyclo[3.3.1.2^{2,8}]undecan-5-ol-3-one (XV).—A solution of 6.4 g. of the crude diketone IV in 5 ml. of anhydrous *t*-butyl alcohol was added dropwise to a solution of 0.13 g. of potassium in 15 ml. of anhydrous *t*-butyl alcohol. The rate of addition was controlled so as to maintain the reaction mixture at room temperature. After the addition was complete (5–15 min.), the solution was allowed to stir at room temperature for 0.5 hr. The mixture was acidified with 1:1 hydrochloric acid, water was added, and the mixture extracted with ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. The yellow solid obtained upon removal of the solvent was triturated with 2 ml. of cold ether and the resulting sticky product was recrystallized from petroleum ether (b.p. 60–68°) to give 4.8 g. of colorless material, m.p. 106.5–108°, $\lambda_{\max}^{CS_2}$ 2.95 μ (OH), 5.90 (C═O); $\lambda_{\max}^{CHCl_3}$ 2.95 μ, 5.92; $\lambda_{\max}^{95\%\ C_2H_5OH}$ 282.5 mμ (ε 20); NMR spectrum at 60 megacycles (carbon tetrachloride solution) (tetramethylsilane internal standard): 3 protons at 62 c.p.s. (unsplit CH_3); 2 protons at 144 c.p.s. (CH_2 alpha to carbonyl); 1 H at 232 c.p.s. (OH). The molecular weight was determined by E. Meier, on a Mechrolab Model 301A osmometer: Calcd. 194, Found: 192 (in butyl acetate), 197 (in benzene).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.2; H, 9.5.

The **oxime** was obtained as colorless crystals from dilute ethanol, m.p. 170.5–173°.

Anal. Calcd. for $C_{12}H_{19}O_2N$: C, 68.86; H, 9.15. Found: C, 68.9; H, 9.3.

The **3,5-dinitrobenzoate** was obtained as pale yellow crystals from absolute ethanol, m.p. 169–171°.

Anal. Calcd. for $C_{19}H_{20}O_7N_2$: C, 58.76; H, 5.19. Found: C, 59.2; H, 5.2.

Acknowledgment.—Support for this project has been provided by the Wisconsin Alumni Research Foundation, the National Science Foundation, and the U. S. Public Health Service.

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[11] E. J. Salmi, *Ber.*, **71B**, 1803 (1938).