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Colchicine Studies. I. Synthesis and Reactions of 2-Arylcyclohept-2-enones[1]

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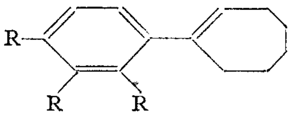
The synthesis of 2-phenylcyclohept-2-enone and its behavior in Michael condensation is described. Cycloheptenoindole is obtained as a by-product in the formation of the oxime of 2-phenylcyclohept-2-enone. Pyrogallol trimethyl ether can be metalated with *n*-butyllithium to give the 4-lithium compound. This product, on treatment with a number of cyclic ketones, yields compounds containing certain features of the colchicine skeleton.

In synthetic experiments designed for the construction of the skeletal structure of morphine, 2-arylcyclohex-2-enones have been prepared[2] and have been shown to undergo Michael condensation with suitable compounds.[3] The products thus obtained have been cyclized to octahydrophenanthrenes.[3] Substances having the skeletal structure of colchicine should be accessible analogously, starting from 2-arylcyclohept-2-enones.

Synthesis of the model compound 2-phenylcyclohept-2-enone (IIIa) was therefore undertaken. The nitroso chloride II of 1-phenylcycloheptene (Ia) was prepared in high yield by reaction of Ia with *n*-amyl nitrite and hydrochloric acid. Compound II was then converted by pyridine into the oxime of 2-phenylcyclohept-2-enone, which smoothly underwent hydrolysis to yield the desired α,β-unsaturated ketone IIIa. The structure of this ketone was proven by reduction to the known 2-phenylcycloheptanone.[4]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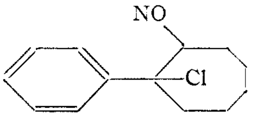
Ib, R = OCH_3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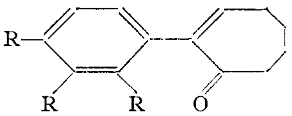
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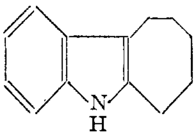
IIIb, R = OCH_3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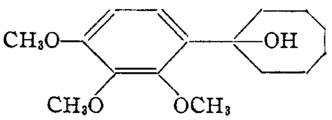
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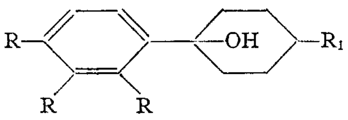
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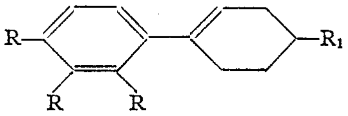
VIb, R = R_1 = OCH_3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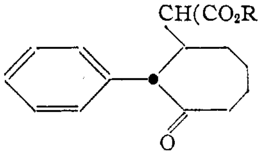
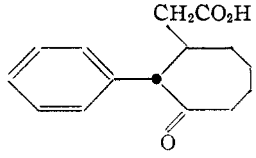
VIIb, R = R_1 = OCH_3


VIIIa, R = $CH_2C_6H_5$
VIIIb, R = H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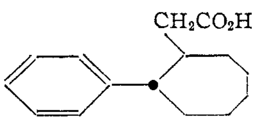
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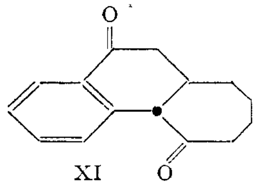
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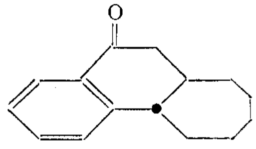
XII

The conversion of the nitrosochloride of 1-phenylcycloheptene into the oxime of IIIa did not proceed as smoothly as in the case of the corresponding derivatives of substituted cyclohexenes. In addition to the oxime of 2-phenylcyclohept-2-enone, another product was obtained. The mechanism of the formation of this product, cycloheptenoindole (IV), is not clear. It may be that this indole is formed by thermal dehydration of one of the forms of the oxime of 2-phenylcyclohept-2-enone when the latter is subjected to high vacuum distillation. The indole IV gives no melting point depression on admixture with an authentic specimen prepared by the Fischer indole synthesis.[5] The infrared spectrum of both specimens is identical. A thermal reaction seems to be indicated in the formation of IV, since evidently, a disproportionation has to be assumed in order to account for the structure obtained. This reaction is being applied to a number of other cases of indole syntheses.

In order to emulate more closely the structure of colchicine, it was desirable to prepare 2-(2′,3′,4′-trimethoxyphenyl)-cyclohept-2-enone. Pyrogallol trimethyl ether was therefore metalated with *n*-butyllithium and the 4-lithium derivative thus obtained was treated with cycloheptanone, and for the sake of comparison with cyclohexanone and 4-methoxycyclohexanone.[6]

The tertiary carbinols V, VIa and VIb, which were obtained from these reactions, were quantitatively dehydrated by means of oxalic acid in boiling

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(1) Presented at the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., September, 1951.

(2) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 516 (1951).

(3) R. Pappo and D. Ginsburg, *Bull. Res. Council Israel*, **1**, No. 1, 145 (1951); D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 938 (1951).

(4) C. D. Gutsche, THIS JOURNAL, **71**, 3513 (1949).

(5) We are indebted to Dr. B. Witkop for the authentic specimen of cycloheptenoindole.

(6) *Cf.* E. Bergmann, R. Pappo and D. Ginsburg, *J. Chem. Soc.*, 1369 (1950).

toluene,[6] to yield the olefins Ib, VIIa and VIIb, respectively.

The 1-(2′,3′,4′-trimethoxyphenyl)-cyclohexene (VIIa) was converted to the corresponding α,β-unsaturated ketone, 2-(2′,3′,4′-trimethoxyphenyl)-cyclohex-2-enone, through the nitroso chloride, but this method failed in the case of Ib and VIIb. Other routes for the preparation of the important intermediate IIIb are being explored.

Pyrogallol trimethyl ether has been metalated previously, using phenyllithium but, judging from the yields reported, metalation was not only incomplete but was accompanied by considerable demethylation, particularly of the central methoxyl group.[7] With *n*-butyllithium, the amount of demethylation was negligible and metalation took place in satisfactory yield.

During the formation of nitroso chlorides from compounds containing the 1,2,3-trimethoxyphenyl group, the temperature must be kept low, as their instability toward nitrous acid is well known.[8] Otherwise, the exothermic reaction leads to extensive decomposition.

It has been indicated above, that, in contradistinction with experience in the 1-arylcyclohexene series, the dehydrochlorination of the nitroso chlorides of the 1-arylcycloheptenes is unsatisfactory and gives only a low or negligible yield of the desired oxime. Such differences in behavior between derivatives of cyclohexane and cycloheptane are in no sense novel. An explanation of this type of phenomenon, based on I strain, has recently been advanced by Brown and co-workers.[9] They have shown that differences in reactivity between representatives of the two series may involve factors of the order of 100.

The Michael condensation with 2-phenylcyclohept-2-enone (IIIa) was studied. As it had been observed that the use of dibenzyl malonate in place of diethyl malonate in the Michael condensation with 2-phenylcyclohex-2-enone, increases the over-all yield of the derived *trans*-3-keto-2-phenylcyclohexaneacetic acid to 88%,[10] IIIa was treated with dibenzyl malonate in the presence of potassium *t*-butoxide, and the adduct VIIIa obtained. Hydrogenolysis of the dibenzyl ester yielded the malonic acid VIIIb, which was decarboxylated to give pure *trans*-3-keto-2-phenylcycloheptaneacetic acid (IX) in 72% over-all yield (based on 2-phenylcyclohept-2-enone).

It has been shown previously that *trans*-adducts are formed in the Michael condensation of 2-phenylcyclohex-2-enone with compounds containing reactive methylene groups.[11,12] The *trans* adduct is obtained also in the case of 2-phenylcyclohept-2-enone. This was shown by Clemmensen reduction of the *trans*-3-keto-2-phenylcycloheptaneacetic acid (IX) to *trans*-2-phenylcycloheptaneacetic acid (X), m.p. 68–69°, and the cyclization of the latter by means of sulfuric acid to give *trans*-6,6a,7,8,9,10,11,11a-octahydro-5-keto-5H-cyclohepta[a]naphthalene (XII). This ketone has been described previously and has been assigned the *trans* configuration on the basis of melting point and ultraviolet absorption data.[13] The *trans*-acid X has not previously been obtained pure but the pure *cis* isomer has been reported.[13]

Work is in progress with a view to forming a tricyclic system containing one aromatic and two alicyclic seven-membered rings.

Experimental[14]

1-Phenylcycloheptene (Ia).—1-Phenylcycloheptanol was prepared by the method of Kleene.[15] Dehydration was accomplished quantitatively by oxalic acid in boiling toluene, the water being removed azeotropically[6]; over-all yield 71%, n^{20}_{D} 1.5619. Pines, Edeleanu and Ipatieff,[16] report n^{20}_{D} 1.5624.

1-Phenylcycloheptenenitrosochloride (II).—To a mixture of 1-phenyl-cycloheptene (58.5 g.), *n*-amyl nitrite (47 g.) and acetic acid (65 ml.), concentrated hydrochloric acid (40 ml.) was added dropwise with stirring. The temperature during the addition which required 30 minutes, was kept at −10° and maintained at this level for 2 additional hours. The nitroso chloride was filtered with suction, washed with ice-cold ethanol and dried; yield 75 g., m.p. 112–115° (dec.).

2-Phenylcyclohept-2-enone Oxime.—The dry nitrosochloride (75 g.) was suspended in pyridine (200 ml.) and the temperature was slowly raised to 75°. An exothermic reaction set in but the temperature was kept below 85°. When all of the solid had dissolved (5–10 minutes), excess 10% hydrochloric acid was added and the precipitated oil was taken up in ether. The ether extract was washed with sodium carbonate solution and with water, dried and the solvent was evaporated. The residue (40 g.) was recrystallized from ethanol. The oxime of 2-phenylcyclohept-2-enone melted at 131–131.5°; yield 22 g.

Anal. Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.46; H, 7.62; N, 7.03.

When a similar quantity of product was subjected to distillation rather than crystallization as a means for the isolation of the oxime, a forerun of oxime, b.p. 155–160° (2 mm.), weighing 7 g. was obtained. Decomposition appeared to be taking place and a second fraction boiling at 170–190° (2 mm.) was obtained (26 g.). This product solidified on cooling and after recrystallization from ethanol gave colorless crystals, m.p. 145°, of the indole, IV, identical with cycloheptenoindole obtained by Dr. B. Witkop from the phenylhydrazone of cycloheptanone.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.06; H, 8.24; N, 7.61.

2-Phenylcyclohept-2-enone (IIIa).—The oxime (4 g.) was added to a mixture of concentrated hydrochloric acid (4 ml.) and water (30 ml.) and refluxed for 8 hours. The free ketone was taken up in ether, the extract washed with dilute sodium carbonate solution and water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled in a vacuum. The product was an oil, b.p. 150° (6 mm.), yield 3.2 g., m.p. 6–7°.

Anal. Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 84.20; H, 7.76.

Semicarbazone, m.p. 180–181° (dec.), from ethanol.

Anal. Calcd. for $C_{14}H_{17}ON_3$: C, 69.11; H, 7.05; N, 17.27. Found: C, 69.22; H, 7.00; N, 17.31.

2,4-Dinitrophenylhydrazone, orange, m.p. 116–117° (dec.), from ethanol–ethyl acetate. A second, yellow, form was obtained, m.p. 180–181° (dec.), from ethanol.

Anal. Calcd. for $C_{19}H_{18}O_4N_4$: N, 15.30. Found: N, 15.26, 15.22.

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(7) G. Wittig and G. Fuhrmann, *Ber.*, **73**, 1217 (1940).

(8) C. Graebe and H. Hess, *Ann.*, **340**, 232 (1905).

(9) H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951).

(10) Unpublished results in this Laboratory.

(11) W. E. Bachmann and E. J. Fornefeld, THIS JOURNAL, **72**, 5529 (1950).

(12) R. Pappo and D. Ginsburg, *Bull. Res. Council Israel*, **1**, No. 3, 121 (1951).

(13) C. D. Gutsche, THIS JOURNAL, **73**, 786 (1951).

(14) M.ps. and b.ps. are uncorrected.

(15) R. D. Kleene, THIS JOURNAL, **63**, 1482 (1941).

(16) H. Pines, A. Edeleanu and V. N. Ipatieff, *ibid.*, **67**, 2193 (1945).

Proof of Structure of 2-Phenylcyclohept-2-enone.—The ketone IIIa (1.3 g.) was dissolved in 95% ethanol (50 ml.) and was hydrogenated in the presence of 10% palladium–charcoal (0.13 g.) at an initial pressure of 55 p.s.i. After 1 hour, one mole of hydrogen had been absorbed. The catalyst was removed by filtration, the ethanol evaporated and the residue distilled in a vacuum, b.p. 141° (5 mm.). The following derivatives of 2-phenylcycloheptanone were prepared: **semicarbazone**, m.p. 153–154°, from ethanol; **2,4-dinitrophenylhydrazone**, m.p. 170° (dec.), from ethanol. Tiffeneau and co-workers[17] report 156° for the m.p. of the semicarbazone and Gutsche[4] reports 171–172° for the m.p. of the 2,4-dinitrophenylhydrazone of 2-phenylcycloheptanone.

trans-**3-Keto-2-phenylcycloheptanemalonic Acid** (**VIIIb**).—A mixture of 2-phenylcyclohept-2-enone (6 g.), dibenzyl malonate (12 g.) and potassium *t*-butoxide (from 0.14 g. of potassium in 2.2 ml. of *t*-butanol), was kept at 50° for 3 hours and then overnight at room temperature. Acetic acid (0.3 ml.) and ethyl acetate (50 ml.) were added and the mixture was subjected to hydrogenation in the presence of 10% palladium–charcoal (1.1 g.) at an initial pressure of 60 p.s.i. The theoretical amount of hydrogen (2 moles) was taken up during 1 hour. The catalyst was removed by filtration, the solution extracted with 5% sodium carbonate solution and the alkaline extract was washed once with ether. Upon acidification of the alkaline extract, *trans*-3-keto-2-phenylcycloheptanemalonic acid precipitated. It melted at 185–190° (dec.) (from ethyl acetate); yield 7 g. of pure product.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.10; H, 6.21.

Dibenzyl malonate was prepared by a modification of the method of Bowman[18] for the preparation of benzyl esters of acylmalonic acids, by transesterification of diethyl malonate in benzene solution by means of benzyl alcohol in the presence of a catalytic amount of sodium methoxide.

trans-**3-Keto-2-phenylcycloheptaneacetic Acid** (**IX**).—Half-decarboxylation of VIIIb (7 g.) was effected by heating at 180–190° for 15 minutes. The product was recrystallized from benzene; m.p. 115°, yield 5.6 g.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.28; H, 7.41.

trans-**Methyl 3-Keto-2-phenylcycloheptaneacetate.**—This ester was formed by the addition of an ethereal solution of diazomethane to a solution of the acid in ether. After removal of the ether, the residue was recrystallized from methyl cyclohexane and melted at 110–111°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.56; H, 7.52.

trans-**2-Phenylcycloheptaneacetic Acid** (**X**).—Clemmensen reduction of (IX) (1 g.) was effected by refluxing with concentrated hydrochloric acid (50 ml.) in the presence of amalgamated zinc (20 g.) for 48 hours. Hydrochloric acid (20 ml.) was added to the refluxing mixture at 6-hour intervals during the 48-hour period. The product was extracted with ether, the solvent evaporated and the residue triturated with cold hexane. The starting material was recovered from the hexane insoluble fraction and was retreated as before. The hexane-soluble fraction was evaporatively distilled and recrystallized from hexane; m.p. 68–69°, yield 0.61 g.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.42; H, 8.75.

trans-**6,6a,7,8,9,10,11,11a-Octahydro-5,11-diketo-5H-cyclohepta[a]naphthalene** (**XI**).—*trans*-3-Keto-2-phenylcycloheptaneacetic acid was cyclized by dissolving the acid in 10 times its weight of sulfuric acid and heating on the steam-bath for 10 minutes. The reaction mixture was poured on ice, the product extracted with ether, the extract washed with 10% sodium carbonate solution and the ether evaporated. Trituration of the oily residue with hexane resulted in crystallization of the diketone, m.p. 104°. Recrystallization from hexane raised the m.p. to 106–107°, yield 63%.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07. Found: C, 79.04; H, 7.02.

trans-**6,6a,7,8,9,10,11,11a-Octahydro-5-keto-5H-cyclohepta[a]naphthalene** (**XII**).—*trans*-2-Phenylcycloheptaneacetic acid (1 g.) was treated with 95% sulfuric acid (5 ml.) for 10 minutes on the steam-bath. The ketone was obtained as above, m.p. 60–61°, from hexane; yield 0.67 g.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.92; H, 8.45. Semicarbazone, m.p. 176–177° (dec.), from ethanol. Gutsche[13] reports m.p. 60.5–61° and 175.5–177.5° (dec.) for the ketone and its semicarbazone, respectively.

Metalation of Pyrogallol Trimethyl Ether.—A solution of 2,3,4-trimethoxyphenyllithium was prepared from ethereal *n*-butyllithium [from 164 g. (1.2 moles) of *n*-butyl bromide in 200 ml. of ether and 18.5 g. of lithium in 420 ml. ether] and pyrogallol trimethyl ether (127 g.) in ether (150 ml.). The reaction mixture was stirred for 6 hours at room temperature in an atmosphere of nitrogen.

Preparation of Tertiary Carbinols V, VIa, VIb (**a**).—To the above filtered solution of 2,3,4-trimethoxyphenyllithium, there was added with stirring, cycloheptanone (135 g.) in ether (100 ml.). After 12 hours, water was added, the ether layer separated, washed with 10% sodium hydroxide solution and water, dried over anhydrous sodium sulfate and concentrated. The residue was distilled in a high vacuum. After a forerun of unchanged cycloheptanone and pyrogallol trimethyl ether and an intermediate fraction, there was obtained **1-(2′,3′,4′-trimethoxyphenyl)-cycloheptanol** (**V**), b.p. 165–175° (0.05 mm.). The oily product crystallized after refrigeration, m.p. 46–47° from hexane; yield 69 g.

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.72; H, 8.40.

(**b**).—To the above solution of 2,3,4-trimethoxyphenyllithium, was added cyclohexanone (110 g.). The mixture was worked up as described in (a) and **1-(2′,3′,4′-trimethoxyphenyl)-cyclohexanol** (**VIa**), b.p. 160–165° (0.04 mm.), obtained as an oil which crystallized spontaneously, m.p. 66–67°, from hexane; yield 54 g. *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.60; H, 8.13.

(**c**).—To the above solution of the organolithium compound, was added 4-methoxycyclohexanone (143 g.).[19] **1-(2′,3′,4′-Trimethoxyphenyl)-4-methoxycyclohexanol** (**VIb**) was obtained as an oil, b.p. 190° (1 mm.), yield 61 g.

Anal. Calcd. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.20; H, 8.45.

1-(2′,3′,4′-Trimethoxyphenyl)-cycloheptene (**Ib**).—This compound was obtained in quantitative yield (40.5 g.) by dehydration of the corresponding carbinol (V) (43 g.) with oxalic acid (6 g.) in boiling toluene (200 ml.), the water being removed azeotropically in a water separator (30 minutes). The product was obtained as an oil, b.p. 145–150° (0.05 mm.). It solidified on refrigeration, m.p. 38–38.5°, from hexane. On admixture with a specimen of the carbinol V, the mixture became liquid at room temperature (23°), n^{20}_D 1.5439.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.46. Found: C, 73.11; H, 8.31.

1-(2′,3′,4′-Trimethoxyphenyl)-cyclohexene (**VIIa**).—Oil, b.p. 145° (0.04 mm.), yield quantitative.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.67; H, 7.94.

1-(2′,3′,4′-Trimethoxyphenyl)-4-methoxycyclohexene (**VIIb**).—Oil, b.p. 150–155° (0.05 mm.), yield quantitative.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.88; H, 7.80.

2-(2′,3′,4′-Trimethoxyphenyl)-cyclohex-2-enone.—This preparation is recorded as an example for the care which must be taken in forming the nitrosochloride.

(**a**) **1-(2′,3′,4′-Trimethoxyphenyl)-cyclohexenenitrosochloride.**—A mixture of the olefin VIIa (9 g.), *n*-amyl nitrite (5 g.) and acetic acid (12 ml.) was stirred at −10°, the flask being immersed in an acetone–Dry Ice-bath. Concentrated hydrochloric acid (4.3 ml.) was added dropwise during 30 minutes, only about 1–2 drops per minute being added during the first 10 minutes. After all of the acid had been added, the mixture was maintained at −10° for 3 additional hours. The microcrystalline nitroso chloride

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[17] M. Tiffeneau, P. Weill, J. Gutmann and B. Tchoubar, *Compt. rend.*, **201**, 277 (1935).

[18] R. E. Bowman, *Nature*, **162**, 111 (1948); *J. Chem. Soc.*, 325 (1950).

[19] L. Helfer, *Helv. Chim. Acta*, **7**, 950 (1924); P. Ruggli, O. Leupin and A. Businger, *ibid.*, **24**, 339 (1941).

was filtered and washed with ice-cold ethanol; m.p. 98–100° (dec.), yield 5 g.

(b) **Oxime of 2-(2′,3′,4′-Trimethoxyphenyl)-cyclohex-2-enone.**—The nitroso chloride (5 g.) was suspended in pyridine (8 ml.) and the mixture warmed gently until all of the precipitate had dissolved. Acetic acid (6 ml.) was added and the mixture diluted with water (to 50 ml.). The semi-crystalline precipitate was filtered and recrystallized from ethanol; m.p. 182–184°, yield 3 g.

Anal. Calcd. for $C_{15}H_{19}O_4N$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.02; H, 7.00; N, 4.98.

(c) **Hydrolysis of the Oxime.**—The oxime (3 g.) was refluxed for 1 hour with a mixture of water (30 ml.) and hydrochloric acid (3 ml.). The mixture was extracted with ether, the extract washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue of 2-(2′,3′,4′-trimethoxyphenyl)-cyclohex-2-enone was recrystallized from heptane, m.p. 61–62°, yield 2.1 g.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.43; H, 7.05.

2,4-Dinitrophenylhydrazone, orange, m.p. 143–144°, from ethanol–benzene.

Anal. Calcd. for $C_{21}H_{22}O_7N_4$: N, 12.66. Found: N, 12.72.

2-(2′,3′,4′-Trimethoxyphenyl)-cyclohexanone.—2-(2′,3′,4′-Trimethoxyphenyl)-cyclohex-2-enone (1 g.) was reduced with 10% palladium–charcoal (0.1 g.) in ethanol (25 ml.) at an initial hydrogen pressure of 60 p.s.i. The theoretical amount of hydrogen (1 mole) was taken up during 2 hours. Removal of the catalyst and solvent and distillation in a high vacuum gave 0.92 g. of the substituted cyclohexanone, b.p. 165° (0.08 mm.).

Semicarbazone, m.p. 199–200°, from aqueous ethanol.

Anal. Calcd. for $C_{16}H_{23}O_4N_3$: C, 59.80; H, 7.21; N, 13.08. Found: C, 59.72; H, 7.12; N, 13.22.

2,4-Dinitrophenylhydrazone, orange, m.p. 110–111°, from ethanol.

Anal. Calcd. for $C_{21}H_{24}O_7N_4$: C, 56.75; H, 5.44; N, 12.61. Found: C, 56.90; H, 5.38; N, 12.56.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Syntheses of Degradation Products of Aureomycin. III

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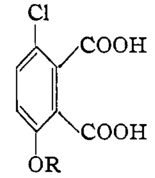
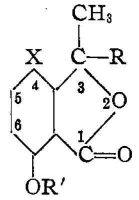
The unequivocal synthesis of 4-chloro-7-hydroxy-3-methylphthalide and 4-chloro-7-hydroxy-3-methylphthalide-3-carboxylic acid, degradation products of aureomycin, are described utilizing as starting material 2-amino-3-methoxyacetophenone. Ring chlorination of the phthalides is accomplished in the final step with the attachment at the 4-positions. Since the phthalides have been degraded to 6-chloro-3-methoxyphthalic acid, which itself has been synthesized unequivocally, the structures of the phthalides are established.

In previous preliminary communications[1,2] aureomycin has been shown to be degraded to tetrasubstituted benzene derivatives, principally phthalides.



I, = R = H
Ia, = R = CH_3



II, R = H, R′ = H, X = H
IIa, R = H, R′ = CH_3, X = H
III, R = H, R′ = H, X = Cl
IIIa, R = H, R′ = CH_3, X = Cl
IV, R = COOH, R = CH_3, X = H
IVa, R = COOH, R = CH_3, X = Cl
V, R = CH_2COOH, R = CH_3, X = Cl

3-Chloro-6-hydroxyphthalic acid (I) or its methyl ether (Ia), the simplest of the isolated tetrasubstituted products, was prepared by subjecting commercially available 5-chloro-2-methoxyaniline with chloral and hydroxylamine to the isatin synthesis followed by peroxide oxidation to 2-amino-6-chloro-3-methoxybenzoic acid.[3] This compound was readily diazotized, the NH_2 group was replaced by the Sandmeyer reaction with CN, and the product was then hydrolyzed to the phthalic acid. This acid, on the steam-cone, was converted to its more stable anhydride.

The synthetic samples, thus prepared, of I and Ia which were identical in all respects with the degradation products[2] fixed the relative position of the chlorine atom in respect to the hydroxy group in the same ring.

Although this phthalic acid theoretically could be converted to the simple phthalides, it in itself, because of its own asymmetry, could lead to two different phthalides and thus necessitate further structure proof. To avoid this a method of synthesis of the phthalides was chosen that not only would be unequivocal but in itself would be versatile enough for synthesis of the higher homologs. In the degradation of aureomycin Hutchings[2] converted 4-chloro-7-methoxy-3-methylphthalide (IVa) by a sequence of decarboxylation and oxidation to 3-chloro-6-methoxyphthalic acid (I). On this basis, therefore, the chlorine atom in the structure of a synthetic monochlorinated phthalide, identical with the isolated phthalide, would be fixed in the 4-position and not in the 6-position. Moreover, as far back as 1881, Prinz,[4] in a study of opianic acid and its derivatives, showed that these compounds which are 6- and 7-hydroxylated phthalides were rapidly halogenated in the 4-position. Although our phthalides had a free 6-position, it was found that the first point of attack gave the desired 4-chlorophthalides.

As starting material for the phthalides we used 2-amino-3-methoxyacetophenone which was prepared in large quantity by the method of Simpson and co-workers.[5]

This readily reactive aminoketone was first reduced with lithium aluminum hydride, diazotized,

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[1] S. Kushner, *et al.*, THIS JOURNAL, **74**, 3709 (1952).

[2] B. L. Hutchings, *et al.*, *ibid.*, **74**, 3709 (1952).

[3] B. R. Baker, *et al.*, *J. Org. Chem.*, **17**, 160 (1952).

[4] O. Prinz, *J. prakt. Chem.*, **24**, 353 (1881).

[5] J. C. E. Simpson, *et al.*, *J. Chem. Soc.*, 646 (1945).