troleum ether and passed through an alumina column. Part of the tertiary alcohol formed during the reaction underwent partial dehydration and flowed out, while the rest which was adsorbed on the alumina was dehydrated there, and subsequently eluted by petroleum ether. Removal of petroleum ether gave a blue oil in 45% yield, the trinitrobenzene complex of which was recrystallized from alcohol, m.p. 85–86°.

Anal. Calcd. for $C_{18}H_{22}\cdot C_6H_3O_6N_3$: C, 63.85; H, 5.58; N, 9.31. Found: C, 63.72; H, 5.40; N, 9.08.

Reduction of VII.—An alcoholic solution of 0.3 g. of VII was shaken with 0.3 g. of 10% palladium–carbon in a hydrogen stream. After 6 hours 1 mole of hydrogen had been absorbed and the reduction was stopped. The solvent was removed by distillation *in vacuo*, and the residue was dissolved in petroleum ether and chromatographed through an alumina column. The azulene fraction was separated from the effluent and recrystallized as the trinitrobenzene complex. The azulenes in the order in which they were obtained were: (a) unreacted 3-isopropenyl-S-guaiazulene (VII), TNB complex, m.p. 85–86°. (b) 2-Isopropenyl-S-guaiazulene (VIII), TNB complex, m.p. 74–75°. *Anal.* Calcd. for $C_{18}H_{22}\cdot C_6H_3O_6N_3$: C, 63.84; H, 5.58; N, 9.31. Found: C, 63.65; H, 5.32; N, 9.12. (c) I mixed with 2-isopropyl-S-guaiazulene (IX), TNB complex, m.p. 150–153°. *Anal.* Calcd. for $C_{18}H_{24}\cdot C_6H_3O_6N_3$: C, 63.56; H, 6.01; N, 9.27. Found: C, 62.94; H, 5.60; N, 9.02.

I and IX were separated by chromatography and repeated fractional crystallization. The yields of the TNB complexes of VII, VIII and IX were a few mg. each; that of the TNB complex of I was about 30 mg., m.p. 148–149°.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

Seven-membered Ring Compounds. VIII.[1] The Cyclization of Benzosuberane-5,6-diacetic Acid

BY W. J. HORTON, H. W. JOHNSON[2] AND J. L. ZOLLINGER[2]

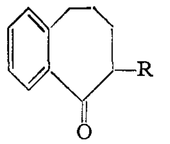
RECEIVED APRIL 1, 1954

Benzosuberone-6-acetic acid has been prepared by two methods, one of which required but three steps from allylbenzene. The cyclization of a mixture of *cis*- and *trans*-benzosuberane-5,6-diacetic acids gave isomeric ketones which were separated by fractional crystallization.

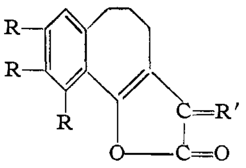
An approach to colchicine[3] involving final closure of the C ring became unpromising when it was found that reactions involving the keto group of methyl 2,3,4-trimethoxybenzosuberone-6-acetate were unsuccessful. This approach has been further explored in a model compound as an introduction to the synthesis of analogs of colchicine which lack a methoxyl group in the 4-position.

The final compounds obtained herein, *cis*- and *trans*-2-keto-1,2,3,3a,4,5,6,10b-octahydrobenz[e]azulene (XI) are related to the 6-keto compound[4] and to 3-keto-1,2,3,4,5,6-hexahydrobenz[e]azulene.[5] The general plan which we have used to obtain a third ring is similar to one which appeared during the progress of this work[6] and which did not report ring closure.

In a previous paper[7] the pyrolysis of methyl benzosuberone-6-glyoxylate (I) was successful only if methanol was repeatedly added to reopen the ring of the enol lactone II which presumably formed during the pyrolysis and was known to decompose when heated. This pyrolysis has now been conducted more easily and in excellent yield in benzyl alcohol at 185°. In support of the above proposed mechanism, the lactone II or the methyl glyoxylate I was used and the benzyl ester III was produced in both cases.



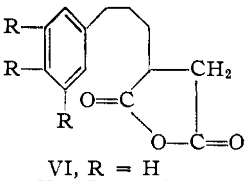
I, R = $COCO_2CH_3$
III, R = $CO_2CH_2C_6H_5$
IV, R = CO_2CH_3
V, R = CH_2CO_2H



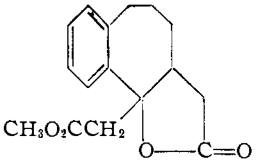
II, R = H; R′ = O
VIII, R = OCH_3; R′ = H_2

The alkylation of either III or IV with methyl bromoacetate followed by hydrolysis gave benzosuberone-6-acetic acid (V).

A second preparation of V arose from the investigation which demonstrated that γ-3,4,5-trimethoxyphenylpropylsuccinic anhydride (VII) cyclized in polyphosphoric acid to VIII.[3] By hydrogenation of γ-phenylallylsuccinic anhydride[8] the required material VI was obtained and although it failed to react in polyphosphoric acid it cyclized when aluminum chloride was used producing V in 75% yield.



VI, R = H
VII, R = OCH_3



IX

The methyl ester of V in the Reformatsky reaction with methyl bromoacetate gave the lactone IX.[9] Hydrogenolysis of this lactone and saponification gave benzosuberane-5,6-diacetic acid (X).

It seems likely that the geometrical isomers of IX were obtained in the Reformatsky reaction and that the form present in smaller amount was

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[1] Paper VII, THIS JOURNAL, **76**, 1909 (1954).

[2] From the Doctoral Research of H. W. Johnson and J. L. Zollinger.

[3] P. D. Gardner and W. J. Horton, THIS JOURNAL, **75**, 4976 (1953).

[4] J. R. Nunn and W. S. Rapson, *J. Chem. Soc.*, 1051 (1949).

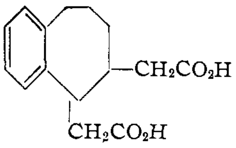
[5] J. W. Cook, R. Philip and A. R. Somerville, *ibid.*, 164 (1948).

[6] A. G. Anderson, Jr., and H. F. Greef, THIS JOURNAL, **74**, 5203 (1952).

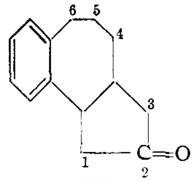
[7] W. J. Horton, C. E. Hummel and H. W. Johnson, *ibid.*, **75**, 944 (1953).

[8] C. S. Rondesvedt, Jr., *Org. Syntheses*, **31**, 85 (1951).

[9] Lactone formation in the Reformatsky reaction has been reported. W. E. Bachmann and G. D. Johnson, THIS JOURNAL, **71**, 3463 (1949).



X



XI

unknowingly discarded in the purification procedure since hydrogenation of the crude lactone gave a diacetic acid, m.p. 152.5–153.5°, and material, m.p. 137–144°, insufficient for further work. Cyclization of the purified diacetic acid (m.p. 148–152°) using acetic anhydride[10] gave 2-keto-1,2,3,3a,4,5,6,10b-octahydrobenz[e]azulene (XI), m.p. 95–96°, designated here as α. If the crude mixture of the supposed *cis–trans*-diacetic acids (X) was cyclized, the α-isomer was separable by means of light petroleum ether. The second form (β), m.p. 68–69.5°, was obtained from the petroleum ether filtrates.

A Dieckmann cyclization of the dimethyl esters of X gave a small amount of the α-ketone XI.

The assistance of a Frederick Gardner Cottrell grant and a University Research Fund grant are gratefully acknowledged.

Experimental[11]

Benzyl Benzosuberone-6-carboxylate (III). (a).—Methyl benzosuberone-6-glyoxylate (I) (48.5 g., 0.197 mole), m.p. 51–54°,[7] and 70 cc. (0.68 mole) of benzyl alcohol were heated at 180–200° for 45 minutes. The excess benzyl alcohol was removed by distillation at 18 mm. and the product was collected as a pale yellow oil at 175–180° (0.25 mm.); 55.0 g. (0.187 mole, 95%). It gave an immediate deep violet color with alcoholic ferric chloride.

(b).—When 56.9 g. (0.255 mole) of the enol lactone of benzosuberone-6-glyoxylic acid (II) was dissolved in 100 cc. of benzyl alcohol by warming for 20 minutes at 100–110° and then held at 185° for 1 hour gas evolution had ceased. After distillation of the benzyl alcohol as above the product boiled at 183–190.5° (0.34–0.38 mm.); 69.1 g. (0.235 mole, 88.5%). The nearly colorless material for analysis boiled at 173–175° (0.23 mm.).

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.70; H, 6.13.

Benzosuberone-6-acetic Acid (V). (a).—Methyl benzosuberone-6-carboxylate (IV) (57.0 g., 0.26 mole) in 50 cc. of anhydrous benzene was added during 1.5 hours with stirring to 6.27 g. (0.26 mole) of sodium hydride suspended in 150 cc. of boiling benzene in a nitrogen atmosphere. After an additional hour of refluxing 26.9 cc. (0.295 mole) of methyl bromoacetate was added with continued refluxing over a one-hour period. The mixture was then refluxed and stirred for 24 hours. The cooled solution was combined with 600 cc. of 5% sulfuric acid and the aqueous layer extracted thrice with ether. The dried benzene–ether portion on distillation of the solvents gave a pale yellow oil which was negative to alcoholic ferric chloride. Distillation caused some decomposition; a portion, b.p. 157° (0.37 mm.), was analyzed.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.95; H, 6.19.

The yellow oil above was heated with 150 cc. of 45% potassium hydroxide and 500 cc. of methanol for 2 hours. After addition of water and distillation of the methanol at 20 mm. the solution was extracted with ether. From the aqueous layer on acidification a light brown oil V separated and partially solidified. Washing a solution of this material in 5% sodium bicarbonate with ether gave a solid (40.9 g., 80.5%) on acidification, pure enough for use in the next step. Recrystallization from ethyl acetate gave material, m.p. 131–131.5°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.27; H, 6.46.

(b).—To 3.33 g. (0.085 g. atom) of powdered potassium in 50 cc. of dry toluene under nitrogen was added 25.0 g. (0.085 mole) of III in 50 cc. of dry toluene. When the potassium had reacted, 9.4 cc. (0.10 mole) of methyl bromoacetate was added to the ice-cold solution. An additional 50 cc. of toluene was added and the mixture was refluxed for 3 hours with stirring. The cooled mixture was then combined with 100 cc. of 2 *N* hydrochloric acid and the aqueous layer was extracted with benzene. The combined benzene and toluene solution was distilled at 18 mm. and the residue was treated with 40 cc. of 45% potassium hydroxide and 150 cc. of methanol with refluxing for 2 hours. After addition of 150 cc. of water and removal of the methanol by distillation, the cooled solution was extracted with ether and the ether extract was washed with water and with 5% sodium hydroxide. The alkaline solution on acidification gave 14.2 g. of slightly oily crystals, m.p. 100–125° after standing overnight in the refrigerator. Recrystallization from aqueous methanol gave 8.6 g. (0.039 mole, 46%) of colorless crystals m.p. 128–132° and undepressed when mixed with V above.

(c).—γ-Phenylallylsuccinic anhydride[8] (21.6 g., 0.10 mole) was dissolved in 100 cc. of purified dioxane and reduced with 1.0 g. of Raney nickel at 75° and 900 lb. hydrogen pressure for 1 hour. The bomb contents were transferred with benzene and the filtered solution was concentrated to 40 cc. Addition of petroleum ether (60–100°) to the hot solution caused an oil to separate on cooling which crystallized when rubbed. The solid, washed with cold benzene–petroleum ether (1:1) on the filter, weighed 18.0 g. (0.0826 mole) m.p. 68–70°; reported[12] for γ-phenylpropylsuccinic anhydride (VI), m.p. 64°. An additional 1.5 g. from the mother liquor brought the yield to 89.5%.

A solution of 14.2 g. (0.065 mole) of γ-phenylpropylsuccinic anhydride in 65 cc. of nitrobenzene was added slowly with stirring to a solution of 17.3 g. (0.13 mole) of anhydrous aluminum chloride in 65 cc. of nitrobenzene held at 0°. The yellow-orange solution was allowed to come to room temperature and stand for 90 hours. It was then stirred for 3.5 hours. The usual procedure with steam distillation of the nitrobenzene gave a non-volatile brown oil which crystallized on cooling. The solid was refluxed with 100 cc. of 15% sodium hydroxide for 10 minutes and the product obtained on acidification was dissolved in 1.8 l. of boiling water, filtered hot to remove insoluble oils and allowed to stand for 2 days. The colorless crystals obtained weighed 9.5 g. (0.044 mole), m.p. 128–132°. An additional 1.2 g. recovered from the filtrate brought the yield to 75%. The material melted undepressed when mixed with V above.

The cyclization with polyphosphoric acid[13] at 140° for 2 hours gave only starting compound.

5-Hydroxy-5-carbomethoxymethylbenzosuberane-6-acetic Acid Lactone (IX).—Benzosuberone-6-acetic acid (4.35 g., 0.02 mole) was esterified with excess ethereal diazomethane and the excess was removed by the addition of glacial acetic acid. The filtered solution was heated on the water-bath at 18 mm. to remove the solvents and a solution of the residue in reagent benzene was thrice washed with 10% sodium bicarbonate and then twice with water. Overnight drying with sodium sulfate and filtration gave material suitable for the following reaction. Distillation of the methyl ester was less satisfactory. Material for analysis boiled at 129° (0.24 mm.).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.95. Found: C, 72.79; H, 7.14.

The dried benzene solution was refluxed for 7 hours with 8.0 g. of cleaned 20-mesh zinc, several crystals of iodine and 3.3 cc. of methyl bromoacetate. Six additional 8.0-g. portions of zinc and a crystal of iodine and 5.8 cc. of the bromoester (two portions) were added during refluxing. The mixture was then allowed to stand overnight.

The product was isolated by the usual procedure[14] and the product crystallized at once. After standing overnight,

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[10] F. C. Uhle, THIS JOURNAL, **71**, 761 (1949).

[11] Melting points are uncorrected.

[12] Mme. Ramart-Lucas and M. Z. Papadakis, *Ann. chim. (Paris)*, **18**, 32 (1932).

[13] R. C. Gilmore and W. J. Horton, THIS JOURNAL, **73**, 1411 (1951).

[14] R. Adams, ed., "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 18.

5.0 g. (0.018 mole, 90%), m.p. 97–112°, was obtained. After seven crystallizations from dilute methanol it melted at 118–119°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.09; H, 6.56.

The lactone IX gave a yellow-green color in concentrated sulfuric acid.

Enol Lactone of Benzosuberone-6-acetic Acid.—In a distillation of 2.0 g. of the methyl ester of V at low pressure some decomposition was indicated by a rise in pressure and unchanged ester distilled at *ca.* 150° (0.7 mm.). The residue in the flask distilled at 150–210° (0.6–1.0 mm.). This distillate with 2 cc. of ethyl acetate at −20° overnight gave 0.350 g. (20%) of orange needles. From ethyl acetate nearly colorless needles, m.p. 123.7–124.2°, were obtained.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.37; H, 6.08.

The compound was insoluble in cold but soluble in hot 5% sodium hydroxide. On acidification, the material obtained dissolved at once in cold 5% alkali.

Benzosuber-5-ene-5,6-diacetic Acid.—Saponification of 5.2 g. (0.019 mole) of the lactone IX, m.p. 110–116°, with 50 cc. of methanol and 15 cc. of 45% potassium hydroxide with refluxing for 2.5 hours gave an oil after distillation of the alcohol and acidification. An ether-washed sodium bicarbonate solution similarly did not produce crystals on acidification but the oil solidified slowly in 20 cc. of boiling benzene. The product weighed 2.26 g. (0.0087 mole, 46%) m.p. 159–169°. Purification from aqueous ethanol and four times from water gave colorless crystals, m.p. 180–181.5°. The compound decolorized dilute potassium permanganate but gave no reaction with 5% bromine–carbon tetrachloride.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20; neut. equiv., 130.1. Found: C, 69.39; H, 6.30; neut. equiv., 130.

Benzosuberane-5,6-diacetic Acid (X).—In a hydrogenation bomb 3.27 g. (0.0119 mole) of the above crude lactone IX with 50 cc. of methanol, 2 cc. of dimethylaniline and 0.5 g. of Raney nickel was heated at 150° under 2500 lb. hydrogen pressure for 1 hour. The filtered solution was combined with 10 cc. of 10% potassium hydroxide and refluxed for 2 hours. After addition of water and distillation of the methanol the acidified solution was extracted three times with benzene. The benzene solution was washed with water and saturated salt solution and the benzene was removed by distillation. The light amber oil in 10% sodium bicarbonate (charcoal) gave material on acidification which crystallized after 2 days at room temperature; 2.23 g. (0.00852 mole, 71.5%), m.p. 115–130°. Treatment of 1.74 g. of this material with 37 g. of 2% sodium amalgam in 25 cc. of 2 *N* sodium hydroxide gave crystals on acidification, m.p. 130–140°. Extraction of this material with 30 cc. of boiling benzene with filtration while hot gave insoluble solid which was digested with 10 cc. of boiling water and then allowed to stand overnight. The colorless crystals weighed 0.5 g., m.p. 148–152°. Further crystallization from dilute methanol gave a m.p. 152.5–153.5°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.76; H, 6.87.

From the above hot benzene extract, solid was obtained which was crystallized twice from dilute methanol, digested with 5 cc. of hot benzene and the benzene solution after 2 hours standing decanted from crystals, m.p. 146–152°. Concentration of the decantate, addition of petroleum ether (30–60°) and standing for several days gave colorless crystals, m.p. 137–144°, in insufficient amount for further investigation.

α-2-Keto-1,2,3,3a,4,5,6,10b-octahydrobenz[e]azulene (XI).—After refluxing 0.16 g. (0.00061 mole) of the diacetic acid X, m.p. 148–152°, in 17 cc. of acetic anhydride containing 20 mg. of potassium cyanide for 21 hours[10] on a sandbath the solvent was removed by distillation *in vacuo*. The residue was refluxed with 7 cc. of ethanol and 7 cc. of 10% potassium hydroxide for 1.5 hours. Water was added (10 cc.) and the alcohol was distilled at 18 mm. Ether extraction gave 0.10 g. (0.0005 mole, 82%) of light brown solid. In a micro-sublimer at 20 mm. and 120–145° (bath temperature) 70 mg. (57%) of colorless leaflets, m.p. 92–93°, was obtained. These gave a positive test with 2,4-dinitrophenylhydrazine and on further purification from dilute methanol melted at 95–96°.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.27; H, 7.70.

The colorless **semicarbazone** was insoluble in hot ethanol, ethyl acetate or benzene but crystallized from hot dimethylformamide, m.p. 220.5–221.5° dec. The compound was pale yellow within 4 minutes on exposure to northern daylight but the melting point was unchanged even after 4 hours exposure. It was not changed by incandescent light.

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44. Found: C, 70.01; H, 7.72.

β-2-Keto-1,2,3,3a,4,5,6,10b-octahydrobenz[e]azulene (XI).—Treatment of 2.8 g. of a liquid mixture of the isomeric diacetic acids obtained by catalytic reduction, with acetic anhydride as before, gave 0.8 g. of non-saponifiable brown oil. Micro-sublimation gave three fractions: 0.118 g. at 18 mm. and 135° (all bath temperatures), m.p. 70–85°; 0.284 g. of 13 mm. and 135–160°, m.p. 73–86°; and 50 mg. at 0.2 mm. and 160°, m.p. 65–86°. The first two fractions, combined and recrystallized from dilute methanol, gave 0.30 g. of colorless crystals, m.p. 68–78°. Trituration with several cc. of petroleum ether (32–52°) gave 0.144 g., m.p. 91–95°, as the insoluble fraction and the filtrate and washings at −20° gave 58 mg., m.p. 68–83°. From this filtrate colorless solid, m.p. 63–66°, was obtained. Additional trituration of the ketone mixture gave the low melting ketone. This combined product after crystallization from petroleum ether (32–52°) and sublimation gave fine crystals, m.p. 68–69.5°.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.33; H, 8.23.

On admixture with the α-isomer it melted at 67–85°. A substance, m.p. 207–208°, believed to be the semicarbazone was obtained in insufficient amount for analysis.

Cyclization of the Dimethyl Ester of Benzosuberane-5,6-diacetic Acid.—The dimethyl ester of the diacetic acid prepared with diazomethane on a mixture of *cis* and *trans* acids was distilled and 0.30 g. (0.001 mole), b.p. 135–145° (bath temperature) (0.1 mm.), in 20 cc. of anhydrous benzene was added to sodium methoxide (from 50 mg., 0.002 g. atom of sodium). The mixture was refluxed for 24 hours. The solution was cooled in an ice-bath, ice-water was added and the layers were separated. The benzene layer was washed twice with cold 2% sodium hydroxide and the aqueous layers were extracted with ether. From the aqueous part 40 mg. (15%) of rust colored solid, m.p. 74–84°, giving a light brown color with ferric chloride was obtained but not investigated.

From the organic layers 0.110 g. (0.00043 mole, 43%) of oil was obtained. This gave a violet color with alcoholic ferric chloride but was insoluble in cold 10% sodium hydroxide. The oil was refluxed for 2 hours with 10 cc. of acetic acid, 5 cc. of concentrated hydrochloric acid and 1 cc. of water. By extraction with benzene an oil negative to ferric chloride was obtained. This on sublimation at 0.15 mm. and 120° (bath temperature) gave 30 mg. (0.00012 mole, 12%) of colorless crystals, m.p. 83–91°, and after crystallization from dilute methanol, m.p. 94.5–95.5°.

SALT LAKE CITY 1, UTAH