1-Amino-3,4-dihydro-2(1H)-quinolone (IX) was prepared by the procedure of Hammick, Roe and Voaden,[26,27] m.p. 143.5–144° (lit.[26] m.p. 144°).

1-Benzalamino-3,4-dihydro-2(1H)-quinolone was prepared in 81% crude yield from the reaction of 1-amino-3,4-dihydro-2-quinolone with benzaldehyde following the procedure described above for 1-benzalaminoöxindole. The product (m.p. 91–93°) was recrystallized from ethanol, forming colorless rods, m.p. 94–95°, in 58% yield.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.10. Found: C, 76.81; H, 5.75; N, 11.01.

Benzylaldehyde α-acetylphenylhydrazone was prepared in 92% crude yield, m.p. 119–122°, by the procedure of Widman.[28] Recrystallization of the crude product from 80% ethanol gave 63% of fine, colorless needles, m.p. 120.5–122° (Kofler hot-stage m.p. 122.5–123°; lit.[27] m.p. 122°).

(26) D. L. Hammick, A. M. Roe and D. J. Voaden, *Chemistry & Industry*, 251 (1954).

(27) *Cf.* S. Kluger, *ibid.*, 465 (1954).

(28) O. Widman, *Ber.*, **27**, 2964 (1894).

N-Methylacetanilide.—A solution of 3.0 g. (0.028 mole) of N-methylaniline, 3.9 ml. (0.028 mole) of triethylamine and 25 ml. of dry carbon tetrachloride was stirred and cooled below 15° while a solution of 2 ml. (0.028 mole) of acetyl chloride in 25 ml. of carbon tetrachloride was added dropwise. After the mixture had stood overnight in the refrigerator the triethylamine hydrochloride was removed by filtration and the carbon tetrachloride by flash evaporation. The white solid residue was recrystallized three times from ether, giving 2.7 g. (65%) of N-methylacetanilide as white crystals, m.p. 99–100° (lit.[29] m.p. 102°).

β-Acetyl-α-methylphenylhydrazine was prepared using a procedure like that described for N-methylacetanilide. After two recrystallizations from ether and one from benzene 8.8 g. (66%) of white crystals, m.p. 92.5–93° (lit.[30] m.p. 92–93°), was obtained from 10 g. (0.08 mole) of *unsym*-methylphenylhydrazine.

(29) P. Hepp, *ibid.*, **10**, 327 (1877).

(30) E. Fischer, *Ann.*, **239**, 250 (1887).

LINCOLN 8, NEBR.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Syntheses in the Colchicine Field

BY K. I. H. WILLIAMS, S. E. CREMER, F. W. KENT,[1] E. J. SEHM[2] AND D. S. TARBELL

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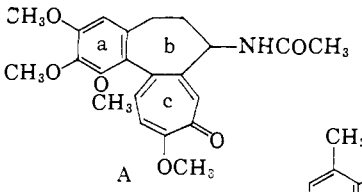
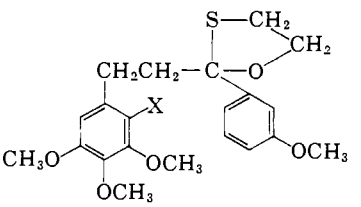
As part of a synthetic approach to colchicine the compounds 2-(3′-methoxyphenyl)-2-[β-(2″-amino-3″,4″,5″-trimethoxyphenyl)]-ethyl-1,3-dioxolane (N-2) and the corresponding oxathiolane (B-2) have been synthesized. Pschorr-type ring closure of N-2 led exclusively to 2-(3′-methoxyphenyl)-6,7,8-trimethoxyquinoline (R). The mixed anhydride (D) has been used to acylate di-*t*-butyl 3,4,5-trimethoxybenzylmalonate to give 2-methoxy-4-[α-keto-β,β-dicarbo-*t*-butoxy-γ-(3′,4′,5′-trimethoxyphenyl)]-propyltropone (C).

In an earlier publication,[3] it was suggested that colchicine (A) might be synthesized by a ring closure of the preformed "a" and "c" rings by a



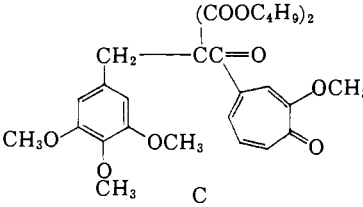
A



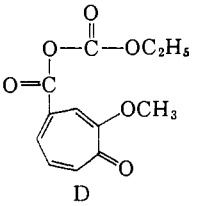
B-1, X = NO_2
2, X = NH_2
3, X = $NHCOCH_3$

Pschorr cyclization. A similar approach has been investigated by Nozoe.[4] Some progress was reported[5] recently in our program by the preparation, by practical procedures, of 4-carboxytropolone and numerous derivatives.

The present paper describes the synthesis of the model compound B for the Pschorr cyclization, of the acyltropolone derivative C (formed *via* the crystalline carboxylic-carbonic anhydride D) and of numerous other related compounds; some of these may be useful as intermediates in a colchicine synthesis of the above type.

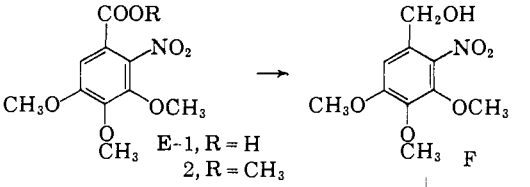


C



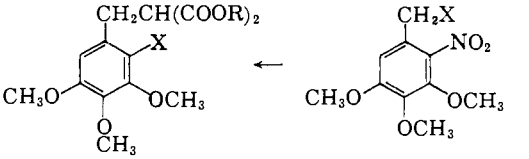
D

Methyl 3,4,5-trimethoxybenzoate[6] was nitrated in yields of 60% or better, with acetic anhydride–



E-1, R = H
2, R = CH_3

F



H-1, R = *t*-C_4H_9, X = NO_2
2, R = *t*-C_4H_9, X = NH_2
3, R = *t*-C_4H_9, X = $NHCOCH_3$
4, R = *t*-C_4H_9, X = $NHCOC_6H_4OCH_3$-*m*

G-1, X = OTS
2, X = Cl
3, X = Br

(1) Union Carbide Fellow, 1956–1957.

(2) Elon Huntington Hooker Fellow, 1956–1957.

(3) D. S. Tarbell, R. F. Smith and V. Boekelheide, THIS JOURNAL, **76**, 2470 (1954).

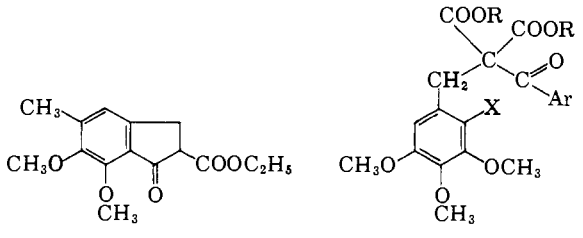
(4) T. Nozoe, K. Takase, Y. Kitahara and K. Doi, Abstracts of Papers Presented at the 132nd Meeting of the American Chemical Society, Sept. 8-13, 1957, p. 47. While this paper was in press, the synthesis of colchicine was reported by A. Eschenmoser, *et al.*, *Angew. Chem.*, **71**, 637 (1959), and by E. E. van Tamelen, *et al.*, THIS JOURNAL, **81**, 6341 (1959).

(5) D. S. Tarbell, K. I. H. Williams and E. J. Sehm, *ibid.*, **81**, 3443 (1959).

(6) M. T. Bogert and R. M. Isham, *ibid.*, **36**, 514 (1914).

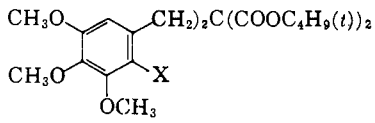
cupric nitrate.[7,8] The nitro ester E-2 was reduced to 2-nitro-3,4,5-trimethoxybenzyl alcohol (F) in 70% yield by sodium borohydride–aluminum chloride[9] and also by reduction of the free nitro acid E-1 with diborane[10] in 93% yield. The alcohol F was converted to the tosylate G-1 with tosyl chloride and sodium hydride dispersion in benzene[11]; the corresponding chloride G-2 was prepared in good yield with phosphorus pentachloride in cold benzene.[12] The bromide G-3 was prepared by the action of lithium bromide on the tosylate in refluxing acetone.

The more readily available unnitrated malonate, diethyl 3,4,5-trimethoxybenzylmalonate,[13] was not nitrated by the cupric nitrate procedure; the action of nitric acid in glacial acetic acid gave cyclization with loss of ethanol, to form varying amounts of 2-carbethoxy-5,6,7-trimethoxyindanone (J).



J K

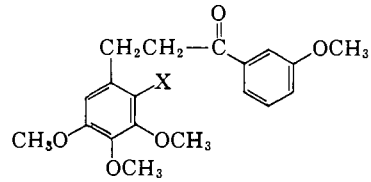
K-1, Ar = $CH_3OC_6H_4$(*m*), R = *t*-C_4H_9, X = H
2, Ar = $CH_3OC_6H_4$(*m*), R = *t*-C_4H_9, X = NO_2
3, Ar = $CH_3OC_6H_4$(*m*), R = *t*-C_4H_9, X = $NHCOC_6H_4OCH_3$(*m*)



L-1, X = NO_2
2, X = NH_2
3, X = $NHCOCH_3$

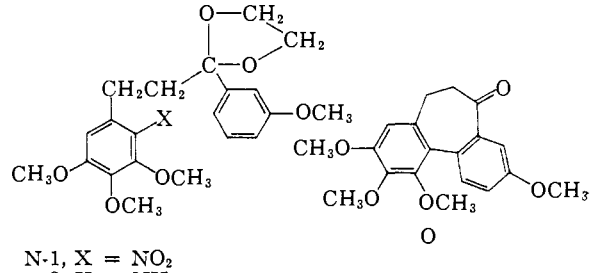
A procedure[14] in which the tosylate G-1, di-*t*-butyl malonate and sodium hydride in a 1:3:2 molar ratio were used in *t*-butyl alcohol yielded the bis-alkylated malonate L-1, which was characterized by reduction to the oily bis-amine L-2, and conversion to the crystalline bisamide L-3. The desired monoalkylation product, di-*t*-butyl 2-nitro-3,4,5-trimethoxybenzylmalonate (H-1), was obtained with a 1:1 molar ratio of tosylate to sodium hydride dispersion, and a 25-fold excess of di-*t*-butyl malonate; only small amounts of the bis-alkylation product L-1 were isolated. The monoalkylation product was obtained free of the dialkylation product by using the chloride G-2 instead of the tosylate as the alkylating agent.

Acylation of the malonate H-1 with *m*-methoxybenzoyl chloride and lithium amide[15] gave a high and reproducible yield of the desired crystalline



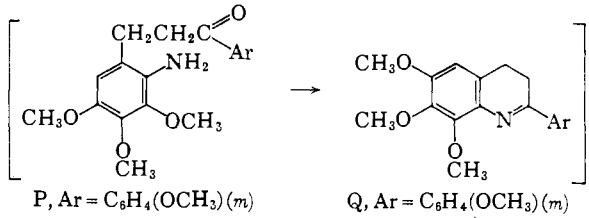
M-1, X = NO_2
2, X = $NHCOC_6H_4(OCH_3)$(*m*)
3, X = $NHCOCH_3$
4, X = H

di-*t*-butyl 2-nitro-3,4,5-trimethoxybenzyl-3′-methoxybenzoylmalonate (K-2).[16] In most runs the malonate was not isolated and purified but was treated directly with acid to effect decarbo-*t*-butoxylation to the ketone M-1, which was also characterized by its crystalline oxime.

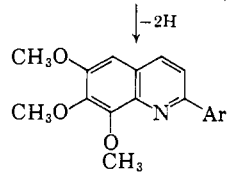


O

N-1, X = NO_2
2, X = NH_2
3, X = $N{=}CHC_6H_4(OCH_3)$(*m*)
4, X = $NHCOCH_3$



P, Ar = $C_6H_4(OCH_3)$(*m*) Q, Ar = $C_6H_4(OCH_3)$(*m*)



R, Ar = $C_6H_4(OCH_3)$(*m*)

The ketone was converted to the ethylene ketal N-1 in the usual way[17]; catalytic reduction of the

(7) J. B. Menke, *Rec. trav. chim.*, **44**, 141, 269 (1925); G. Bacharach, THIS JOURNAL, **49**, 1522 (1927).

(8) Nitration with acetic anhydride–nitric acid (C. J. Overmyer, *ibid.*, **49**, 499 (1927)) is reported to give E-2 in high yield; however, the procedure is hazardous. *Cf.* also G. C. Buchanan, *et al.*, *J. Chem. Soc.*, 325 (1944).

(9) H. C. Brown and B. C. Subba Rao, THIS JOURNAL, **78**, 2582 (1956).

(10) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

(11) The hydroxyl group in alcohol F is very strongly hydrogen bonded by the nitro group, judging from the infrared spectrum, which is doubtless the reason why attempted tosylation with tosyl chloride–pyridine was completely unsuccessful; *cf.* J. K. Kochi and G. S. Hammond, THIS JOURNAL, **75**, 3443 (1953), for a similar preparation of benzyl tosylates using sodium hydride.

(12) F. W. Kay and A. Pictet, *J. Chem. Soc.*, **103**, 947 (1913); attempts to prepare G-2 with thionyl chloride or with dry HCl were unsuccessful.

(13) Prepared by modification of the method of N. L. Drake and W. B. Tuemmler, THIS JOURNAL, **77**, 1204 (1955).

(14) G. S. Fonken and W. S. Johnson, *ibid.*, **74**, 831 (1952).

(15) *Cf.* C. R. Hauser and W. H. Puterbaugh, *ibid.*, **75**, 1068 (1953); sodium hydride as base gave irreproducible results.

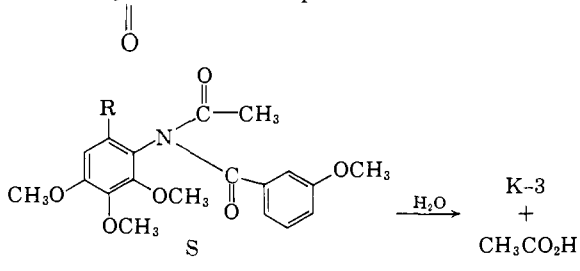
(16) It is of interest to note that the crystalline benzoylated malonates prepared showed *four* bands in the carbonyl region of the infrared; K-2, 1770, a close doublet at 1725 and 1695 cm.$^{-1}$. The bis-alkylated di-*t*-butyl malonates L-1 all showed 2 bands, one at 1730–1740 cm.$^{-1}$ and the other at 1710–1725 cm.$^{-1}$.

(17) *Cf.* M. Sulzbacher, E. Bergmann and E. R. Pariser, THIS JOURNAL, **70**, 2827 (1948), and references therein.

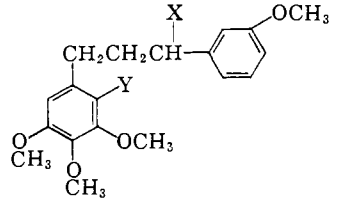
ketal in ethanol failed, but with Adams catalyst in benzene[18] the aminoketal N-2 was obtained in excellent yields; the amine was characterized as its Schiff base N-3, and as the amide N-4. Numerous attempts to effect a Pschorr-type ring closure of N-2 to the desired dibenzocycloheptadiene O were unsuccessful; although in each run, some diazotization of N-2 took place, as shown by a coupling test with β-naphthol, the only crystalline compound isolated from the various runs was 2-(3′-methoxyphenyl)-6,7,8-trimethoxyquinoline (R). This compound apparently arose from hydrolysis of the ketal N-2 during diazotization, followed by cyclization of the aminoketone P to the dihydroquinoline Q, which either air oxidized or disproportionated to the completely aromatic system R. The structure of R was supported by analysis of it and of its hydrochloride, and also by its ultraviolet spectrum, which closely resembles that of 2-phenylquinoline; R also was formed by dissolving the aminoketal N-2 in 0.1 *N* hydrochloric acid and extracting thoroughly with ether.

The nitromalonate H-1 was reduced to the aminomalonate H-2 with Adams catalyst and hydrogen in hot benzene solution; H-2 was further characterized by acylation with acetic anhydride to give the amide H-3 and with *m*-methoxybenzoyl chloride to give H-4.

Acylation of the lithium salt (from 2 moles of base and 1 of H-3) of H-3 with excess *m*-methoxybenzoyl chloride gave, after acid treatment, an oil which gave a dinitrophenylhydrazone of the composition required for that of K-3. Presumably S was formed as an intermediate and underwent loss of $CH_3C(=O)-$ in the workup.



The nitrophenylpropiophenone derivative M-1 was reduced to the alcohol T-1 in good yield with sodium borohydride, and the nitro group of T-1 was reduced to the amine T-2 with hydrazine–Raney nickel.[19] The resulting aminoalcohol T-2 was characterized by acetylation to form the amide ester T-3. The aminoalcohol T-2 was diazotized and treated with potassium iodide, in an attempted Sandmeyer reaction, but oxidation–reduction took place instead,[20] and a 42% yield of β-(3,4,5-trimethoxyphenyl)-3′-methoxypropiophenone, identical to the sample synthesized below, was obtained.



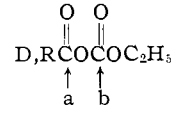
T-1, X = OH, Y = NO_2
2, X = OH, Y = NH_2
3, X = $OCOCH_3$, Y = $NHCOCH_3$

The extreme ease of acid hydrolysis of the ethylene ketal N-2 led to the study of the possibly more acid stable hemithioketal[21] B-2. The nitroketone M-1 yielded the corresponding hemithioketal B-1 by the usual procedure; catalytic hydrogenation of the nitro group in B-1, using either platinum or palladium, failed, presumably due to sulfur poisoning of the catalyst. The aluminum amalgam procedure[22] gave the amine B-2 in good yield; this compound was treated with acetic anhydride–pyridine, followed by acidic hydrolysis, which yielded β-(2-acetamido-3,4,5-trimethoxyphenyl)-3′-methoxypropiophenone (M-3); the intermediate B-3 was not isolated. This product was identical with that obtained by hydrolysis of the acetamido-ketal N-4.

Alkylation of di-*t*-butyl malonate with 3,4,5-trimethoxybenzyl chloride gave the expected malonate in good yield; acylation of the lithium salt of this malonate with *m*-methoxybenzoyl chloride afforded, after acid treatment, β-(3,4,5-trimethoxyphenyl)-3′-methoxypropiophenone,[23] which was characterized as the oxime.[23b]

From 2-methoxy-4-carboxytropone[5] we prepared the crystalline mixed anhydride[24] D, and used it to acylate the lithium salt of the malonate to give the methoxytroponoylmalonate C. Further experiments are in progress.

The reactivity of the carboxylic carbonyl "a" of the mixed anhydride



is of the same order of magnitude as the reactivity of the carbonic carbonyl "b"[25]; treatment of D with aniline gave a 1:1 mixture of 2-methoxy-4-carboxytropone and its anilide.

Experimental[26]

Methyl 2-Nitro-3,4,5-trimethoxybenzoate (E-2).—Methyl 3,4,5-trimethoxybenzoate[6] (45 g., 0.2 mole) was dissolved in 225 ml. of acetic anhydride. Finely ground

(18) Similar behavior of a hindered aromatic nitro group was observed by K. W. Gopinath, T. R. Govindachari, K. Nagarajan and K. K. Purushothaman, *J. Chem. Soc.*, 504 (1958); *cf.* also D. S. Tarbell and G. N. Nicholls, THIS JOURNAL, **74**, 4935 (1952).

(19) R. E. Moore and A. Furst, *J. Org. Chem.*, **23**, 1504 (1958), and preceding papers.

(20) *Cf.* D. F. DeTar and T. Kosuge, THIS JOURNAL, **80**, 6072 (1958).

(21) *Cf.* J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 4961 (1951); C. Djerassi and M. Gorman, *ibid.*, **75**, 3704 (1953).

(22) J. H. Boyer and H. Alul, *ibid.*, **81**, 2136 (1959).

(23) (a) R. G. Christiansen, R. R. Brown, A. S. Hay, A. Nickon and R. B. Sandin, *ibid.*, **77**, 948 (1955). (b) Both M-4 and its oxime have been reported as oils by H. Lettré and E. Hartwig, *Z. physiol. Chem.*, **291**, 164 (1952).

(24) *Cf.* D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **21**, 144 (1956); **22**, 245 (1957); *Org. Syntheses*, **37**, 20 (1957); D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958).

(25) *Cf.* N. A. Leister and D. S. Tarbell, *ibid.*, **23**, 1152 (1958).

(26) Microanalyses by Miss Annette Smith, T. Montzka, W. Manser and the Micro-Tech Laboratories, Skokie, Ill. Melting points are uncorrected. Infrared spectra were taken as Nujol mulls or in potassium bromide disks with a Perkin–Elmer model 21 spectrometer. Ultraviolet spectra were taken with a Cary recording spectrophotometer by Mr. Carl Whiteman. "50% Sodium hydride dispersion" refers to the commercial (Metal Hydrides) dispersion in mineral oil.

cupric nitrate (61 g., 0.25 mole) was added at such a rate that the temperature of the exothermic reaction was maintained between 50–65° (there was an initial induction period of some 15 min.); after the addition was complete, the solution was stirred at room temperature for 1 hr. The reaction mixture then was poured over 1 kg. of ice; when the ice had melted, the precipitated product was collected on a filter and air-dried overnight. The crude ester then was taken up in 200 ml. of benzene and the resultant solution passed over a column of 25 g. of alumina; the column was eluted with 30 ml. of 4:3 benzene–ether mixture. The solvents were then removed at room temperature to yield 36 g. (67%) of methyl 2-nitro-3,4,5-trimethoxybenzoate, m.p. 67–68°, reported[8] m.p. 67°. Cupric nitrate in acetic anhydride at −70°[27] failed to nitrate methyl 3,4,5-trimethoxybenzoate. The free acid,[28] m.p. 165–166°, was prepared by basic hydrolysis of the ester.

2-Nitro-3,4,5-trimethoxybenzyl Alcohol (F). (A) By Diborane Reduction of 2-Nitro-3,4,5-trimethoxybenzoic Acid (E-1).—2-Nitro-3,4,5-trimethoxybenzoic acid (12.35 g.) was added slowly to a solution of 1.7 g. of sodium borohydride in 50 ml. of diglyme. To the resultant solution, placed under a nitrogen atmosphere with provision for the exiting gases to be passed through acetone to remove any stray diborane, at 0° was added 7.8 g. of boron trifluoride etherate over 1 hr. The reaction was stirred at room temperature for an additional hour; 5 ml. of ethanol was added to destroy the excess diborane and the entire system was swept well with nitrogen. The mixture was poured over 600 ml. of ice and water, the product was filtered off and dried, to give 7.57 g. of yellow product, m.p. 70.5–71.5°. The above filtrate was extracted twice with 100-ml. portions of chloroform and the organic phases combined, dried and evaporated to dryness. The residue was recrystallized from a benzene–heptane mixture to give an additional 3.3 g. of alcohol, m.p. 70.5–71.5°. The total yield was 10.87 g. (93%). The product was identical with that prepared below (melting point and mixed melting point).

(B) By Sodium Borohydride–Aluminum Chloride Reduction of Methyl 2-Nitro-3,4,5-trimethoxybenzoate (E-2).—A solution of 6.4 g. of aluminum chloride in 60 ml. of diglyme was added dropwise to a stirred solution consisting of 54 g. of methyl 2-nitro-3,4,5-trimethoxybenzoate, 5.5 g. of sodium borohydride and 200 ml. of diglyme. The reaction mixture was stirred at room temperature for 3 hr., then at 75–80° for 1 hr.; it then was poured into a mixture of 700 ml. of water and 500 g. of ice. After acidification with 3 *N* hydrochloric acid, the precipitated product was collected by filtration and air-dried. The crude product was recrystallized from 4 l. of heptane to yield 33 g. (68%) of pale yellow needles, m.p. 70–71°.

Anal. Calcd. for $C_{10}H_{13}NO_5$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.54; H, 5.52; N, 6.10.

2-Nitro-3,4,5-trimethoxybenzyl Tosylate (G-1).—To a solution of 6 g. of 2-nitro-3,4,5-trimethoxybenzyl alcohol in 140 ml. of anhydrous benzene was added, with ice-bath cooling, 1.2 g. of 50% sodium hydride dispersion followed by 4.6 g. of purified *p*-toluenesulfonyl chloride.[29] The mixture was stirred at room temperature for 13 hr. and then centrifuged. The benzene was removed at room temperature and the residue suspended in 75 ml. of 95% ethanol for 2 hr. at room temperature. The mixture next was cooled to 0° and filtered, affording 8.8–9.2 g. of off-white crystals, m.p. 123–125° dec. (90–94%).

Anal. Calcd. for $C_{17}H_{19}NO_8S$: C, 51.39; H, 4.82. Found: C, 51.52; H, 5.02.

2-Nitro-3,4,5-trimethoxybenzyl Chloride (G-2).—To a solution of 2.43 g. of 2-nitro-3,4,5-trimethoxybenzyl alcohol in 10 ml. of anhydrous benzene at 5° was added 2.1 g. of phosphorous pentachloride over 15 min. with agitation. The mixture was maintained at *ca.* 5° for 1 hr. during which time the phosphorus pentachloride went into solution. The benzene was removed, the residue taken up in toluene and the toluene likewise removed. The residue then was taken up in ether and washed with dilute sodium bicarbonate followed by water, dried and the solvent was evaporated. The semi-solid residue was chromatographed on 25 g. of alumina; elution with benzene gave 1.83 g. (70%) of a pale yellow oil which solidified. Recrystallization from heptane gave the analytical sample as pale yellow needles, m.p. 42–43°.

Anal. Calcd. for $C_{10}H_{12}ClNO_5$: C, 45.90; H, 4.62. Found: C, 45.74; H, 4.73.

Further elution of the above column with ether gave 115 mg. of a white crystalline solid which was recrystallized from a benzene–hexane mixture to give very pale yellow crystals of m.p. 133.5–134°, which were identical to bis-(2-nitro-3,4,5-trimethoxybenzyl) ether prepared by the action of the tosylate G-1 on the alcohol F in the presence of sodium hydride.

Anal. Calcd. for $C_{20}H_{24}N_2O_{11}$: C, 51.27; H, 5.17. Found: C, 51.59; H, 5.29.

2-Nitro-3,4,5-trimethoxybenzyl Bromide (G-3).—The tosylate G-1 was refluxed with excess lithium bromide in acetone for 20 hr. to give the bromide, as very pale yellow needles (from heptane), m.p. 46.5–47.5°.

Anal. Calcd. for $C_{10}H_{12}BrNO_5$: C, 39.25; H, 3.95. Found: C, 39.65; H, 3.84.

Diethyl 3,4,5-Trimethoxybenzylmalonate.—To a solution of 5.5 g. of 50% sodium hydride dispersion in 100 ml. of diethyl malonate was added 21.7 g. of 3,4,5-trimethoxybenzyl chloride[13] in 50 ml. of dimethylformamide (DMF) with stirring. The resultant mixture solidified almost immediately, was broken up and stirred well for 20 hr. at room temperature during which time the precipitated sodium chloride coagulated to a filterable state. After filtration the solvents were removed and the solid residue was recrystallized from heptane to give 27.7 g. (81.5%) of pale yellow needles, m.p. 79°, reported[13] m.p. 78–79°. The method of Tuemmler,[13] which omitted the DMF, gave a 54% yield of diethyl 3,4,5-trimethoxybenzylmalonate.

2-Carbethoxy-5,6,7-trimethoxyindanone (J).—To a solution of 1.4 g. of diethyl 3,4,5-trimethoxybenzylmalonate in 5 ml. of acetic acid was added with stirring 0.25 g. of concentrated nitric acid. After standing at room temperature for 30 min., the mixture was poured over ice. The tarry material that formed was taken up in ether and the aqueous solution was extracted with ether. The organic solutions were combined and washed with saturated sodium bicarbonate solution. The ether was removed and the residue was triturated with a small amount of ether. The tan crystals that formed were recrystallized from dilute ethanol affording 0.4 g. of white needles, m.p. 184–186°. No ferric chloride test was obtained and the compound was insoluble in cold dilute sodium hydroxide solution. The ultraviolet absorption spectrum showed a maximum at 275 mμ (log ε 4.19). The infrared spectrum showed two peaks in the carbonyl region (1727 and 1658 cm.$^{-1}$).

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.66; H, 6.27.

Di-*t*-butyl Bis-(2-nitro-3,4,5-trimethoxybenzyl)-malonate (L-1).—To 2.2 g. of di-*tert*-butyl malonate[30] in 15 ml. of freshly purified tetrahydrofuran (distilled from lithium aluminum hydride) was added 0.48 g. of 50% sodium hydride dispersion; when the reaction subsided, the solution was cooled and a solution of 2 g. of 2-nitro-3,4,5-trimethoxybenzyl tosylate in 10 ml. of tetrahydrofuran was added. The stirred reaction mixture was allowed to come to room temperature over a 2-hr. period, then was refluxed for 30 min. The cooled solution was poured onto a column of 5 g. of alumina; the column was eluted with 10 ml. of chloroform. After removal of the solvents by distillation under reduced pressure, there remained 1.75 g. (66%) of yellow crystals, m.p. 178–183° dec. Recrystallization from benzene–cyclohexane raised the m.p. to 187–188° dec.

Anal. Calcd. for $C_{31}H_{42}O_{14}N_2$: C, 55.85; H, 6.35; N, 4.20. Found: C, 56.27; H, 6.48; N, 4.14

The bis-nitro compound L-1 was reduced to the noncrystalline **bis-amine L-2** by Raney nickel–hydrazine reduction.[19] The amine L-2 was converted to the **bis-amide L-3** by the action of acetic anhydride in pyridine. The analytical sample, after three crystallizations from benzene–heptane, melted at 179–180°.

Anal. Calcd. for $C_{35}H_{50}N_2O_{12}$: C, 60.85; H, 7.29. Found: C, 60.85; H, 7.19.

(27) *Cf.* A. G. Anderson, Jr., J. A. Nelson and J. J. Tazuma, THIS JOURNAL, **75**, 4980 (1953).

(28) R. C. Elderfield and G. L. Krueger, *J. Org. Chem.*, **17**, 358 (1952).

(29) S. W. Pelletier, *Chemistry & Industry*, 1034 (1953).

(30) *Org. Syntheses*, **34**, 26 (1954).

Di-*t*-butyl 2-Nitro-3,4,5-trimethoxybenzylmalonate (H-1). (A) By Alkylation of Di-*t*-butyl Malonate with 2-Nitro-3,4,5-trimethoxybenzyl Tosylate (G-1).—Sodium hydride (1 g. of 50% dispersion) was "dissolved" in 100 ml. of di-*t*-butyl malonate; this was added to a stirred solution containing 8 g. of 2-nitro-3,4,5-trimethoxybenzyl tosylate, 100 ml. of dry DMF and 100 ml. of dry benzene. The inverse procedure worked equally well. The reaction mixture was stirred at room temperature for 16 hr., then at reflux for 30 min. After cooling, the mixture was poured into 250 ml. of ice-water; after shaking, the layers were separated, the organic phase was extracted with a fresh 50-ml. portion of water and the water layers were back-extracted with 50 ml. of benzene. Magnesium oxide (0.2 g.) was added to the combined benzene extracts, the benzene was removed by distillation at atmospheric pressure and the excess malonic ester was recovered by distilling under reduced pressure. The resulting oil was taken up in 70 ml. of heptane; the solution was filtered, and the filtrate placed in a freezer. The crystalline product, collected by filtration, weighed 7.1 g. (80%), m.p. 54–57°.

The crude material contained a small amount of the bis-product and was used as such in subsequent reactions. A small sample was chromatographed on alumina; center fractions had m.p. 59–60°.

Anal. Calcd. for $C_{21}H_{31}O_9N$: C, 57.13; H, 7.08. Found: C, 56.88; H, 7.18.

(B) By Alkylation of Di-*t*-butyl Malonate with 2-Nitro-3,4,5-trimethoxybenzyl Chloride (G-2).—The alkylation was carried out with a 1:1:3 molar ratio of the benzyl chloride–sodium hydride dispersion–di-*t*-butyl malonate in 1:1 benzene–DMF solution with stirring for 3 hr. at room temperature. The reaction yielded, after chromatography, 61% of H-1. No bis-alkylation product (L-1) was isolated.

(C) The Method of Fonken and Johnson[14] gave varying amounts of L-1 as the major product.

Di-*t*-butyl 2-Nitro-3,4,5-trimethoxybenzyl-3′-methoxybenzoylmalonate (K-2).—A suspension of lithium amide was made from 0.23 g. of lithium and 100 ml. of liquid ammonia, using a catalytic amount of ferric nitrate to initiate the reaction. To this was added a solution of 13.3 g. of 2-nitro-3,4,5-trimethoxybenzylmalonate in 125 ml. of dry ether; after stirring at reflux for 30 min., 50 ml. of ether was added and the ammonia boiled off. Finally dry nitrogen was passed through the system of refluxing ether until only a faint test with moist litmus paper was obtained. Then a solution of 6 g. of *m*-methoxybenzoyl chloride in 30 ml. of ether was added and the resulting mixture was stirred for 2 hr. at room temperature. The reaction mixture then was filtered and the ether removed under reduced pressure to yield a yellow solid. Usually this was decarboalkoxylated without purification.

A small sample was recrystallized from heptane and had m.p. 104–105°.

Anal. Calcd. for $C_{29}H_{37}O_{11}N$: C, 60.51; H, 6.48. Found: C, 60.73; H, 6.85.

β-(2-Nitro-3,4,5-trimethoxyphenyl)-3′-methoxypropiophenone (M-1). (A).—To the flask containing the crude malonic ester (K-2) (from the above procedure) were added 147 ml. of glacial acetic acid, 3 ml. of acetic anhydride and 0.4 g. of *p*-toluenesulfonic acid. The mixture was refluxed for 1 hr., cooled, poured over 1 kg. of ice, and made basic with 40% sodium hydroxide solution. The basic solution was extracted with three 200-ml. portions of benzene; the combined benzene fractions were dried and passed over a column of 20 g. of alumina. After eluting the column with 50 ml. of 4:3 benzene–ether, the solvent was removed and the resulting solid recrystallized from 125 ml. of heptane to give 9–9.5 g. (80–85) of yellow needles, m.p. 92–93°.

(B).—The use of the mixed anhydride of ethyl chlorocarbonate and *m*-methoxybenzoic acid,[24] instead of *m*-methoxybenzoyl chloride, gave a 71% yield of the ketone M-1.

Anal. Calcd. for $C_{19}H_{21}NO_7$: C, 60.79; H, 5.64. Found: C, 61.02; H, 5.98.

The **oxime** was prepared by refluxing a mixture of the ketone (M-1) and hydroxylamine hydrochloride in ethanol–pyridine (1:1) for 14 hr. and was recrystallized from aqueous ethanol to give yellow needles, m.p. 97–99°.

Anal. Calcd. for $C_{19}H_{22}N_2O_7$: C, 58.45; H, 5.68. Found: C, 58.84; H, 5.82.

2-(3′-Methoxyphenyl)-2-[β-(2″-nitro-3″,4″,5″-trimethoxyphenyl)-ethyl]-1,3-dioxolane (N-1).—A solution of 10.5 g. of the ketone M-1, 4 g. of ethylene glycol and 0.3 g. of *p*-toluenesulfonic acid in 100 ml. of benzene was refluxed for 48 hr. under a water separator. Then, as benzene was added dropwise to keep the volume constant, benzene was distilled from the reaction mixture until the distillate became clear. The cooled benzene solution was washed with sodium carbonate solution and was dried over potassium carbonate. The solvent was removed and the resultant oil crystallized from heptane to give 10.6 g. (90%) of almost colorless prisms, m.p. 53–55°.

Anal. Calcd. for $C_{21}H_{25}O_8N$: C, 60.13; H, 6.01. Found: C, 60.21; H, 6.08.

Another dimorph was obtained in one run as a second crop from the mother liquor as yellow needles, m.p. 71–72°.

Anal. Found: C, 60.01; H, 6.13.

Acidic hydrolysis of both dimorphs yielded the ketone M-1, shown to be identical by mixed m.p. and infrared spectra.

2-(3′-Methoxyphenyl)-2-[β-(2″-amino-3″,4″,5″-trimethoxyphenyl)-ethyl]-1,3-dioxolane (N-2).—Platinum oxide (3 g.) in 500 ml. of benzene was reduced with hydrogen at 60°; a solution of 8.5 g. of the nitro ketal N-1 in 400 ml. of benzene then was added. The mixture was stirred under one atmosphere of hydrogen pressure at 60° for 12 hr. The platinum was filtered from the mixture and the benzene removed from the filtrate by distillation under reduced pressure; the resultant oil was crystallized from heptane to give 7.5 g. (95%) of tan crystals, m.p. 80–82.°

The analytical sample was prepared by distilling the crude product in a small sublimation apparatus; the product distilled at a bath temperature of 100° (5×10^{-4} mm.). The purified sample was almost colorless, m.p. 84–85°.

Anal. Calcd. for $C_{21}H_{27}O_6N$: C, 64.76; H, 6.99. Found: C, 64.72; H, 7.16.

The Schiff base N-3 was prepared by heating 400 mg. of the amine and 1 ml. of *m*-methoxybenzaldehyde at 140° for 4 hr.; the solution then was poured into 20 ml. of boiling heptane. Upon cooling the crude product crystallized. After collecting the product on a filter, it was taken up in 10 ml. of ether and passed over 5 g. of alumina. The column was eluted with 15 ml. of ether and the solvent removed to yield a bright yellow solid. The Schiff base was recrystallized from heptane to give 320 mg. of yellow needles, m.p. 93–94°.

Anal. Calcd. for $C_{29}H_{33}O_7N$: C, 68.62; H, 6.55. Found: C, 68.59; H, 6.73.

The amide (N-4) was obtained by the action of acetic anhydride in pyridine as square, white plates (from aqueous methanol), m.p. 116–118°.

Anal. Calcd. for $C_{23}H_{29}NO_7$: C, 64.02; H, 6.77; N, 3.24. Found: C, 63.79; H, 6.63; N, 3.24.

Attempted cyclizations of 2-(3′-methoxyphenyl)-2-[β-(2″-amino-3″,4″,5″-trimethoxyphenyl)-ethyl]-1,3-dioxolane (N-2) under a variety of conditions[31] gave small amounts of 2-(3′-methoxyphenyl)-6,7,8-trimethoxyquinoline (R) as the only crystalline product.

2-(3′-Methoxyphenyl)-6,7,8-trimethoxyquinoline (R) and its Hydrochloride.—A solution of 100 mg. of the amino-ketal N-2 in 5 ml. of 0.1 *N* hydrochloric acid was extracted with ether to yield 8 mg. of the free base R which melted at 104–105°.

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89. Found: C, 69.75; H, 6.20.

The presence of nitrogen was shown by a micro-qualitative test. The ultraviolet spectra of R and 2-phenylquinoline were quite similar: R, λ_{max} 218 mμ (log ε 4.52), 265 mμ (log ε 4.65), 335 mμ (log ε 4.07), 345 mμ (log ε 4.05), 2-phenylquinoline, λ_{max} 210 mμ (log ε 4.5), 260 mμ (log ε 4.6), 320 mμ (log ε 3.8).

Evaporation of the above aqueous solution and recrystalzation of the residue from tetrahydrofuran gave 60 mg. of the quinoline hydrochloride, m.p. 146–150°.

Anal. Calcd. for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57. Found: C, 62.74; H, 5.86.

(31) *Cf.* P. H. Leake, *Chem. Revs.*, **56**, 27 (1956); D. F. DeTar, "Organic Reactions," Vol. IX, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 409.

1-(3′-Methoxyphenyl)-3-(2″-nitro-3″,4″,5″-trimethoxyphenyl)-propanol (T-1).—To a suspension of 8 g. of β-(2-nitro-3,4,5-trimethoxyphenyl)-3′-methoxypropiophenone (M-1) in 100 ml. of methanol was added 2.5 g. of sodium borohydride in 50 ml. of methanol over 15 min.; stirring was continued for 7 hr. with occasional ice-bath cooling (<40°). The solvent was removed and 10 ml. of 25% hydrochloric acid was added to the residue, which then was extracted with three 50-ml. portions of benzene. The benzene solution was dried and evaporated and the residue was recrystallized three times from aqueous methanol to give 7.2 g. (90%) of nitro-alcohol T-1, m.p. 90–91°.

Anal. Calcd. for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14. Found: 60.44; H, 6.33.

1-(3′-Methoxyphenyl)-3-(2″-amino-3″,4″,5″-trimethoxyphenyl)-propanol (T-2).—To a near-boiling mixture of 6 g. of the nitro-alcohol T-1, 2 g. of freshly prepared Raney nickel[32] and 900 ml. of 95% ethanol was added 1 ml. of 95% hydrazine. After 10 min. two more 1-ml. portions of 95% hydrazine were added at 5-min. intervals. Refluxing was continued for 3 hr.; the mixture was filtered hot and evaporated to give a purple oil. Distillation of this oil at bath temperature of 200° (10^{-4} mm.) and recrystallization of the solid distillate from benzene–petroleum ether (30–60°) gave the analytical sample with m.p. 72–74°.

Anal. Calcd. for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.04. Found: C, 65.32; H, 7.22; N, 4.06.

1-(3′-Methoxyphenyl)-1-acetoxy-3-(2″-acetamido-3″,4″,5″-trimethoxyphenyl)-propane (T-3) was prepared from the amino-alcohol T-2 by the action of acetic anhydride in pyridine and melted at 118–120° after three crystallizations from benzene–petroleum ether (30–60°).

Anal. Calcd. for $C_{23}H_{29}NO_7$: C, 64.02; H, 6.77; N, 3.25. Found: C, 64.06; H, 6.61; N, 3.35.

Attempted Sandmeyer Reaction on 1-(3′-Methoxyphenyl)-3-(2″-amino-3″,4″,5″-trimethoxyphenyl)-propanol (T-2).—A solution of 2 g. of the amino-alcohol T-2 in 16 ml. of 1*N* sulfuric acid was treated dropwise at 0° with a solution of 0.4 g. (0.006 mole) of sodium nitrite in 5 ml. of water. The resultant mixture was poured into a mixture of 1 g. of potassium iodide, 0.5 g. of sodium acetate, 0.2 g. of cuprous iodide, 5 ml. of water and 50 ml. of acetone. A lively evolution of gas took place and the temperature rose rapidly to about 33°. After the gas evolution ceased the mixture was stirred on the steam-bath until most of the acetone had evaporated and an orange-red oil had separated from solution. The mixture then was extracted with ether, the ether washed successively with 5% sodium carbonate, 5% sodium thiosulfate and water then dried and evaporated. The orange-red residue, which solidified upon trituration with petroleum ether (30–60°), was taken up in benzene and passed over 35 g. of alumina. Elution of the column with ether gave 0.8 g. (42%) of white crystalline β-(3,4,5-trimethoxyphenyl)-3′-methoxypropiophenone of m.p. 71–73° (from heptane) identical to an authentic sample (see below). The reported[23] m.p. is 69–70°.

Anal. Calcd. for $C_{19}H_{22}O_6$: C, 69.07; H, 6.71. Found: C, 69.13; H, 6.76.

2-(3′-Methoxyphenyl)-2-[β-(2″-nitro-3″,4″,5″-trimethoxyphenyl)-ethyl]-1,3-oxathiolane (B-1).—A solution of 15 g. of β-(2-nitro-3,4,5-trimethoxyphenyl)-3′-methoxypropiophenone (M-1) 30 ml. of 2-mercaptoethanol and 0.3 g. of *p*-toluenesulfonic acid in 100 ml. of benzene was refluxed under a water separator for 2 days. The cooled solution was washed with aqueous sodium bicarbonate, then with water, dried and evaporated. The residue was crystallized from aqueous methanol or heptane to give 17.1 g. (98%) of pale yellow crystals, m.p. 74–75°.

Anal. Calcd. for $C_{21}H_{25}NO_7S$: C, 57.92; H, 5.79. Found: C, 57.72; H, 5.93.

2-(3′-Methoxyphenyl)-2-[β-(2″-amino-3″,4″,5″-trimethoxyphenyl)-ethyl]-1,3-oxathiolane (B-2).—To a stirred mixture of 17.1 g(. 0.039 mole) of the nitrohemithioketal B-1 and 24 g. of aluminum amalgam[22] in 500 ml. of ether was added, at such a rate as to maintain gentle refluxing, sufficient water (*ca.* 10 ml.) to consume all the amalgam. The mixture was stirred for an additional 2 hr., filtered and the filter cake washed with ether. The combined organic phases were dried and evaporated and the residual oil crystallized from aqueous methanol to give 10 g. (63%) of yellow solid. The analytical sample was prepared by distillation at 160° (bath temperature, 3×10^{-4} mm.) and had m.p. 76–78°.

Anal. Calcd. for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45. Found: C, 62.44; H, 6.91; N, 3.92.

β-(2-Acetamido-3,4,5-trimethoxyphenyl)-3′-methoxypropiophenone (M-3). (A).—Acidic hydrolysis (aqueous ethanolic hydrochloric acid) of the ketal N-4 gave the acetamido-ketone M-3 in 72% yield as thin white plates, m.p. 136.5–138°, from aqueous methanol.

(B).—Treatment of the amino-hemithioketal B-2 with acetic anhydride in pyridine gave the oily acetamido-hemithioketal B-3 which was hydrolyzed as above to give the acetamido-ketone M-3, identical to that prepared above.

Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 64.76; H, 6.37; N, 3.59.

3,4,5-Trimethoxybenzyl Alcohol. (A).—Diborane reduction of 3,4,5-trimethoxybenzoic acid by an analogous procedure to that used above for reduction of 2-nitro-3,4,5-trimethoxybenzoic acid (E-1) gave the alcohol in 86% yield on a 0.5-mole scale.

(B).—Reduction of methyl 3,4,5-trimethoxybenzoate with lithium aluminum hydride in tetrahydrofuran gave the alcohol in 66–68% yields. Use of diethyl ether as solvent[33] gave yields of 24–37%.

The alcohol had a b.p. of 137–140° (0.4 mm.). The 3,5-dinitrobenzoate melted at 144–146°, reported[33] m.p. 143–144°.

β-(3,4,5-Trimethoxyphenyl)-3′-methoxypropiophenone.—Acylation of the lithium salt of di-*t*-butyl 3,4,5-trimethoxybenzylmalonate with *m*-methoxybenzoyl chloride and decarbo-*t*-butoxylation of the intermediate malonate (K-1) by the usual procedure gave the ketone as white silken needles (from heptane), m.p. 69–70°, reported[23a] m.p. 69–70°.

The oxime was recrystallized from aqueous ethanol and melted at 94.5–95.5°. It has been reported[23b] previously as being an oil. *Anal.* Calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71. Found: C, 66.38; H, 6.85.

Mixed Anhydride of Ethyl Hydrogen Carbonate and 2-Methoxy-4-carboxytropone (D).—To a stirred suspension of 0.9 g. of 2-methoxy-4-carboxytropone[5] and 0.5 g. of triethylamine in 100 ml. of anhydrous ether at 0° was added a solution of 0.54 g. of ethyl chlorocarbonate in 25 ml. of ether. The mixture was stirred at 0° for 2 hr., then at room temperature for an additional hr. The triethylamine hydrochloride then was filtered off, the solution taken to dryness at room temperature and the residue recrystallized from absolute ether to give pale yellow transparent crystals of the mixed anhydride which melted at 84–85° (sealed tube). The infrared spectrum of D had a strong broad peak from 1810–1790 cm.$^{-1}$ and a very small peak at 1730 cm.$^{-1}$ in contrast to the usual mixed anhydride spectrum which has peaks of almost equal intensity at 1802–1795 cm.$^{-1}$ and 1739–1754 cm.$^{-1}$ in the liquid state.[34]

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.58; H, 4.83.

2-Methoxy-4-[α-keto-β,β-dicarbo-*t*-butoxy-γ-(3′,4′,5′-trimethoxyphenyl)]-propyltropone (C).—To a suspension of 0.002 mole of the lithium salt of di-*t*-butyl 3,4,5-trimethoxybenzylmalonate was added a solution of 0.51 g. (0.002 mole) of the mixed anhydride D in 15 ml. of anhydrous toluene. The mixture was stirred overnight, washed with water, dried and evaporated. The residue was chromatographed on Florisil; ether with 5% of methanol eluted a yellow glass which was taken up in hot heptane and redeposited as a yellow powder with a rather indefinite m.p. around 75°. The compound gave a negative ferric chloride test in 95% ethanol but when warmed with dilute mineral acid the residue gave a positive ferric chloride test. The infrared spectrum of C displayed a strong peak at 1720 cm.$^{-1}$ with shoulders at 1740, 1713 and 1683 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{38}O_{10}$: C, 64.40; H, 6.86. Found: C, 64.62; H, 7.15.

(32) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

(33) M. U. Tsao, THIS JOURNAL, **73**, 5495 (1951). A similar observation was made by Drake and Tuemmler[31] in the case of the ethyl ester of 3,4,5-trimethoxybenzoic acid.

(34) *Cf.* D. S. Tarbell and E. J. Longosz, *J. Org. Chem.*, **24**, 774 (1959).

Reaction of the Mixed Anhydride D with Aniline.—A solution of 0.252 g. of the mixed anhydride D and 0.093 g. of aniline in 15 ml. of benzene was warmed briefly to 60° and then allowed to stand at room temperature overnight, during which time 0.071 g. of 2-methoxy-4-carboxytropone separated out. The filtered solution was washed with 10% sodium bicarbonate, followed by water, dried and evaporated. The residual oil deposited 0.08 g. of white solid (m.p. 148–150°) when triturated with warm heptane. Two recrystallizations from benzene–heptane gave the analytical sample of 2-methoxy-4-carboxytropone anilide which melted at 153–153.5°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.66; H, 5.29; N, 5.52.

Di-*t*-butyl 2-Amino-3,4,5-trimethoxybenzylmalonate (H-2).—Di-*t*-butyl 2-nitro-3,4,5-trimethoxybenzylmalonate was reduced to the amine (H-2) in 82% yield in hot (70–80°) benzene solution upon shaking with Adams catalyst under 2 atmospheres of hydrogen for 13 hr. The amine was recrystallized from pentane and melted at 74–75°.

Anal. Calcd. for $C_{21}H_{33}NO_7$: C, 61.29; H, 8.08. Found: C, 61.00; H, 7.89.

Treatment of the amine H-2 with acetic anhydride in pyridine gave the amide **H-3**, m.p. 135.5–136° (from heptane).

Anal. Calcd. for $C_{23}H_{35}NO_8$: C, 60.91; H, 7.78. Found: C, 61.01; H, 7.89.

Similar treatment of the amine H-2 with *m*-methoxybenzoyl chloride in pyridine gave the **N-*m*-methoxybenzoyl derivative H-4**, m.p. 110–110.5° (from heptane).

Anal. Calcd. for $C_{29}H_{39}NO_9$: C, 63.83; H, 7.21. Found: C, 63.94; H, 7.52.

β-[2-N-*m*-Methoxybenzamido)-3,4,5-trimethoxyphenyl]-3′-methoxypropiophenone (M-2).—Acylation of the lithium salt of the amide H-3 (prepared with 2 equivalents of lithium amide) with 6 equivalents of *m*-methoxybenzoyl chloride gave, after decarbo-*t*-butoxylation, an oily ketone mixture which gave the 2,4-dinitrophenylhydrazone of M-2. Recrystallization from ethyl acetate–ethanol gave the analytical sample with m.p. 215.5–216°.

Anal. Calcd. for $C_{33}H_{33}N_5O_{10}$: C, 60.08; H, 5.04. Found: C, 60.55, 60.50; H, 5.13, 5.00.

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

Alkylhydrazines in the Mannich Reaction; a Convenient Synthesis of Δ^3-Pyrazolines[1]

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The behavior of a number of alkylhydrazines under the conditions of the Mannich reaction has been examined. With acetophenone and formaldehyde, trimethylhydrazine yielded β-trimethylhydrazinopropiophenone (I). Under similar conditions 1,2-dimethyl-, 1,2-diethyl- and 1,2-di-*n*-propylhydrazine yielded the corresponding 1,2-dialkyl-3-phenyl-Δ^3-pyrazolines (III). This is the first simple, generally useful synthesis of Δ^3-pyrazolines to be reported. The structure of the dimethyl member of the series was established by its ultraviolet and infrared spectra, by ozonolysis, and by hydrogenation to 1,2-dimethyl-3-phenylpyrazolidine (IV), which was also synthesized by reduction of 1,2-dimethyl-3-phenyl-5-pyrazolone with lithium aluminum hydride. The reaction of ethyl benzoylacetate with 1,2-dimethylhydrazine and formaldehyde produced a mixture of 1,2-dimethyl-3-phenyl-4-carbethoxy-Δ^3-pyrazoline (VI) and IIIa. Saponification and decarboxylation converted VI to IIIa. With benzyl methyl ketone and formaldehyde, 1,2-dimethylhydrazine yielded a mixture of isomers, including 1,2-dimethyl-3-benzyl-Δ^3-pyrazoline. No product was obtained from the reaction of methylhydrazine with paraformaldehyde and acetophenone, but 1-methyl-3-phenyl-Δ^2-pyrazoline (XIII) was prepared by the reaction of methylhydrazine with the Mannich base, β-dimethylaminopropiophenone.

Although the Mannich reaction has been extended to a wide variety of amines, the use of hydrazines in this reaction has received little attention.[3] This paper describes the behavior of a number of alkylhydrazines under the conditions of the Mannich reaction.

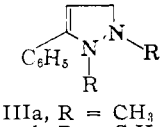
Trimethylhydrazine.—When trimethylhydrazine, as the hydrochloride, was refluxed with acetophenone and paraformaldehyde in ethanol, an oil was obtained which decomposed when distillation was attempted. The undistilled oil was identified as β-trimethylhydrazinopropiophenone (I) by means of the analysis of its metho-*p*-toluenesulfonate, and the fact that its methiodide absorbed strongly in the carbonyl region of the infrared.

$$C_6H_5COCH_3 + (CH_2O)_x + CH_3NHN(CH_3)_2 \xrightarrow{H^+} C_6H_5COCH_2CH_2N(CH_3)N(CH_3)_2$$

I

1,2-Dialkylhydrazines.—In the hope that both nitrogens of the hydrazine might undergo the Mannich reaction, molar ratios of 1:2:2 of 1,2-dimethylhydrazine dihydrochloride, acetophenone and paraformaldehyde were chosen. The product, however, contained no oxygen. Its composition was that of 1,2-dimethyl-3-phenyl-Δ^3-pyrazoline (IIIa), presumably formed by acid-catalyzed ring closure of the Mannich base formed initially.

$$\begin{matrix} C_6H_5COCH_3 \\ + \\ (CH_2O)_x \\ + \\ RNHNHR\cdot 2HCl \end{matrix} \longrightarrow \underset{\text{II}}{(C_6H_5COCH_2CH_2NRNHR)} \longrightarrow$$



IIIa, R = CH_3
b, R = C_2H_5
c, R = *n*-C_3H_7

(1) Abstracted from the Ph.D. thesis of R. D. Ellefson, State University of Iowa, August, 1958. Presented before the Organic Division of the American Chemical Society at the Atlantic City Meeting, September 15, 1959.

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(3) (a) W. Ried and K. Wesselborg (*Ann.*, **611**, 71 (1958)) have recently reported the use of hydrazine and some 1,2-dialkylhydrazines in the Mannich reaction with antipyrene and formaldehyde. Both nitrogens of the hydrazines underwent condensation to yield products of the type $YCH_2NRNRCH_2Y$, where Y is the group derived from antipyrene. (b) An intramolecular Mannich reaction between benzaldehyde and 1-phenyl-1-skatylhydrazine has been reported (J. Thesing and C. H. Willersinn, *Ber.*, **89**, 1195 (1956)).