[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Preliminary Experiments on the Synthesis of Colchicine. The Synthesis of 4b,5,6,7,8,8a,9,10-Octahydro-2,3,4-trimethoxy-10-ketophenanthrene and its B-Ring and C-Ring Homologs[1]

BY C. DAVID GUTSCHE AND FREDERICK A. FLEMING

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4b,5,6,7,8,8a,9,10-Octahydro-2,3,4-trimethoxy-10-ketophenanthrene and its B-ring and C-ring homologs, compounds of interest in syntheses in the colchicine series, have been prepared as follows: 2,3,4-Trimethoxyiodobenzene was converted to the Grignard compound by the entrainment method, and this was allowed to react with cyclohexanone or cycloheptanone to yield the corresponding trimethoxyphenylcycloalkene; treatment of the olefins with perbenzoic acid followed by sulfuric acid yielded the corresponding trimethoxyphenylcycloalkanones; Reformatsky reactions with the ketones followed by dehydration, reduction and saponification yielded the trimethoxyphenylcycloalkaneacetic acids which were cyclized to the corresponding tricyclic ketones; Arndt–Eistert homologation of the acetic acids yielded the propionic acids which were similarly cyclized to the corresponding tricyclic ketones. The ultraviolet spectra of the four ketones were measured, and characteristic differences dependent upon the size of the B-ring were noted.

The following discussion deals with certain aspects of a program concerned with syntheses in the colchicine series and is divided into three parts: (a) the synthesis of trimethoxyphenylcycloalkanones; (b) the synthesis of trimethoxyphenylcycloalkaneacetic and -propionic acids; (c) the preparation of the corresponding tricyclic ketones.

Trimethoxyphenylcycloalkanones.—A number of methods are reported in the literature for the synthesis of 2-phenylcyclohexanones including: (a) the action of the appropriate phenylmagnesium bromide on 2-chlorocyclohexanone[2–4]; (b) the action of the appropriate phenyllithium on cyclohexene oxide followed by oxidation of the carbinol[5]; (c) the conversion of 2-phenylcyclohexene derivatives to 2-phenylcyclohexanones by epoxidation and rearrangement,[4,6,7] *via* the chlorohydrin,[8] by the nitrosyl chloride method[9,10] or by allylic oxidation[10]; (d) the cyclization of α-phenylpimelic acid derivatives[4,11]; (e) *via* Diels–Alder reactions between ω-nitrostyrenes and butadiene followed by hydrolysis.[12,13] 2-Phenylcycloheptanones have been obtained by some of these methods and also by rearrangement of the oxide from benzalcyclohexanes[14] and by the action of benzylnitrosourethans on cyclohexanone.[15]

The initial attempts in the present investigation to obtain 2-(2′,3′,4′-trimethoxyphenyl)-cyclohexanone (VII) involved the reaction of the Grignard derivative II with 2-chlorocyclohexanone. The best conditions for the preparation of the Grignard compound included the use of the iodide I in preference to the bromide, at least two equivalents of magnesium and at least one equivalent of ethyl bromide; under these "entrainment" conditions[16] II was obtained in almost quantitative yield as measured by carbonation to 2,3,4-trimethoxybenzoic acid. The reaction with 2-chlorocyclohexanone, however, failed to yield the desired product and attention was turned, therefore, to the preparation of trimethoxyphenylcyclohexene (III) as a more promising route to the ketone.

The reaction of a dilute ethereal solution of II (*ca.* 0.25 *M*) with a slight excess (20–40%) of cyclohexanone proceeded smoothly to yield 70% of the olefin III. Although Ginsburg and Pappo[17] observed the tertiary carbinol as the initial product of this reaction, under the conditions employed in our preparation only the olefin was obtained. The structure of the olefin was substantiated by the ultraviolet spectrum, by the absorption of one mole of hydrogen, and by dehydrogenation to a trimethoxybiphenyl. Similarly, the reaction of II with cycloheptanone yielded 76% of an olefin IV which had an ultraviolet spectrum similar to that of III and which underwent oxidation to ϵ-(2,3,4-trimethoxybenzoyl)-caproic acid.

The conversion of the olefin III to the ketone VII was effected by two methods: (a) performic acid treatment followed by saponification and fusion with oxalic acid; (b) perbenzoic acid treatment followed by heating with dilute sulfuric acid. The first of these, patterned after the description by Bergman, *et al.*,[7] gave only 15–27% of product, however, and attention was focused on the second method. A complication in the latter arose from the known[18–20] tendency of perbenzoic acid to attack the aromatic ring, but by the proper choice of solvent this effect could be minimized. Thus, with ethyl acetate or diethyl ether as the reaction medium the attack of the first mole of perbenzoic

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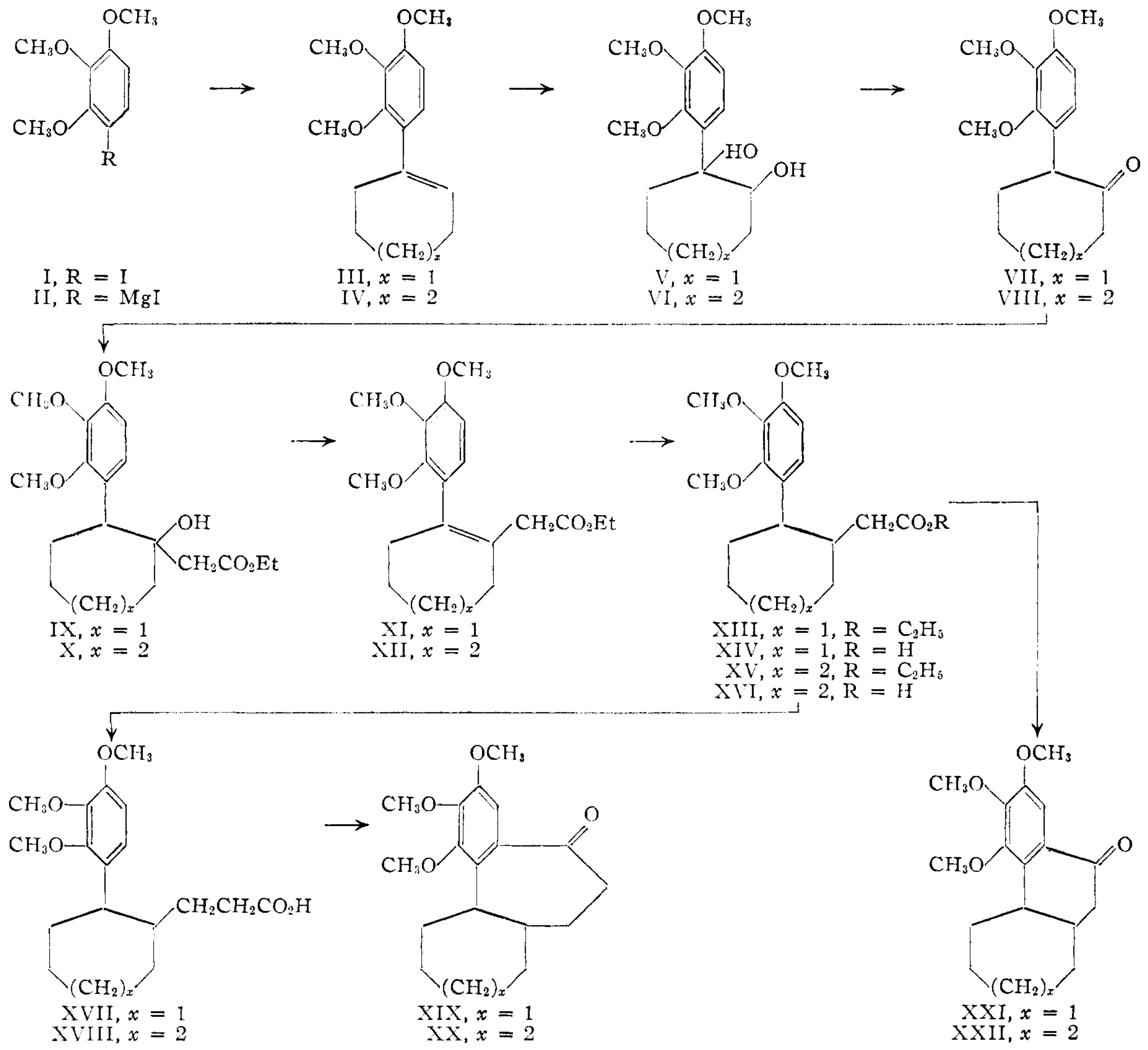

acid was primarily at the olefinic linkage, whereas in chloroform solution it appeared to be equally directed to the aromatic ring and the double bond. Similar effects have been noted previously[19,20] but the precise effect of the solvent appears to be somewhat unpredictable. The product was not the expected oxide but a mixture containing only a small amount of the oxide, the diol V and the monobenzoate of the diol. Fortunately, separation was unnecessary, for upon treatment of the mixture with hot, dilute sulfuric acid each of the constituents was converted to the ketone VII,[21] and an over-all yield of 78% was achieved. It was possible to isolate the diol V as a crystalline solid and effect its conversion to VII. However, this was not only unnecessary but undesirable, since lower yields of ketone were thereby obtained. In similar fashion the olefin IV was converted in 83% yield to the ketone VIII.

Trimethoxyphenylcycloalkane Aliphatic Acids.—The ketones VII and VIII reacted smoothly with ethyl bromoacetate in the presence of zinc to furnish the hydroxy esters IX and X in 90% yield. Dehydration by the thionyl chloride–pyridine method produced the unsaturated esters XI and XII in 90% yield. It is probable that these are mixtures of the compound with an endocylic double bond (XI and XII) and the isomeric compound with an exocyclic double bond. The ultraviolet spectra of the unsaturated esters showed a strong but undifferentiated absorption in the 230–250 mμ region (III has $\epsilon_{241 m\mu}$ 9,300; IV has $\epsilon_{243 m\mu}$ 11,900) suggesting a predominance of the endocyclic structure. Catalytic reduction followed by saponification yielded the saturated acids XIV and XVI as mixtures of the *cis* and *trans* isomers from which one of the pure isomers could be isolated;

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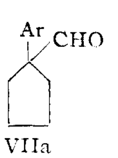
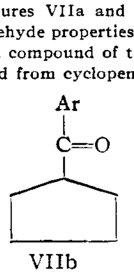
(21) The theoretically possible structures VIIa and VIIb can be ruled out, for the product exhibits no aldehyde properties and has only a weak absorption in the ultraviolet. A compound of the type VIIb where Ar = $(CH_3O)_2(OH)C_6H_2$, prepared from cyclopentanecarbonyl chloride and 1,2,3-trimethoxybenzene, has $\epsilon_{283 m\mu}$ 18,000, whereas VII has $\epsilon_{283 m\mu}$ 900.



VIIa



VIIb

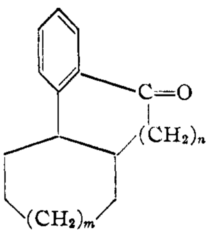
50% in the case of XIV and 27% in the case of XVI. Insufficient data are available to fix securely the stereo configurations of these acids, but by analogy to the unmethoxylated series[22] it is supposed that they possess the *cis* configuration.

The homologation of XIV to XVII and XVI to XVIII was carried out with the pure, crystalline isomers (presumably *cis*) by the Wilds–Meader method[23] and by the Newman–Beal method.[24] The latter proved to be somewhat superior in that the yield of pure product was slightly higher, difficulties in removing benzyl alcohol were avoided, and the speed and extent of the rearrangement could be followed easily on the basis of the nitrogen evolution. The propionic acid XVII was a solid and could be purified by recrystallization, but the propionic acid XVIII was a liquid and could not be similarly purified. On the well-substantiated assumption that no configurational rearrangement takes place during the Arndt–Eistert reaction,[25] and on the assumption that the Wolff rearrangement was without complication (nitrogen evolution 97% of theory) it is assumed that the product is a single pure isomer of XVIII.

Tricyclic Ketones.—Treatment of the pure, solid isomer of XIV with anhydrous hydrogen fluoride yielded 91% of the tricyclic ketone XXI as a crystalline solid. Similar treatment of the mixture of isomers of XIV yielded the ketone as a mixture of isomers from which a higher-melting, but impure form of XXI could be isolated but not purified completely. From the mixture of *cis*- and *trans*-XVI a mixture of ketones XXII was produced in like fashion from which one of the isomers was isolated as a crystalline solid.

The propionic acids XVII and XVIII failed to undergo cyclization under the conditions which sufficed for the acetic acids XIV and XVI (3 hours or less contact with anhydrous hydrogen fluoride), although prolonged contact (48 hours) with anhydrous hydrogen fluoride effected a significant amount of ring closure. More convenient than this procedure, however, which necessitated the use of special equipment for the exclusion of atmospheric moisture, was the recently popularized "polyphosphoric acid" method.[26] In the presence of this reagent XVII and XVIII yielded the corresponding ketones XIX and XX in good yield and without the complication of demethylation.

The ultraviolet spectra of the ketones XIX–XXII are given in Table I along with the spectra of the corresponding unmethoxylated tricyclic ketones XXIII–XXVI which have been described previously.[22] The intensity differences in the second band absorption between the compounds containing a six-membered and a seven-membered B ring are seen to appear in both the methoxylated and unmethoxylated series.



XXIII, $n = 1, m = 1$
XXIV, $n = 1, m = 2$
XXV, $n = 2, m = 1$
XXVI, $n = 2, m = 2$

TABLE I[a]

Compound	B ring	C ring	First band λmax, mμ	First band εmax	Second band λmax, mμ	Second band εmax	Third band[b] λmax, mμ	Third band[b] εmax
XXI	6	6	223	22,600	276	9500	317	3700
XXII	6	7	225	23,800	274	9450	315	3700
XIX	7	6	223	18,800	270	5500	312	2540
XX	7	7	222	12,700	270	5200	316	2060
XXIII	6	6			249.5	11,580	294	1910
XXIV	6	7			249	11,420	294	1860
XXV	7	6			249	7970	288	1460
XXVI	7	7			248	7250	287	1300

[a] The spectra were measured in 95% ethanol solution. [b] Point of inflection rather than a definite peak.

This characteristic difference in which the seven-membered B ring ketones have a significantly lower absorption intensity than the six-membered B ring ketones has served as an invaluable diagnostic tool for syntheses in an unmethoxylated series[27] and, it is now apparent, can also be of use in methoxylated series.

Experimental[28,29]

1-(2',3',4'-Trimethoxyphenyl)-cyclohexene (III).—In a 12-liter, 3-necked flask fitted with an addition funnel, an efficient condenser and a sealed stirrer (preferably with some flexibility at the seal) of considerable strength was placed 240 g. (0.82 mole) of 4-iodopyrogallol trimethyl ether (I),[30] 39.7 g. (1.64 g. atoms) of magnesium turnings and 3.8 l. of anhydrous ether. To this vigorously agitated and gently refluxing mixture was added 90 g. (0.82 mole) of ethyl bromide, 25% over a period of one hour and the remaining 75% over a period of 24 hours. The initiation of the reaction, usually after 1–3 hours, is indicated by the formation of a white precipitate which increases in amount as the reaction proceeds to completion. To the stirred reaction mixture was then added, over a period of 24 hours, 192 g. (1.96 moles) of cyclohexanone dissolved in 2.7 l. of ether. When smaller amounts of solvent were used the reaction intermediate had a tendency to coalesce to a gum which made efficient mixing impossible. The reaction mixture was refluxed for an additional 24 hours, cooled in an ice-bath, hydrolyzed with 1 *N* sulfuric acid, and washed with saturated sodium chloride solution. The ether was removed and the oily residue was distilled through a 50-cm., glass-helix packed column to yield: 45.0 g. of a mixture of cyclohexanone and 1-ethylcyclohexanol, b.p. 30–68° (5 mm.); 38.0 g. of pyrogallol trimethyl ether, b.p. 95–109° (5 mm.); 46.0 g. of cyclohexenylcyclohexanone, b.p. 110–120° (5 mm.); 4.1 g. of 4-iodopyrogallol trimethyl ether, b.p. 127–145° (5 mm.); and 142 g. (70%) of 1-(2',3',4'-trimethoxyphenyl)-cyclohexene, b.p. 149–159° (5 mm.). The last fraction, which crystallized upon standing, m.p. 38–40°, was obtained as colorless rhombs after several recrystallizations from petroleum ether (b.p. 63–69°): m.p. 41.5–43.5°, $\lambda_{\max}^{\text{EtOH}}$ 241 mμ (ε 9300).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.51; H, 7.96.

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2,3,4-Trimethoxyphenylcyclohexane.—Hydrogenation of III in the presence of 10% palladium-on-charcoal catalyst yielded 93% of a solid, m.p. 46–48°. Two recrystallizations from petroleum ether (b.p. 32–37°) yielded colorless needles, m.p. 46–48°.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.70; H, 8.72.

2,3,4-Trimethoxybiphenyl.—Dehydrogenation of III at 310° in the presence of 10% palladium-on-charcoal catalyst yielded, after distillation, 49% of a colorless oil, b.p. 128–132° (0.5 mm.), n^{25}D 1.5845.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.85; H, 6.46.

1-(2′,3′,4′-Trimethoxyphenyl)-cycloheptene (IV).—The reaction was carried out as described above for the preparation of III substituting cycloheptanone for cyclohexanone. From 240 g. (0.82 mole) of 4-iodopyrogallol trimethyl ether, 39.7 g. (1.64 g. atoms) of magnesium, 90 g. (0.82 mole) of ethyl bromide and 184 g. (1.64 moles) of cycloheptanone in a total of 10 l. of anhydrous ether there was obtained an oily crude product which was fractionally distilled through a 55-cm., glass helix-packed column to yield, in addition to the lower-boiling components corresponding to those enumerated previously, 163 g. (76%) of the olefin IV, b.p. 170–175° (5 mm.). A portion was redistilled for analysis: b.p. 145° (0.5 mm.), n^{25}D 1.5435, $\lambda_{\max}^{\mathrm{EtOH}}$ 243 mμ (ε 11,900). Ginsburg and Pappo[17] obtained this olefin as a solid with m.p. 38–38.5° and n^{20}D 1.5439.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.29; H, 8.23.

2-(2′,3′,4′-Trimethoxyphenyl)-cyclohexanone (VII).—A solution of 68 g. (0.274 mole) of 1-(2′,3′,4′-trimethoxyphenyl)-cyclohexene in 383 ml. of ethyl acetate was cooled to 3° and then added, all at once, to a solution of 56.5 g. (0.41 mole) of perbenzoic acid in 1120 ml. of ethyl acetate also at 3°. The reaction mixture was kept in the refrigerator until slightly more than 1 equivalent of perbenzoic acid had been consumed, as determined by periodic titrations of aliquot samples (51 hours for this particular experiment). The benzoic acid was then removed by base extraction, and the ethyl acetate was evaporated to leave 82 g. of a yellow oil. This was dissolved in 150 ml. of ethanol, treated with 15.3 ml. (0.273 mole) of sulfuric acid in 150 ml. of water, and refluxed for 2 hours. The product, obtained in the usual way, consisted of 71.5 g. of a neutral oil which, after distillation through a 30-cm. Vigreux column, yielded 56 g. (78%) of a very pale yellow oil, b.p. 178–190° (mainly 182°) at 5 mm., n^{25}D 1.5390.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.41; H, 7.24.

The semicarbazone of VII was obtained, after several recrystallizations from ethyl acetate, as colorless rhombs, m.p. 192–194°.

Anal. Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21. Found: C, 59.71; H, 7.01.

The oxime of VII was obtained as fine, white needles by recrystallization from petroleum ether (b.p. 63–69°); m.p. 156–158°.

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58. Found: C, 64.49; H, 7.62.

The 2,4-dinitrophenylhydrazone of VII was obtained as fine, orange needles by recrystallization from ethanol; m.p. 112–114°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.67; H, 5.35.

1-(2′,3′,4′-Trimethoxyphenyl)-1,2-dihydroxycyclohexane (V).—A 10.2-g. sample of the crude product from III and perbenzoic acid in ethyl acetate was triturated with petroleum ether (b.p. 63–69°)-ethyl acetate (4:1) to yield 6.0 g. of a white powder, m.p. 122–125°. After several recrystallizations from petroleum ether (b.p. 63–69°) colorless plates were obtained, m.p. 127–129°.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.74; H, 7.61.

2-(2′,3′,4′-Trimethoxyphenyl)-cycloheptanone (VIII).—Following the method described above, 101 g. (0.39 mole) of 1-(2′,3′,4′-trimethoxyphenyl)-cycloheptene and 64.0 g. (0.46 mole) of perbenzoic acid in 2000 ml. of ethyl acetate were allowed to stand at 5° for 65 hours. The crude material, amounting to 148 g., was refluxed for 4.5 hours with 15 ml. of sulfuric acid in 500 ml. of 50% aqueous ethanol, and the product was obtained by distillation through a 30-cm. Vigreux column as 89 g. (83%) of a yellow oil, b.p. 152–170° (0.5 mm.). Redistillation through a 50-cm. glass-helix packed column yielded 55.5 g. (51%) of a very pale yellow oil, b.p. 164–167° (0.45 mm.), n^{25}D 1.5365.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.65; H, 7.77.

The semicarbazone of VIII was obtained as a white powder; double m.p. 145–155° and 185–195°. Two recrystallizations from aqueous ethanol yielded blunt, microscopic needles, m.p. 148–155°.

Anal. Calcd. for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51. Found: C, 60.73; H, 7.29.

The 2,4-dinitrophenylhydrazone of VIII was obtained as fine, yellow-orange plates upon recrystallization from aqueous ethanol; m.p. 153–154°.

Anal. Calcd. for $C_{22}H_{26}N_4O_7$: C, 57.63; H, 5.72. Found: C, 57.65; H, 5.56.

1-(2′,3′,4′-Trimethoxyphenyl)-1,2-dihydroxycycloheptane (VI).—A 4.5-g. sample of the crude product from IV and perbenzoic acid in ethyl acetate was triturated with petroleum ether (b.p. 63–69°) to leave 2.1 g. of yellow amorphous powder, m.p. 78–94°. Several recrystallizations yielded colorless needles, m.p. 111–112°.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 64.80; H, 8.16. Found: C, 64.27; H, 7.80.

Ethyl 1-Hydroxy-2-(2′,3′,4′-trimethoxyphenyl)-cyclohexaneacetate (IX).—Following the general procedure of Bachmann and co-workers[4] 21.1 g. (0.077 mole) of 2-(2′,3′,4′-trimethoxyphenyl)-cyclohexanone was dissolved in 250 ml. of benzene and treated with 15.2 g. (0.232 g. atom) of activated zinc,[31] 25.6 g. (0.153 mole) of ethyl bromoacetate, 20 ml. of ether and a few crystals of iodine. The reaction mixture was maintained at reflux for 2.5 hours during which period four additions of 5.0 g. of zinc and 12.8 g. of ethyl bromoacetate were made. The crude product, obtained in the usual fashion, was distilled to yield 25.4 g. (90.5%) of a yellow oil, b.p. 185–187° (0.5 mm.), n^{25}D 1.5188.

Anal. Calcd. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 65.04; H, 7.67.

Ethyl 2-(2′,3′,4′-Trimethoxyphenyl)-cyclohexeneacetate (XI).—Dehydration of the Reformatsky product described above with thionyl chloride and pyridine[5] yielded 91% of an oil, b.p. 165–167° (0.5 mm.), n^{25}D 1.5278.

Anal. Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.31; H, 7.29.

Ethyl 2-(2′,3′,4′-Trimethoxyphenyl)-cyclohexaneacetate (XIII).—Reduction of the olefin XI with hydrogen at atmospheric pressure in the presence of 10% palladium-on-charcoal proceeded very slowly (several days) but to completion to yield 97.5% of distilled product, b.p. 163–164° (0.5 mm.), n^{25}D 1.5150. The reaction time was reduced to a few hours by increasing the pressure to 1500 pounds per square inch.

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 67.85; H, 8.39. Found: C, 67.43; H, 8.03.

2-(2′,3′,4′-Trimethoxyphenyl)-cyclohexaneacetic Acid (XIV).—Saponification of the saturated ester XIII yielded 98% of a white solid, m.p. 110–127°. Several recrystallizations from benzene–petroleum ether (b.p. 63–69°) yielded 50% of a pure isomer, m.p. 135–136°.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.01; H, 7.72.

The S-benzylthiouronium salt of XIV was obtained, after several recrystallizations from absolute ethanol, as colorless rhombs, m.p. 161–161.5°.

Anal. Calcd. for $C_{25}H_{34}N_2O_5S$: C, 63.26; H, 7.22. Found: C, 63.09; H, 7.06.

Ethyl 1-Hydroxy-2-(2′,3′,4′-trimethoxyphenyl)-cycloheptaneacetate (X).—From 20.0 g. of 2-(2′,3′,4′-trimethoxyphenyl)-cycloheptanone there was obtained, by the method described above for IX, 23.6 g. (90%) of an oil; b.p. 183–185° (0.5 mm.), n^{25}D 1.5234.

Anal. Calcd. for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.23; H, 7.93.

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Ethyl 2-(2′,3′,4′-trimethoxyphenyl)-cyclohepteneacetate (XII) was obtained as an oil in 90.5% yield by dehydration of the above product, b.p. 174.5–175° (0.5 mm.), $n^{25}\mathrm{D}$ 1.5286.

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.44; H, 8.01. Found: C, 68.76; H, 7.87.

Ethyl 2-(2′,3′,4′-trimethoxyphenyl)-cycloheptaneacetate (XV) resulted in 97.5% yield (distilled product) upon catalytic reduction of XII, b.p. 167–180° (mainly at 168.5°) at 0.5 mm., $n^{25}\mathrm{D}$ 1.5179.

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.61; H, 8.36.

2-(2′,3′,4′-Trimethoxyphenyl)-cycloheptaneacetic Acid (XVI).—Saponification of XV yielded 82.5% of a very viscous, yellow oil, b.p. 185–200° (0.5 mm.), which partially solidified after four months. Three recrystallizations from petroleum ether (b.p. 63–69°) gave a 27% yield of one of the pure isomers, m.p. 82–83°.

Anal. Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.06; H, 8.00.

β-[2-(2′,3′,4′-Trimethoxyphenyl)-cyclohexane]-propionic Acid (XVII).—A 4.18-g. sample of 2-(2′,3′,4′-trimethoxyphenyl)-cyclohexaneacetic acid (m.p. 135–136°) was converted to the acid chloride with phosphorus pentachloride and then to the diazoketone with ethereal diazomethane. Rearrangement of the diazoketone by the benzyl alcohol–collidine method[23] followed by saponification of the benzyl ester yielded 3.44 g. of a dark colored oil. This was dissolved in petroleum ether (b.p. 63–69°), treated with decolorizing charcoal, filtered, seeded with previously prepared XVII and allowed to stand overnight in the refrigerator. Filtration then yielded 2.34 g. (47%) of a tan solid, m.p. 81–82°, which was recrystallized from the same solvent and obtained as colorless needles, m.p. 82.5–83°.

Anal. Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.75; H, 8.19.

A similar sequence employing the oxalyl chloride method for the preparation of the acid chloride[32] and the Newman–Beal[24] method for the rearrangement of the diazoketone yielded 76% of crude XVII as a slightly sticky solid from which, after molecular distillation and recrystallization, there was obtained 51% of pure material.

The S-benzylthiouronium salt of XVII was obtained as white needles after recrystallization from absolute ethanol; m.p. 159.5–160°.

Anal. Calcd. for $C_{26}H_{36}N_2O_5S$: C, 63.90; H, 7.43. Found: C, 63.65; H, 7.42.

A mixed m.p. of the benzylthiouronium salts of XIV and XVII showed a depression of 5°.

4b,5,6,7,8,8a,9,10-Octahydro-2,3,4-trimethoxy-10-ketophenanthrene (XXI).—A 2.00-g. sample of 2-(2′,3′,4′-trimethoxyphenyl)-cyclohexaneacetic acid (m.p.1 35–136°) was treated for 2.5 hours with 120 g. of anhydrous hydrogen fluoride in a system protected from the atmosphere. The crude product consisted of 1.70 g. (90.5%) of almost colorless solid, m.p. 77–78°, and, after molecular distillation and recrystallization from petroleum ether (b.p. 63–69°), was obtained as colorless prisms, m.p. 78–79°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ in cm.$^{-1}$ 863, 913, 973, 1018, 1084, 1102, 1115, 1150, 1267, 1292, 1325, 1342, 1400, 1422, 1455, 1470, 1560, 1590, 1675, 2840, 2900.[33]

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.72.

The 2,4-dinitrophenylhydrazone of XXI was obtained as dark red, very fine needles after recrystallization from ethanol–ethyl acetate; m.p. 242–242.5° dec.

Anal. Calcd. for $C_{23}H_{26}N_4O_7$: C, 58.71; H, 5.57. Found: C, 58.64; H, 5.42.

Cyclization of a mixture of isomers of XIV (m.p. 110–127°) yielded a solid, m.p. 68–79°, which after six recrystallizations from aqueous methanol, produced white needles, m.p. 86–89.5°. This material still contained appreciable amounts of the 78° isomer; conversion to a 2,4-dinitrophenylhydrazone yielded, after several recrystallizations, the same compound as described above.

6,6a,7,8,9,10,11,11a-Octahydro-1,2,3-trimethoxy-5-keto-5H-cyclohepta[a]naphthalene (XXII).—A 5.98-g. sample of 2-(2′,3′,4′-trimethoxyphenyl)-cycloheptaneacetic acid (b.p. 200° at 0.5 mm.) was treated for 4.5 hours with 100 g. of anhydrous hydrogen fluoride to yield 5.52 g. of a pale yellow solid; m.p. 81–98°. Several recrystallizations from aqueous ethanol gave fine, white needles: m.p. 109–110.5°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ in cm.$^{-1}$ 855, 964, 1010, 1080, 1105, 1280, 1305, 1340, 1403, 1458, 1480, 1590, 1675, 2840, 2900.[33]

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.75; H, 7.67.

The 2,4-dinitrophenylhydrazone of XXII was obtained, after recrystallization from ethanol, as fine, dark red needles, m.p. 201–202° dec.

Anal. Calcd. for $C_{24}H_{28}N_4O_7$: C, 59.49; H, 5.82. Found: C, 59.23; H, 5.52.

6,7,7a,8,9,10,11,11a-Octahydro-1,2,3-trimethoxy-5-keto-5H-dibenzo[a,c]cycloheptatriene (XIX).—A 4.30-g. sample of β-[2-(2′,3′,4′-trimethoxyphenyl)-cyclohexane]-propionic acid (m.p. 81–82°) was heated for 25 minutes at 65–70° with a solution containing 75 g. of phosphorus pentoxide and 50 ml. of 90% phosphoric acid. The neutral product consisted of 3.10 g. (77%) of a pale yellow solid, m.p. 97–105°. The pure product was obtained after evaporative distillation followed by several recrystallizations from petroleum ether (b.p. 63–69°) as colorless prisms, m.p. 112.5–113.5°; $\lambda_{\max}^{\mathrm{CHCl_3}}$ in cm.$^{-1}$ 844, 910, 962, 1015, 1086, 1114, 1138, 1267, 1322, 1336, 1355, 1400, 1444, 1460, 1475, 1562, 1586, 1670, 2840, 2900.[33]

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.01; H, 7.98.

The 2,4-dinitrophenylhydrazone of XIX was obtained, after recrystallization from ethanol–ethyl acetate, as bright orange, felted needles, m.p. 249–251° dec.

Anal. Calcd. for $C_{24}H_{28}N_4O_7$: C, 59.49; H, 5.83. Found: C, 59.50; H, 6.20.

A cyclization, according to the conditions described above, of the oily mixture of isomers of the propionic acid XVII yielded the ketone as an oil from which two 2,4-dinitrophenylhydrazones could be isolated: (a) dark red needles with m.p. 234–234.5°.

Anal. Calcd. for $C_{24}H_{28}N_4O_7$: C, 59.49; H, 5.83. Found: C, 59.35; H, 6.01.

(b) Red needles with m.p. 201–203°. *Anal.* Calcd. for $C_{24}H_{28}N_4O_7$: C, 59.49; H, 5.83. Found: C, 59.51; H, 5.98.

5,6,7,7a,8,9,10,11,12,12a-Decahydro-1,2,3-trimethoxy-5-ketobenzo[a]heptalene (XX).—A 2.20-g. sample of 2-(2′,3′,4′-trimethoxyphenyl)-cycloheptaneacetic acid (m.p. 81.5–83.5°) was subjected to the Arndt–Eistert reaction according to the method of Newman and Beal (nitrogen evolution 88% of theory) to yield XVIII as a pale yellow oil. This was treated directly, without further purification, with 25 g. of phosphorus pentoxide dissolved in 16 ml. of 90% phosphoric acid for a period of 25 minutes at 65–70°. The neutral product, consisting of 1.46 g. of a yellow oil, was evaporatively distilled at 145° and 0.005 mm. to give a pale yellow oil which failed to crystallize; $\lambda_{\max}^{\mathrm{CHCl_3}}$ in cm.$^{-1}$ 840, 962, 1008, 1095, 1128, 1322, 1395, 1452, 1570, 1590, 1670, 2840, 2900.[33]

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 72.77; H, 8.11.

A 2,4-dinitrophenylhydrazone of XX was obtained as orange-red needles after recrystallization from ethanol; m.p. 190–191°.

Anal. Calcd. for $C_{25}H_{30}N_4O_7$: C, 60.23; H, 6.07. Found: C, 60.60; H, 6.30.

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[32] R. Adams and L. H. Ulich, THIS JOURNAL, **42**, 599 (1920); A. L. Wilds and C. H. Shunk, *ibid.*, **70**, 2427 (1948).

[33] We are indebted to Dr. Verner L. Stromberg of the National Heart Institute, Bethesda, Md., for the infrared spectra.