[CONTRIBUTION NO. 271 FROM THE DEPARTMENT OF BIOCHEMISTRY AND NUTRITION, UNIVERSITY OF SOUTHERN CALIFORNIA AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF UTAH]

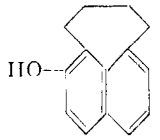
Seven-membered Ring Compounds. I. 7,8,9,10-Tetrahydrocyclohepta[de]naphthalene

BY RICHARD C. GILMORE, JR.,[1] AND W. J. HORTON[2]

Two syntheses devised to give 7,8,9,10-tetrahydrocyclohepta[de]naphthalene (IV) lead to an identical compound. The usefulness of phosphorus pentoxide in phosphoric acid for the cyclization of aryl-aliphatic acids in high yield is indicated particularly in cases in which the conventional methods fail.

Attention has recently been focused on seven-membered ring systems by the great interest shown in the tropolones[3] and especially in the question of the structure of colchicine,[4] apparently a compound containing two fused seven-membered rings. The limited investigations in this field may be indicated by the paucity of literature on compounds whose six-membered ring analogs are common. Apparently benzosuberol, the simple reduction product of benzosuberone, is unreported. The literature on ring structures containing two mutually fused seven-membered rings is not extensive[5] and the two possible naphthosuberans are still unreported.[6]

In a previous paper[7] we reported the preparation of 1-hydroxy-7,8,9,10-tetrahydrocyclohepta[de]-naphthalene (I). The ease with which peri-cyclization occurred when aided by an activating group encouraged an investigation of γ-1-tetrylbutyric acid (II).


I

The necessary γ-1-tetrylbutyric acid was obtained from 1-tetralone and methyl γ-bromocrotonate.[8] The Reformatsky ester so obtained[9] lost water on distillation and after reduction followed by saponification gave the desired tetrylbutyric acid.

A study of the reported[10] cyclization of γ-1-tetrylbutyric acid confirmed the low yield and decomposition when aluminum chloride in carbon disulfide was used on the acid chloride. Attempts to moderate the losses from tar formation by the use of stannic chloride in benzene,[11] aluminum chloride in nitrobenzene or anhydrous hydrogen fluoride[12] resulted in improved but still impractical yields.

It is therefore surprising that excellent yields (92–94%) of cyclized product (III) are obtainable without great expenditure of time and labor by the action of exaggerated amounts of a solution of phosphorus pentoxide in 85% orthophosphoric acid[13] on the tetrylbutyric acid. That the cyclization product of this acid by the phosphoric acid method is the ketone (III) previously obtained was indicated by the agreement in m.p. of the ketone and the oxime with those reported.[10] That the large amount of the reagent is responsible for the nearly quantitative results is indicated by a slightly decreased yield when less reagent is used.[14,15] The rapidity of the cyclization is indicated by one experiment which yielded 88% of ketone after only 10 minutes at ninety-five degrees. It has been convenient to ignore the small amount of acidic material which is readily separated from the product. In some cases it is anticipated that the yield may be increased by retreatment of recovered acid. The quantity of the reagent is a disadvantage with larger amounts. However, as much as 35.5 g. of the acid has been converted to III in a single run.[14]

Reduction of von Braun's ketone (III) by the Clemmensen procedure and dehydrogenation produced IV. The structure III, assigned by von Braun, rests solely on analytical data and on the fact that it is the simplest structure obtainable from a ring closure of tetrylbutyric acid. Other work in progress in this Laboratory which is not, as yet, completely understood has drawn attention to the lack of degradative evidence for the structure of III and therefore a confirmation of this structure was sought by means of a second synthesis of IV.

From benzosuberone (V) by a Reformatsky procedure[9] the benzosuberylidenacetic acid ester (VI)[16] was obtained. The carbinol ester resists straightforward dehydration when distilled *in vacuo*

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[1] In part from the Doctoral Dissertation of Richard C. Gilmore, Jr., University of Utah, 1949.

[2] Address inquiries about the manuscript to the University of Utah.

[3] J. D. Loudon, "Ann. Repts. on Progress Chem.," (Chem. Soc. London), **45**, 187 (1948); D. S. Tarbell, G. P. Scott and A. D. Kemp, THIS JOURNAL, **72**, 379 (1950); W. von E. Doering and L. H. Knox, *ibid.*, **72**, 2305 (1950); J. W. Cook and P. Somerville, *Nature*, **163**, 410 (1949).

[4] G. P. Scott and D. S. Tarbell, THIS JOURNAL, **72**, 240 (1950); H. Rapoport, A. R. Williams and M. E. Cisney, *ibid.*, **72**, 3324 (1950).

[5] D. H. S. Horn, J. R. Nunn and W. S. Rapson, *Nature*, **160**, 829 (1947); G. Büchi and O. Jeger, *Helv. Chim. Acta*, **32**, 538 (1949); D. H. S. Horn and W. S. Rapson, *J. Chem. Soc.*, 2421 (1949); C. D. Gutsche, Abstracts of Chicago Meeting of the American Chemical Society, September, 1950, p. 96 N.

[6] These will be the subject of a later paper in this series.

[7] R. C. Gilmore and W. J. Horton, THIS JOURNAL, **72**, 733 (1950). This paper contains refs. to all of the known 7,8,9,10-tetrahydrocyclohepta[de]naphthalene derivatives. We reserve the name, cyclohepta[de]naphthalene, henceforth for the completely conjugated parent, $C_{14}H_{10}$ to conform to *C. A.* nomenclature.

[8] K. Ziegler, A. Späth, E. Schaff, W. Schumann and E. Winkelmann, *Ann.*, **551**, 118 (1942).

[9] W. E. Bachmann and N. L. Wendler, THIS JOURNAL, **68**, 2582 (1946).

[10] J. von Braun and E. Rath, *Ber.*, **60**, 1186 (1927).

[11] W. S. Johnson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 138.

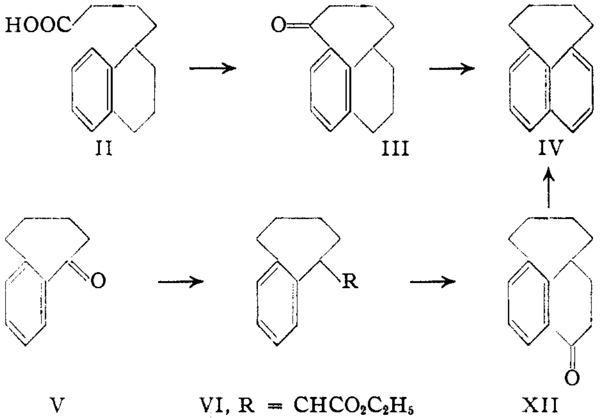
[12] Preliminary experiments by P. B. Horton in the laboratory of The Tulane University of Louisiana.

[13] A. Koebner and R. Robinson, *J. Chem. Soc.*, 1995 (1938); W. E. Bachmann and W. J. Horton, THIS JOURNAL, **69**, 58 (1947); H. R. Snyder and F. X. Werber, *ibid.*, **72**, 2966 (1950), have shown the usefulness of a commercially available polyphosphoric acid for ring closure.

[14] Work of P. D. Gardner.

[15] Note that R. T. Arnold and P. N. Craig, THIS JOURNAL, **70**, 2793 (1948), used a reagent of like composition but in decreased amounts on a different acid and obtained a yield of 45% of pure ketone.

[16] C. Mentzer, Buu-Hoï and P. Cagniant, *Bull. soc. chim. France*, **10**, 139 (1943).



II III IV

V XII

VI, R = $CHCO_2C_2H_5$
VII, R = $CH_2CO_2C_2H_5$
VIII, R = $(CH_2)_2OH$
IX, R = $CHBrCH_3$
X, R = $CHCO_2HCH_3$
XI, R = $(CH_2)_2CO_2H$

but could be dehydrated with improved yield by means of 98% formic acid.[16] The olefinic ester (VI) reduced poorly in absolute alcohol but rapidly in glacial acetic acid with hydrogen and platinum oxide. Treatment of VII with lithium aluminum hydride gave an oil thought to be VIII. However, dehydration of VIII to an olefin probably occurred in the reduction or in the distillation of the compound for the product absorbed bromine in carbon tetrachloride and would not form alcohol derivatives. When the supposed olefin was treated with hydrobromic and sulfuric acids, a mixture of bromides was obtained by addition to the double bond. That the larger fraction of the material was the unwanted bromide (IX) seems certain in that the reaction of the bromide mixture with magnesium followed by carbonation gave a crystalline acid, presumed to be X, which did not yield the expected final product. When, however, the non-crystalline fraction (XI) from the carbonation was cyclized with phosphorus pentoxide–phosphoric acid, a crystalline low melting ketone (XII) was obtained. This when reduced by the Clemmensen method and dehydrogenated gave IV, identical to the material previously prepared.

We have extended the use of phosphorus pentoxide–phosphoric acid to the production of other six- and seven-membered cyclic ketones with excellent yields. For example, we have prepared benzosuberone (V) in good yield with a greatly shortened working time.[17,18] The yield in the case of benzosuberone is reduced only very slightly when a 75-g. quantity of δ-phenylvaleric acid is used. Furthermore, reduction in the amount of phosphorus pentoxide–phosphoric acid did not greatly decrease the yield.

The attack of various reagents on the alicyclic ring of IV is under study in an attempt to prepare cyclohepta[de]naphthalene. Substitution reactions on the aromatic portion of IV are likewise under way.

This work was assisted by a Frederick Gardner Cottrell grant for which the authors express their great appreciation. The gift of a generous sample of crotonic acid by the Tennessee Eastman Corporation is gratefully acknowledged.

Experimental[19]

1,2,3,4-Tetrahydro-1-naphthylidenecrotonic Acid.—A solution of 15 g. of 1-tetralone in 100 cc. of 1:1 anhydrous benzene and ether was treated with 10 g. of zinc, 100 mg. of iodine and 13.3 g. of methyl γ-bromocrotonate.[9] The mixture was refluxed on the water-bath at 60° for a total of 15 hours. Hourly over the first 3 hours, 2 g. of bromoester, 5 g. of zinc and a crystal of iodine were added. After standing at room temperature for 20 hours with occasional agitation, the reaction mixture was treated in the usual fashion and the product distilled, b.p. 177–183° (0.15 mm.). The distillate, 12.2 g. (52%), could not be crystallized. One gram of distillate was saponified by refluxing 30 minutes with 1 g. of potassium hydroxide in 20 cc. of 1:1 ethanol-water with addition of 20 cc. of water during the first 15 minutes. The solution was then concentrated *in vacuo*, the residue cooled and the acid precipitated with 5 *N* hydrochloric acid in quantitative yield. After repeated recrystallization from carbon tetrachloride the material melted at 194–195°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.04; H, 6.55.

γ-1,2,3,4-Tetrahydro-1-naphthylbutyric Acid (II).—Hydrogenation over platinum at room temperature of 9.6 g. of the above distilled ester required 45 minutes and indicated the presence of two double bonds. After the removal of the catalyst and saponification as above, a sticky cake and some crystals were obtained. The cake was dissolved in benzene, dried and the benzene removed. The residue, 8.95 g. (98%), crystallized in the ice-chest on seeding, and after recrystallization from petroleum ether (30–60°) melted at 36–38.5° (reported[10] to crystallize readily but no m.p. is given).

7-Keto-1,2,3,7,8,9,10,10a-octahydrocyclohepta[de]-naphthalene (III).—In a flask protected from moisture, 6.2 g. of phosphorus pentoxide was dissolved in 4 cc. of 85% orthophosphoric acid by heating on a steam-bath for 2 hours with occasional shaking. Solution was facilitated by cooling only slightly by occasional immersion in water as the phosphoric acid was added so as to form a lower layer. The cyclization results seemed to discourage heating over a burner. Similarly mechanical stirring during the cyclization appeared to have a deleterious effect. After 2 hours of warming, the remaining particles were ignored, 0.25 g. of tetrylbutyric acid was added and the flask was immersed in boiling water (*ca.* 95°)[20] for a 2-hour period during which time the solution was frequently mixed by swirling. The light brown solution was then cooled and poured on ice and water with stirring. The milky solution was extracted with benzene and the benzene washed twice with 5% sodium hydroxide. The benzene was cleared with calcium chloride, filtered and removed leaving 0.22 g. (93%) of light brown oil, b.p. 128–133° (0.3 mm.). From petroleum ether (30–60°), crystals, m.p. 61.5–63°, were obtained (reported[10] m.p. 63°). Acidification of the alkaline washes gave negligible amounts of material. On larger runs, 2.67 g. to 35.5 g., the yield was 95–85%, respectively, if the amount of phosphoric anhydride–phosphoric acid was not decreased below the proportional amount. The oxime, after recrystallization from dilute alcohol, melted at 160.5–162° (reported[10] 162°).

The 2,4-dinitrophenylhydrazone, prepared in the usual manner, melted at 162–165° when purified repeatedly by solution in ethyl acetate, concentration and addition of alcohol.

Anal. Calcd. for $C_{20}H_{20}N_4O_4$: N, 14.73. Found: N, 14.62.

The phenylhydrazone melted at 108.5–109.5° but decomposed on standing at room temperature.

When γ-1-tetrylbutyryl chloride in benzene was allowed to stand with stannic chloride for 48 hours, no crystallizable ketone could be isolated. The acid chloride was allowed to stand in nitrobenzene at room temperature with aluminum chloride for 3 days and then warmed for 6 hours on the water-bath. The ketone, isolated as the semicarbazone, was ob-

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(17) P. A. Plattner, *Helv. Chim. Acta*, **27**, 804 (1944).

(18) J. W. Cook, R. Philip and A. R. Somerville, *J. Chem. Soc.*, 169 (1948), who used Plattner's method to give a 90% yield, report that no reaction took place using hydrogen fluoride.

(19) Melting points are uncorrected.

(20) The mean barometric pressure is 640 mm.

tained in 29% yield. When the heating period was omitted, the amount of ketone, as the oxime, dropped.

In an attempt to cyclize with anhydrous hydrogen fluoride, 1 g. of the acid and 100 cc. of hydrogen fluoride were allowed to stand overnight. A fraction of the neutral product (0.128 g.) formed the semicarbazone of III and 0.336 g. of the acid was recovered.

7,8,9,10-Tetrahydrocyclohepta[de]naphthalene (IV).—The Clemmensen reduction of 2 g. of III over a 20-hour period gave 1.7 g. (93%), of a light brown oil giving no test for a keto group with 2,4-dinitrophenylhydrazine. The material may be obtained as a colorless oil, b.p. 155–158° (23 mm.). With 0.22 g. of 30% palladium–charcoal[21] at 260° for 45 minutes under nitrogen, 0.556 g. of crude Clemmensen product gave off approximately two moles of hydrogen per mole of compound. After cooling, solution in benzene, filtration and evaporation of the solvent, the residue crystallized in long flat plates, 0.442 g. (79.5%). Repeated crystallization from ethanol gave crystals melting at 55.5–57°.

Anal. Calcd. for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.06; H, 7.52.

A mixture of 40 mg. of the compound and 60 mg. of picric acid gave a picrate at once. By dissolving in warm alcohol and cooling 40 mg. of long bright red needles, m.p. 114–115.5°, were obtained.

Anal. Calcd. for $C_{20}H_{17}N_3O_7$: N, 10.21; neut. equiv., 411. Found: N, 10.64; neut. equiv., 401.

Similarly a styphnate, m.p. 118.5–121°, was obtained as long golden needles.

Anal. Calcd. for $C_{20}H_{17}N_3O_8$: N, 9.83. Found: N, 10.12.

δ-Phenylvaleric Acid (a) from γ-Benzoylbutyric Acid.—To 9.9 g. of γ-carbethoxybutyryl chloride,[22] b.p. 114–117° (19 mm.) in 25 cc. of anhydrous benzene, was added 14.8 g. of anhydrous aluminum chloride in portions while maining the temperature at 5–10°.[23] The mixture was allowed to come to room temperature and stand overnight. After refluxing for 2.5 hours, the mixture was decomposed as usual, steam distilled and the product was collected in ether. The material remaining on evaporation of the ether was saponified by refluxing for 30 minutes with 4 g. of sodium hydroxide dissolved in alcohol and water. After distillation of the alcohol and addition of water, a small amount of insoluble material was removed and the acid precipitated. The acid melted at 119–123.5°, 9.3 g. (87.4%) (reported[24] m.p. 132°).

In a subsequent run, 14.7 g. of less pure material was obtained from 19.6 g. of the acid chloride. The unsaponifiable fraction weighed 5.1 g., m.p. 54–62°, and recrystallization from petroleum ether (60–70°) raised the m.p. to 64–66° (reported[25] for 1,3-dibenzoylpropane, m.p. 67.5°).

Reduction of 9.3 g. of the keto acid by the Clemmensen–Martin method gave 8.1 g. of somewhat sticky solid, m.p. 43.5–53°. By removal of material insoluble in hot petroleum ether (60–70°), 5.8 g. of compound, m.p. 51–54°, was obtained (reported[24] m.p. 59°, but no yield is given).

(b) From Cinnamaldehyde.—The reported procedure[18] with reduction of cinnamylidenemalonic acid with Raney nickel followed by decarboxylation is decidedly the preferred method for large scale preparation. When cinnamaldehyde and malonic acid were allowed to react for 4 days instead of 10, the yield decreased by 3%.

Benzosuberone (V).—A mixture of 306 g. of phosphorus pentoxide and 195 cc. of 85% orthophosphoric acid, after moderation of the heat of reaction by occasional cooling in water, was warmed on the water-bath for 2 hours with swirling from time to time. Ten grams of δ-phenylvaleric acid was added and the flask immersed in boiling water (95°)[20] for 2 hours. Within 7 minutes an amber-brown homogeneous solution, with some as yet undissolved phosphorus pentoxide particles, was obtained. The color after 40 minutes was cherry red. The reaction mixture was poured into ice-water and allowed to stand overnight. After extraction with benzene and removal of acidic material by washing with 5% sodium hydroxide, the product was distilled, b.p. 90–93° (1 mm.), and obtained as a water white oil (7.5 g.) (reported[17] b.p. 80–85° (0.5 mm.), 138–139° (12 mm.)).

In an experiment in which 453 g. of phosphorus pentoxide and 290 cc. of 85% orthophosphoric acid were heated for 4 hours to dissolve the phosphorus pentoxide, 75 g. of δ-phenylvaleric acid, m.p. 56–58.5°, was added in five 15-g. portions at 5-minute intervals and the mixture was heated at 100° for 2 hours with occasional vigorous swirling. After standing overnight at room temperature, the solution was treated as before. The acidic material recovered was small and of poor quality. The neutral fraction was distilled *in vacuo* to give 54 g. (80%), b.p. 175–176° (40 mm.). The oxime of this material melted at 106.5–107.5° (reported[26] m.p. 108–109°).

5-Benzosuberylacetic Acid.—Ethyl bromoacetate and zinc were added to benzosuberone using the Bachmann procedure[9] to give the carbinol ester in greatly improved yields (95%), m.p. 65–67.5° (reported[16] 67–70°). The ester did not react with bromine in carbon tetrachloride at room temperature. Similarly methyl bromoacetate gave the corresponding methyl ester. From 7.5 g. of benzosuberone, 9.9 g. of methyl ester, m.p. 53–63°, was obtained. A 5-g. portion of methyl ester recrystallized from petroleum ether (60–70°) gave 4.2 g., m.p. 60–66°, and further purification brought the m.p. to 64–65.5°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.10; H, 7.73.

A solution of 38 g. of the ethyl carbinol ester in 300 cc. of 98–100% formic acid was heated on the water-bath for 30 minutes.[16] The diluted solution was extracted with benzene and the benzene was washed with water and 5% sodium carbonate solution. The product was distilled at 125–126° (0.7 mm.), to yield 35 g. (reported[16] b.p. 177–180° (15 mm.)). The material shaken in glacial acetic acid with platinum absorbed one mole of hydrogen per mole of compound. On saponification of 1.2 g. of the reduced compound with 1 g. of sodium hydroxide in 50 cc. of 1:1 ethanol–water, 0.98 g. of acid, m.p. 100.5–101°, softening at 99°, was obtained. The compound gave no test with bromine in carbon tetrachloride at room temperature.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.50; H, 7.47.

The acid chloride obtained with thionyl chloride was poured into ice-cold ammonia, to give the amide, m.p. 114.5–116°.

Anal. Calcd. for $C_{13}H_{17}NO$: N, 6.89. Found: N, 7.07.

α-5-Benzosuberylpropionic Acid (X) (?).—A solution of 34 g. of ethyl 5-benzosuberylacetate in 50 cc. of anhydrous benzene was added dropwise to a stirred solution of 10 g. of lithium aluminum hydride in 100 cc. of anhydrous ether. The mixture was then refluxed on the water-bath for 1 hour and the complex decomposed in the usual way. Distillation gave 26.5 g. of viscous colorless oil, b.p. 128–130° (0.7 mm.). The oil reacted at once with bromine in carbon tetrachloride. All attempts to prepare a 3,5-dinitrobenzoate, *p*-nitrobenzoate or a urethan failed. A 15.5-g. portion of the distilled oil was refluxed for 5 hours with 28 g. of 48% hydrobromic acid and 9 g. of concentrated sulfuric acid.[27] After dilution with water and washing as usual, the product was distilled at 137–140° (0.7 mm.) to give 18.5 g. of light straw colored oil which gave a precipitate with 2% alcoholic silver nitrate.

A mixture containing 2 g. of distilled bromo compound, 2 g. of magnesium and a crystal of iodine in 15 cc. of ether refluxed under its own heat of reaction. Refluxing was maintained by slow addition of 16 g. of the bromo compound in 50 cc. of ether. After a final reflux period of 1 hour the reaction was allowed to stand overnight and then decanted onto 50 g. of solid carbon dioxide. The reaction mixture was then treated in the usual fashion. The oil obtained was dissolved in 5% aqueous sodium hydroxide and washed with benzene. Acidification gave 11 g. of gummy product after standing cold overnight. When the material was twice re-

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[21] N. D. Zelinski and M. B. Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

[22] W. E. Bachmann, S. Kushner and A. C. Stevenson, This Journal, **64**, 977 (1942).

[23] D. Papa, E. Schwenk and H. Hankin, *ibid.*, **69**, 3021 (1947).

[24] A. Ali, R. D. Desai, R. F. Hunter and S. M. M. Muhammad, *J. Chem. Soc.*, 1015 (1937).

[25] F. R. Japp and A. C. Michie, *ibid.*, **79**, 1017 (1901). J. W. Hill, This Journal, **54**, 4106 (1932), obtained a diaroylalkane using the polyanhydride of adipic acid.

[26] F. S. Kipping and A. E. Hunter, *J. Chem. Soc.*, **79**, 607 (1901).

[27] H. Gilman, ed., "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 30.

crystallized from petroleum ether (28–38°) and had stood at −20° for 24 hours, 8 g. of crystals, m.p. 89–90°, was obtained.

Cyclization of 4.3 g. of this acid by means of a solution of 80 g. of phosphorus pentoxide in 50 cc. of phosphoric acid gave 3.5 g. of a neutral oil which could not be crystallized. A positive test with 2,4-dinitrophenylhydrazine was obtained. Clemmensen reduction of the ketone in the usual way and dehydrogenation over 30% palladium-charcoal[21] gave an oil which would not crystallize, and with picric acid, a picrate which was either too unstable or too impure for isolation.

β-5-Benzosuberylpropionic Acid (XI).—By concentration of the decanted mother liquors from the purification of the above acid (X), 2.4 g. of an oil soluble in aqueous sodium bicarbonate was obtained. Attempts to induce crystallization by cooling to −70° or standing at −20° and seeding with the crystalline acid, produced no solid acid. From 0.215 g. of the oil and 3 cc. of thionyl chloride with 30 minutes refluxing there was obtained the acid chloride which was added to 15 cc. of cold ammonia. The amide, recrystallized repeatedly from aqueous ethanol melted at 101.5–103°, 0.15 g.

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.45.

3-Keto-1,2,3,7,8,9,10,10a-octahydrocyclohepta[de]-naphthalene (XII).—A solution of 50 g. of phosphorus pentoxide in 32 cc. of phosphoric acid prepared as usual was poured into a flask containing 1.88 g. of XI. After 2 hours on the water-bath, the diluted reaction mixture was treated in the usual manner to give 1.6 g. of oil which crystallized from petroleum ether (28–38°) when cooled in a Dry Ice-acetone-bath, m.p. 43–44°.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.18; H, 8.00.

The oxime prepared with hydroxylamine hydrochloride in absolute alcohol and pyridine melted at 151–152° after repeated crystallization from petroleum ether (60–70°).

Anal. Calcd. for $C_{14}H_{17}ON$: N, 6.51. Found: N, 6.66.

7,8,9,10-Tetrahydrocyclohepta[de]naphthalene (IV).—A 200-mg. portion of pale yellow oil obtained by Clemmensen reduction of the ketone (XII) was combined with 50 mg. of 30% palladium-charcoal[21] and heated for 90 minutes at 300° under nitrogen. After dissolving in benzene and separation from the catalyst, the residual oil was combined with 250 mg. of picric acid. The red picrate which formed at once, crystallized from alcohol, 60 mg., m.p. 100–109.5°. A second crop of 140 mg., m.p. 102.5–109°, was also obtained. By washing a benzene solution of the second crop with dilute ammonia and concentration of the benzene followed by sublimation at 1 mm. onto a cold finger, 45 mg. of colorless crystals m.p. 52–56° was obtained. These did not depress the m.p. of the material made by the first method.

Similarly a picrate of the sublimed material melted at 113.5–115° and was unchanged on mixing with the picrate obtained previously.

SALT LAKE CITY, UTAH RECEIVED SEPTEMBER 11, 1950

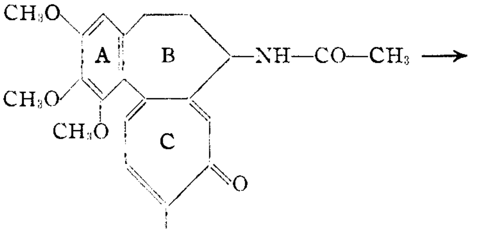
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

The Synthesis of DL-Colchinol Methyl Ether[1,2]

BY HENRY RAPOPORT, ARTHUR R. WILLIAMS AND MERLE E. CISNEY

7-Amino-1,2,3,9-tetramethoxydibenzo[a,c][1,3]cycloheptadiene, prepared by an unambiguous synthesis from 2,3,4,7-tetramethoxy-10-phenanthroic acid, has been shown to be identical with racemized colchinol methyl ether. Thus the position of the amino group and the seven-membered nature of ring **B** in colchinol methyl ether have been established.

The action of the alkaloid colchicine (I) as a mitotic poison[3] has stimulated interest in it and related compounds as possible chemotherapeutic agents against cancer.[4] However, in order to study better the relationship of structure to activity and to synthesize truly analogous compounds, it is necessary to have a detailed knowledge of the structure of the parent compound. The objective of the present work has been to provide some such knowledge through the synthesis of colchinol methyl ether (II), an important degradation product. Since the reactions involved in the degradation may reasonably be assumed to have proceeded without rearrangement in ring B, proving the structure of colchinol methyl ether should establish the structure of colchicine except for ring C.



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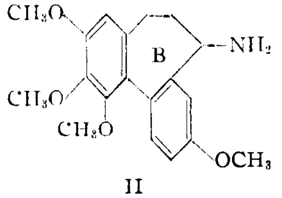

II

The structural features in question in colchinol methyl ether are the nature of ring B and the position of the amino group. Recent elegant degradative work[5] has presented strong evidence that ring B is seven-membered. Assignment of the position of the amino group is based on the isolation of 4-methoxyphthalimide from the chromic oxide oxidation of N-acetylcolchinol methyl ether.[6] We wish to report the confirmation of both these

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[1] This work was supported in part by a grant from the Cancer Research Committee, University of California.

[2] Presented in part before the Division of Organic Chemistry, American Chemical Society, Philadelphia Meeting, April 11, 1950. A preliminary report of this work appeared as a Communication to the Editor, THIS JOURNAL, **72**, 3324 (1950).

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