Spirans. XIII. 3,9-Disubstituted Spiro[5.5]undecane Compounds[1]

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The compound, 3,9-diaminospiro[5.5]undecane has been prepared by two separate synthetic routes. One route, a 12-step synthesis, employed methanetetraacetic acid as the starting material. The alternate method, also a 12-step synthesis, started with 4-carboxycyclohexanone. The final compound obtained by either route, 3,9-diaminospiro[5.5]undecane (X) was identical.

In a previous paper[2] we described the synthesis of various monoaminosubstituted spiranes and their pharmacological properties. It was of interest to extend our work to include spirans symmetrically substituted with two active, functional groups. We now wish to report our investigations that have resulted in the preparation of these types of compounds (1), where R is an amino or carboxyl group.

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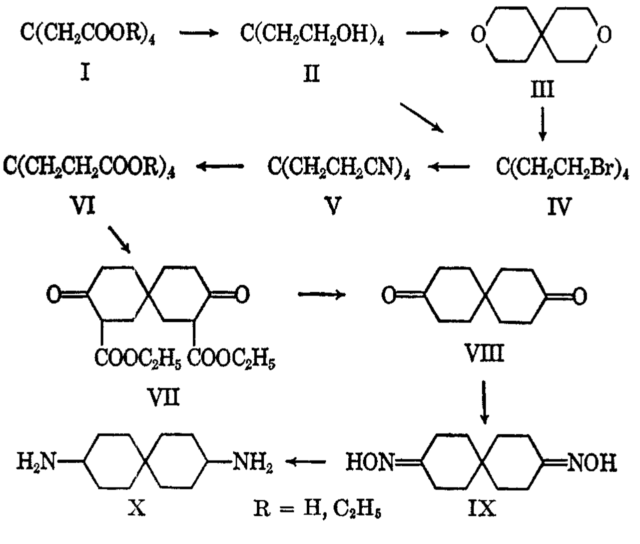
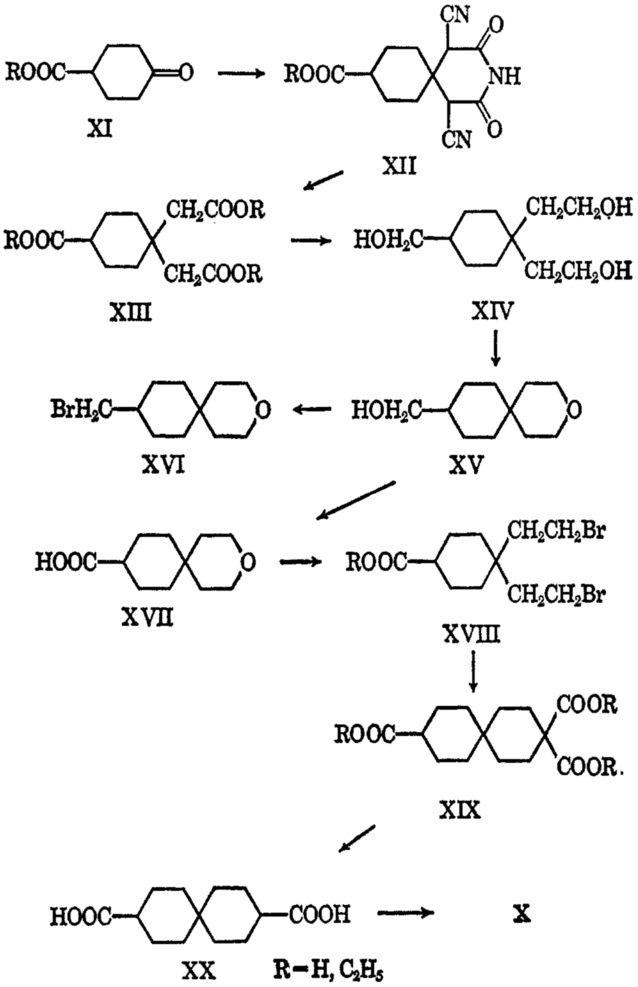
The only examples of this type of compound have appeared in a recent publication by Farges and Dreiding[3] which described the preparation of 2 (compound VIII, Scheme I). The synthesis employed by these workers utilized a Birch reduction of spiro[5.5]undeca-1,8-dien-3-one to form spiro[5.5]undeca-8-en-3-ol followed by acetylation and epoxidation. Ring opening of the oxirane and oxidation gave the dione (2). Although we have followed an entirely different route of synthesis, the diketone obtained by our laboratory agrees in properties to the compound reported by these authors.

SCHEME I



SCHEME II



Our approach to the synthesis of 3,9-diaminospiro[5.5]undecane consisted of two distinct synthetic pathways which are shown in Schemes I and II. In the sequence outlined in Scheme I, the starting material was methanetetraacetic acid (I)[4] which was esterified by the method of Ingold. This ester, which had been previously prepared,[5] was reduced to the tetraol[6] II with lithium aluminum hydride. Preparation of the tetrabromide IV was extensively studied employing a mixture of 48% hydrobromic acid and sulfuric acid. While the tetrabromide could be prepared by the reaction of the tetraol II with a mixture of 48% hydrobromic acid and sulfuric acid, the product was discolored and difficult to purify. A much improved procedure involved heating the crude tetraol II with hydrobromic acid or sulfuric acid at 100° to give a quantitative yield[7] of the spiro diether III. This was cleaved with a mixture of hydrobromic and sulfuric acids to give the tetrabromide IV, analytically pure

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[1] Part XII: C. H. Grogan, R. Kelly, and L. M. Rice, *J. Med. Chem.*, **9**, 654 (1966).

[2] L. M. Rice, E. C. Dobbs, and C. H. Grogan, *ibid.*, **8**, 825 (1965).

[3] G. Farges and A. S. Dreiding, *Helv. Chim. Acta*, **49**, 552 (1966).

[4] C. K. Ingold and L. C. Nicholls, *J. Chem. Soc.*, 1638 (1922).

[5] H. J. Backer, *Rec. Trav. Chim.*, **54**, 62 (1935).

[6] L. M. Rice and C. H. Grogan, U. S. Patent 3,154,590 (1964).

[7] M. E. Freed and L. M. Rice, *J. Heterocyclic Chem.*, **2**, 214 (1965).

and in excellent yield. Conversion of the tetrabromide to the tetranitrile V with potassium cyanide proceeded smoothly in acetonitrile. Methanetetrapropionic acid (VI) was obtained from the hydrolysis of V with concentrated hydrochloric acid. This acid was esterified by the method of Ingold[4] and the resulting ester was treated with potassium *t*-butoxide in benzene solution to yield the bisketo acid VII. In the latter Dieckmann cyclization of the tetraester VI there was always a solid residue remaining which was not investigated. No attempt was made to determine the position of the two carboxyl groups in the bis keto acid (*i.e.*, in the 2,8 or 2,10 position or a mixture of the two) since hydrolysis and decarboxylation produced the same dione VIII.[3] This diketone corresponded in properties to that reported by Farges and Drieding. The diketone was converted into the dioxime IX by means of alcoholic hydroxylamine and pyridine. Tetrahydrofuran proved to be an excellent solvent for the reduction of the dioxime to the diamine X by means of lithium aluminum hydride. This diamine was isolated and characterized as the dihydrochloride and picrate salts and by conversion to the diphenylurea derivative.

In the alternate synthetic route to X, which is outlined in Scheme II, 4-carboxycyclohexanone (XI) was utilized as the starting material. This keto acid was best prepared by reduction of ethyl *p*-hydroxybenzoate using 5% rhodium on alumina.[8] The keto acid (1 mole) was treated at 0–5° with an excess of ammonia in ethanol and 2 moles of ethyl cyanoacetate to yield the ammonium salt of the Guareschi imide XII.[9] The yield obtained from the free keto acid exceeded that obtained from the ethyl ester of the keto acid and was probably due to the increased solubility of the ester in alcohol. It was expected that the carboethoxy group would be converted into an amide but this was not the case. When the ammonium salt of either Guareschi imide XII (R = H or C_2H_5) was dissolved in a minimum amount of water and acidified with hydrochloric acid, the free imide was readily obtained. Hydrolysis of these dicyanoimides employing 65% sulfuric acid gave the triacid XIII (R = H) in excellent yield with almost no discoloration of the reaction mixture. This acid was esterified employing the method of Ingold[4] to yield XIII (R = C_2H_5). Reduction of the triester by means of lithium aluminum hydride, as outlined above for II, produced the triol XIV. Dehydration of this triol to give the spiropyran XV, without affecting the hydroxymethyl group, proved to be unexpectedly difficult. For example, when the triol was heated with various concentrations of sulfuric acid, extensive decomposition occurred; when the triol was treated with thionyl chloride, zinc chloride, or phosphorus pentoxide, no satisfactory yield of XV was isolated. Although the reaction of 48% hydrobromic acid at 100° gave the desired compound, there was always present about 60% of the bromide. This mixture of alcohol and bromide was converted by phosphorus tribromide into the pure bromide with the expectation that the bromide could be converted into the alcohol. However, with silver oxide, silver acetate, or anhydrous potassium acetate, followed by reduction, this was not feasible.

The dehydration of 1,1-bis(β-hydroxyethyl)cyclohexane as a model compound was studied. It was found that concentrated hydrochloric acid for 3 hr on a steam bath produced an almost quantitative yield of 3-oxaspiro[5.5]undecane.[7] When this procedure was employed on the triol XIV, an excellent yield of the spiropyran XV was obtained. There was also produced a very small amount of halogenation of the hydroxymethyl group. The latter could be easily separated by distillation. Oxidation of the hydroxymethyl group, employing potassium permanganate, was carried out to produce the acid XVII in excellent yield. This acid had unusual solubility characteristics, being soluble in either water or ligroin. Successful cleavage of the spiropyran XVII to produce the dibromo acid XVIII was smoothly carried out by means of a hydrobromic and sulfuric acids mixture. Esterification of the dibromo acid with benzene, alcohol, and sulfuric acid in the usual way produced the dibromo ester XVIII (R = C_2H_5), which was cyclized by reaction with ethyl malonate to yield the spiro triester XIX. After hydrolysis with alcoholic potassium hydroxide and thermal decarboxylation, the spiro diacid XX was obtained. This diacid was transformed into the diamine X by means of the Schmidt reaction. The free base was characterized by boiling point and by conversion into its dihydrochloride and picrate salts and its di(phenylurea) derivative. Mixture melting points of the hydrochlorides from both methods of synthesis did not produce any melt at 370°. The picrates and the di(phenylurea) derivatives which were prepared by different routes on mixing showed no depression of the melting points. The infrared spectra of the diamine dihydrochlorides prepared as in Schemes I or II when taken as a potassium bromide disk were identical.

No attempt has been made to separate the *d* and *l* isomers of the diamine X or of the diacid XX but this separation is planned in the near future.

Experimental Section

All melting points were obtained with a Thomas–Hoover capillary-type apparatus and are corrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. All compounds corresponded in structure to their infrared spectra.

Tetraethyl Methanetetraacetate (I).—In 1-l. flask were placed 54 g of methanetetraacetic acid and 500 ml of absolute alcohol. Concentrated sulfuric acid (90 ml) was slowly added with shaking. The reaction mixture was kept at its boiling point while alcohol vapor was passed in from another flask until 2 l. of distillate had been collected. After cooling, the reaction mixture was poured into 2 l. of water and the ester was extracted with three portions of ether. The ether extract was washed with water, potassium bicarbonate solution, and saturated salt solution and dried over anhydrous sodium sulfate. Removal of the ether and distillation gave 70 g of product (90%), bp 137–143° at 0.05 mm (lit.[5] bp 211° at 20 mm).

Anal. Calcd for $C_{17}H_{28}O_8$: C, 56.66; H, 7.83. Found: C, 56.48; H, 8.01.

Tetrakis(β-hydroxyethyl)methane (II).—To a solution of 30 g of lithium aluminum hydride dissolved in 1200 ml of anhydrous ether was slowly added a solution of 25 g of tetraethyl methanetetraacetate (I) dissolved in 100 ml of anhydrous ether. After stirring and refluxing for 2 hr, the reaction mixture was cooled to room temperature and decomposed by the slow, drop-wise addition of water until the ether ceased to reflux. The mixture was stirred for an additional 2 hr and filtered; the ether extract was dried over sodium sulfate. Vacuum evaporation of the ether left only a small amount of the desired polyol as a residue. The inorganic residue was continuously extracted with anhydrous

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(8) R. A. Finnegan and P. L. Bachman, *J. Org. Chem.*, **30**, 4148 (1965).

(9) I. Guareschi, *Atti Accad. Sci. Torino*, **36**, 443 (1900/1901).

ethanol. On removal of the solvent, *in vacuo*, the residue solidified. It was washed with alcohol–ether, anhydrous ether, and dried. The product (11.2 g, 85%) was dissolved in anhydrous methanol, ether was slowly added until turbidity was observed, and the mixture was refrigerated. The melting point (103°) did not change on further recrystallization.

Anal. Calcd for $C_9H_{20}O_4$: C, 56.22; H, 10.49; O, 33.29. Found: C, 56.46; H, 10.57; O, 33.56.

3,9-Dioxaspiro[5.5]undecane (III).—To 14 g of tetrakis(β-hydroxyethyl)methane (II) (the crude product from the reduction above was also used after evaporation of the ethanol) was added 50 ml of 80% sulfuric acid (or 75 ml of 48% hydrobromic acid) and the mixture heated at 100° for 3 hr. After cooling, the reaction mixture was poured into 100 ml of water and neutralized with sodium carbonate. The oil which separated was extracted three times with ether and the extract was dried over sodium sulfate. Upon evaporation of the ether, the residue was distilled, bp 88–89° at 4.5 mm, weight 11 g (95%).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.46; H, 10.45.

Tetrakis(β-bromoethyl)methane (IV). A.—To a solution of 10 g of tetrakis(β-hydroxyethyl)methane (II) in 80 ml of 48% hydrobromic acid was slowly added 40 ml of concentrated sulfuric acid with cooling and stirring. The mixture was heated on a steam bath for 8 hr and allowed to cool. The reaction mixture was poured into 400 ml of ice water and allowed to stand for 1 hr. After filtering, the solid was washed and recrystallized from methanol, mp 167–173°. Four additional recrystallizations from ethyl acetate gave long, light brown needles, mp 183–184°.

Anal. Calcd for $C_9H_{16}Br_4$: C, 24.35; H, 3.63; Br, 72.02. Found: C, 24.54; H, 3.64; Br, 72.24.

The methanol and ethyl acetate filtrates above were concentrated *in vacuo*, and the crude residue was retreated as described above with hydrobromic acid and sulfuric acid, total yield 14 g (60%).

B.—The inorganic residue obtained after decomposition of the reaction mixture from reduction of 150 g of tetraethyl methanetetraacetate (I) as described above was extracted three times with 1 l. of boiling methanol. The methanol extracts were freed of all solvent and the dried mass of polyol (together with some inorganic matter) was treated with 400 ml of 48% hydrobromic acid and 200 ml of sulfuric acid as described in A above. After reworking the low-melting fractions and mother liquids, there was obtained 125 g of IV, mp 183–184° (67.5%).

C.—To a solution of 34 g of 3,9-dioxaspiro[5.5]undecane (III) in 200 ml of 48% hydrobromic acid was added, with stirring and cooling, 100 ml of concentrated sulfuric acid. The mixture was heated on a steam bath overnight and then diluted with an equal volume of water. After cooling, the white crystalline precipitate was filtered and recrystallized from ethyl acetate. The colorless needles melted at 183–184° and weighed 76.8 g (80%).

Tetrakis(β-cyanoethyl)methane (V).—In a three-neck, 2-l. flask equipped with a stirrer, reflux condenser, and a dropping funnel was placed 50 g of tetrakis(β-bromoethyl)methane (IV) and 1400 ml of acetonitrile. The solution was brought to reflux and the clear solution was stirred while a solution of 60 g of potassium cyanide in 100 ml of water was slowly added. The reaction mixture was refluxed overnight with stirring and then allowed to cool. The clear acetonitrile solution was decanted from the water layer and salts, evaporated to dryness *in vacuo*, slurried with water, and filtered. After drying, the solid was recrystallized by dissolving in acetonitrile, filtering, and diluting the filtrate with absolute alcohol until crystallization began. The solid, mp 178–188°, was recrystallized from acetonitrile–alcohol and the product, mp 179–180°, weighed 23 g (89%). The product was insoluble in ether and alcohol but somewhat soluble in hot water.

Anal. Calcd for $C_{13}H_{16}N_4$: C, 68.39; H, 7.07; N, 24.54. Found: C, 68.62; H, 7.33; N, 24.14.

Tetrakis(β-carboxyethyl)methane (VI).—To 53 g of V was added 600 ml of concentrated hydrochloric acid and the mixture was refluxed overnight. The tetranitrile dissolved within 2 hr and crystals began to form after that period. After cooling, the mixture was diluted with two volumes of water and filtered. The crystals (57 g, 80%) melted at 261–264°. One recrystallization from water produced a melting point of 262–263° (constant).

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.63. Found: C, 51.47; H, 6.76.

Tetrakis(β-carboethoxyethyl)methane (VI, R = C_2H_5).—The esterification of VI (R = H) was carried out as described for tetraethyl methanetetraacetate (I) employing 20 g of tetrakis(β-carboxyethyl)methane (VI), 350 ml of absolute alcohol, and 50 ml of sulfuric acid. After the usual work-up, the product was distilled, bp 187–192° at 0.1 mm (23.5 g, 87%).

Anal. Calcd for $C_{21}H_{36}O_8$: C, 60.54; H, 8.72. Found: C, 60.77; H, 8.56.

Spiro[5.5]undecane-3,9-dione-2,8- (or 10-) dicarboethoxylate (VII).—To a refluxing solution of VI, 22 g in 200 ml of benzene, was added with stirring a solution of 25 g of potassium *t*-butoxide in 500 ml of benzene. After refluxing for an additional 2 hr, the benzene solution was cooled and acidified by the addition of 10% hydrochloric acid. The benzene solution was washed with water and sodium bicarbonate and saturated salt solutions and dried over sodium sulfate. The benzene was removed *in vacuo*, and the residue was distilled, bp 174–184° at 0.6 mm with slight evolution of gas. A product (11 g, 70%) was obtained, which gave a positive ferric chloride test.

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 63.12; H, 7.55.

There was a considerable amount of nondistillable solid residue which was not investigated.

Spiro[5.5]undecane-3,9-dione (VIII).—The keto ester VII (11 g) was hydrolyzed with 100 ml of 10% sulfuric acid for 4 hr and poured into 200 ml of water. The solution was extracted three times with ether and the extract was washed successively with water, a 10% sodium bicarbonate solution until neutral to litmus, and a saturated salt solution and dried over sodium sulfate. After removal of the ether by distillation, the residue (3 g) was distilled through a short-path tube and recrystallized from ethyl acetate, mp 110–112°. An additional crystallization from ethyl acetate gave a constant-melting material (2 g, 32%), mp 112–113° (lit.[3] mp 110–111°).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.31; H, 8.95. Found: C, 73.45; H, 9.17.

Spiro[5.5]undecane-3,9-diketoxime (IX).—To a solution of 2 g of the dione VIII dissolved in a mixture of 20 ml of alcohol and 20 ml of pyridine was added 4 g of hydroxylamine hydrochloride, and the mixture was heated on a steam bath for 1 hr. All of the solvents were removed *in vacuo*, and the residue was slurried with water and filtered, mp 260–261°. One recrystallization from tetrahydrofuran gave material with a constant melting point at 262–263°.

Anal. Calcd for $C_{11}N_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.88; H, 8.70; N, 13.38.

3,9-Diaminospiro[5.5]undecane (X).—The diketoxime (2 g) IX was dissolved in tetrahydrofuran and slowly added to a solution of 2 g of lithium aluminum hydride dissolved in 1 l. of anhydrous ether. After stirring for 3 hr, the mixture was decomposed with 8 ml of water and filtered. The ethereal solution was dried and the solvents were removed. Conversion of the residue to the dihydrochloride with alcoholic hydrogen chloride and ether gave the product, mp >360°. The product could easily be recrystallized from ethanol–methanol mixture, mp >370°.

Anal. Calcd for $C_{11}H_{24}Cl_2N_2$: C, 51.76; H, 9.48; Cl, 27.78; N, 10.98. Found: C, 51.78; H, 9.75; Cl, 27.62; N, 10.85.

1,5-Dicyano-9-carboxy-3-azaspiro[5.5]undecane-2,4-dione (XII) (the Guareschi Imide, R = H).—A mixture of 4-carboxycyclohexanone (XI)[8] (71 g, 0.5 mole) and ethyl cyanoacetate (113 g, 1 mole) was dissolved in a 2-l. thick-walled flask and cooled to 0°. To this solution was added 600 ml of ethanol previously saturated with anhydrous ammonia at 0°. The flask was stoppered and secured with wire or tape. After 1 week at 0–5°, the separated ammonium salt of the dicyano imide was filtered, pressed, and washed several times with anhydrous ether. The dried salt (61 g) was dissolved in 160 ml of water, by warming, and 90 ml of concentrated hydrochloric acid was added. The solution slowly crystallized on standing; the process was accelerated with stirring. The product was filtered, washed with ice water, and dried at 90°, mp 236–238° (43 g, 31%). A portion on recrystallization from ethyl acetate–petroleum ether (bp 30–60°) melted at 237–238°.

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.85; H, 4.65; N, 15.11.

1,5-Dicyano-9-carboethoxy-3-azaspiro[5.5]undecane-2,4-dione (XII, R = C_2H_5).—The preparation was carried out essentially as described above for acid XII (R = H). The 4-carboethoxycyclohexanone (42 g, 0.25 mole) and ethyl cyanoacetate (55.8 g, 0.49 mole) were mixed at 0° with excess alcoholic ammonia. After standing for 1 month at 0–5°, the mixture was diluted with two volumes of anhydrous ether and stored for an additional 1 week. The precipitate was filtered, washed with ether, and dissolved in a minimum amount of water. The solution was acidified with concentrated hydrochloric acid and the product was filtered (12 g, 16%). On recrystallization from benzene–petroleum ether the crystals melted at 140.5–142.0°.

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.39; H, 5.65; N, 13.86. Found: C, 59.40; H, 5.69; N, 13.57.

4-Carboxycyclohexane-1,1-diacetic Acid (XIII, R = H).—The imide XII (R = H, 63.6 g) was dissolved in 200 ml of concentrated sulfuric acid and allowed to stand overnight at room temperature. Water (200 ml) was added portionwise with shaking and the mixture was refluxed. During this period, a considerable amount of frothing was noted. After 8 hr, the clear solution, which had ceased to froth, was cooled and diluted with 200 ml of water, in small portions, and the mixture was refluxed overnight. After the reaction mixture had cooled for several hours, the crude product was filtered, washed with cold water, and dried (56 g, mp 184–186°). Two recrystallizations from water raised the melting point to 189–190° which did not change when recrystallized from ethyl acetate–ethanol–petroleum ether (42.4 g, 64%).

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.32; H, 6.67.

Diethyl 4-Carboethoxycyclohexane-1,1-diacetate (XIII, R = C_2H_5).—The acid (XIII, R = H, 56 g), was esterified by the method of Ingold[4] as described under I. The product distilled at 138–142° at 0.05 mm, 71.2 g (94%).

Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 62.21; H, 8.44.

9-Hydroxymethyl-1,1-bis(β-hydroxyethyl)cyclohexane (XIV).—The ester XIII (71 g) was reduced with 30.4 g of lithium aluminum hydride as described under II. The crude product weighed 51 g. A small portion of the product was distilled (bp 204–206° at 1 mm) and was recrystallized from benzene–petroleum ether, mp 72–73°. The infrared spectrum showed no carbonyl absorption.

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.53; H, 11.18.

9-Hydroxymethyl-3-oxaspiro[5.5]undecane (XV).—The crude triol XIV (68.7 g) was heated with 150 ml of concentrated hydrochloric acid on a steam bath. After 2.5 hr, the mixture was poured into an equal volume of water and the solution was neutralized by the addition of solid sodium carbonate. The solution was cooled in ice and the resultant oil was extracted three times with ether. The ethereal extracts were combined and washed with water, potassium bicarbonate solution, and a saturated salt solution. After drying with anhydrous sodium sulfate, the ether was evaporated *in vacuo*, and the product was distilled. Two fractions were obtained: fraction a (7 g) distilled at 90–96° (0.1 mm) and contained 1% chlorine; and fraction b (37 g) which distilled at 96–99° (0.1 mm) showed only a trace of chlorine. Redistillation of fraction b yielded 35 g (55%) of product, bp 98–99° (0.1 mm), which was chlorine free.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.58; H, 10.96.

9-Bromomethyl-3-oxaspiro[5.5]undecane (XVI).—To 30 g of the alcohol XV, dissolved in 250 ml of ether, was added 60 g of phosphorus tribromide dissolved in 100 ml of ether. The mixture was allowed to stand overnight at room temperature. The ether and excess phosphorus tribromide were removed under reduced pressure (*ca.* 5 mm) at 100° and the residual oil was poured into water. The oily layer was extracted with ether and the ethereal solution was washed with water, potassium bicarbonate solution, and a saturated salt solution. After drying over anhydrous sodium sulfate and vacuum evaporation of the ether, the product was distilled, bp 84–87° (0.15 mm), yield 21 g, 54%.

Anal. Calcd for $C_{11}H_{19}BrO$: C, 53.44; H, 7.75; Br, 32.33. Found: C, 53.53; H, 7.68; Br, 32.04.

9-Carboxy-3-oxaspiro[5.5]undecane (XVII).—A solution of 40.6 g of potassium permanganate in 775 ml of water was cooled to 5–10°. A mixture of 3.3 g of sodium hydroxide in 64 ml of water and 35.6 g of 9-hydroxymethyl-3-oxaspiro[5.5]undecane (XV) was added slowly with stirring. After 4 hr the reaction mixture was allowed to warm to room temperature and the stirring was continued for 24 hr. The excess permanganate was destroyed with sodium bisulfite and the solution was filtered. The clear, colorless filtrate was evaporated on a steam bath to dryness. The residue was dissolved in 75 ml of water, acidified with concentrated hydrochloric acid, cooled, and filtered. After drying, the crude solids were extracted continuously with ligroin (bp 65–75°). On concentrating the solution to an oil and cooling, the product was crystallized, mp 96–99° (27 g, 68%). Recrystallization of the product once from water and once from ligroin gave the title compound, mp 99–100°.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; neut equiv, 198. Found: C, 66.68; H, 9.26; neut equiv, 196.

4-Carboxy-1,1-bis(β-bromoethyl)cyclohexane (XVIII, R = H).—To a mixture of 25 g of the acid XVII and 100 ml of 48% hydrobromic acid was slowly added, with cooling, 50 ml of concentrated sulfuric acid. The clear solution was heated on a steam bath for 1 hr whereupon crystals separated. After heating for an additional 8 hr, the mixture was poured into an equal volume of water and cooled. The crude product was filtered (43.4 g), mp 170–173.5°, and one recrystallization from alcohol yielded 31.4 g (71%), mp 173–174.5°. Recrystallization from benzene raised the melting point to 173.5–175.0° which remained constant upon repeated recrystallizations.

Anal. Calcd for $C_{11}H_{18}Br_2O_2$: C, 38.61; H, 5.30; Br, 46.72. Found: C, 38.65; H, 5.54; Br, 46.52.

4-Carboethoxy-1,1-bis(β-bromoethyl)cyclohexane (XVIII, R = C_2H_5).—To a solution of the acid XVIII (R = H, 33.5 g) dissolved in a mixture of 70 ml of anhydrous alcohol and 125 ml of benzene, was added 11 ml of concentrated sulfuric acid. The reaction mixture was refluxed for 24 hr. After cooling, the dark solution was poured into water and extracted three times with ether. The ethereal solution was successively washed with water and potassium bicarbonate and saturated salt solutions and dried over anhydrous sodium sulfate to which 2 g of charcoal was added. This treatment removed most of the color. The filtered solution was vacuum evaporated to remove the solvent and distilled, bp 135–143° (0.1 mm), yield 30 g, 81%.

Anal. Calcd for $C_{13}H_{22}Br_2O_2$: C, 42.18; H, 5.99; Br, 43.19. Found: C, 41.98; H, 5.89; Br, 43.02.

3,3,9-Tricarboethoxyspiro[5.5]undecane (XIX, R = C_2H_5).—A solution of sodium ethoxide was prepared in a 1-l., three-neck flask, equipped with a stirrer, reflux condenser carrying a drying tube, and a dropping funnel, from 6.9 g of sodium (0.3 g-atom) and 500 ml of ethanol. Ethyl malonate (24 g, 0.15 mole) was added and the mixture was heated to reflux. At this point 29 g of the dibromo ester (XVIII, R = C_2H_5) dissolved in 50 ml of alcohol was added and the mixture was refluxed for 24 hr. The mixture was cooled and most of the alcohol was removed at reduced pressure. After adding 500 ml of water, the mixture was acidified with 10% hydrochloric acid and extracted three times with ether. The ethereal extract was washed with water, potassium bicarbonate solution, and a saturated salt solution. After drying over anhydrous sodium sulfate, the ether was removed by distillation. The product was distilled, bp 154–160° (0.25 mm), yield 17.5 g, 61%.

Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.45; H, 9.01.

3,3,9-Tricarboxyspiro[5.5]undecane (XIX, R = H).—The triester XIX (17 g) was dissolved in 50 ml of alcohol and added to a solution of 21 g of potassium hydroxide dissolved in 300 ml of alcohol. After refluxing for 16 hr, the mixture was cooled and filtered. The solid potassium salt was washed with alcohol and ether, and dried. A concentrated solution of the solid in water was treated with charcoal, filtered, and acidified with concentrated hydrochloric acid. The product (8.5 g, 65%) after recrystallization from water melted at 200–201° with decomposition. It resolidified and remelted at 236–241°.

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.31; H, 6.91.

3,9-Dicarboxyspiro[5.5]undecane (XX).—The tricarboxylic acid XIX (8 g) was heated in a round-bottom flask until the temperature of the melt was 200°. The material which had melted resolidified on further heating and then remelted at *ca.* 240°. After the temperature was maintained at 240° for 15 min, the residue was allowed to cool. The crude product was dissolved in potassium bicarbonate solution, treated with charcoal, and filtered. On acidification with concentrated hydrochloric acid, the diacid precipitated and was filtered and dried, mp 241–243°. After two recrystallizations from alcohol the melting point was constant at 241–242.5°.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.89; H, 8.40.

3,9-Diaminospiro[5.5]undecane (X).—The above spiroundecane (XX, 2.5 g) was dissolved in a mixture of 41 g of concentrated sulfuric acid and 80 ml of chloroform in a three-neck, 500-ml flask. The solution was heated to 50° and stirred during the slow addition of 3 g of sodium azide. After the addition was complete, the reaction mixture was maintained at 50° for 30 min, cooled, and diluted with 400 g of ice. The solution was basified by the addition of 30% sodium hydroxide solution and extracted five times with ether. The ethereal solution was extracted five times with 5% hydrochloric acid and the aqueous acid extract was made basic with 15% sodium hydroxide solution. This latter solution was extracted five times with ether and the ethereal solution was separated and dried over potassium hydroxide pellets. Removal of the ether yielded 0.9 g of an oil which was distilled, bp 93-97° (1 mm). The oil was converted into its dihydrochloride, using alcoholic hydrogen chloride and ethanol. Boiling methanol was added until the precipitate redissolved and the product was allowed to cool. The dihydrochloride (0.7 g) did not melt at 370° and when mixed with a sample prepared from the dioxime (as in Scheme I) the mixture did not melt at 370°. The infrared spectra (KBr disk) were identical for samples prepared by Scheme I or II.

The picrate of the compound prepared in Scheme I was the same as that derivative prepared in Scheme II, mp 250-252° dec. A mixture melting point of the picrates showed no depression.

Anal. Calcd for $C_{23}H_{28}N_8O_{14}$: N, 17.50. Found: N, 17.69.

The di(phenylurea) derivative, prepared from either of the diamines X, obtained from the method of Scheme I or II, melted at 251-253° when the compound was immersed in the bath at 245°. A mixture melting point showed no depression.

Anal. Calcd for $C_{25}H_{32}N_4O_2$: C, 71.40; H, 7.67; N, 13.32. Found: C, 71.19; H, 7.61; N, 13.07.

Registry No.—I (R = Et), 10428-65-6; II, 10428-66-7; III, 180-47-2; IV, 5794-98-9; V, 10428-68-9; VI (R = H), 10428-69-0; VI (R = C_2H_5), 10428-70-3; VII, 10428-71-4; VIII, 5607-35-2; IX, 10428-73-6; X, 1042-74-7; dihydrochloride of X, 10428-75-8; picrate of X, 10428-76-9; di(phenylurea) derivative of X, 10428-77-0; XII (R = H), 10428-78-1; XII (R = C_2H_5), 10428-79-2; XIII (R = H), 10428-80-5; XIII (R = C_2H_5), 10428-81-6; XIV, 10428-82-7; XV, 10428-83-8; XVI, 10428-84-9; XVII, 10428-85-0; XVIII (R = H), 10428-86-1; XVIII (R = C_2H_5), 10428-87-2; XIX (R = C_2H_5), 10428-88-3; XIX (R = H), 10428-89-4; XX, 10428-90-7.

Nuclear Magnetic Resonance Investigation of Acyl Azulenes

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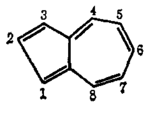
Nuclear magnetic resonance (nmr) spectra of 1-acetylazulene, 1,3-diacetylazulene, 1,3-diacetyl-4,6,8-trimethylazulene, diguaiazulyl ketone, and 1-formylguaiazulene have been measured at 60 Mc. Ring-proton resonance assignments have been made, and the influence of acyl substituents on ring-proton positions has been determined.

Azulene (1) and its derivatives constitute an exceedingly interesting class of compounds due to the fused five-seven bicyclic aromatic ring system. The two rings are physically and chemically quite different (as predicted from molecular orbital calculations), and thus the system should be especially vulnerable to a systematic investigation of substituent effects as a function of ring position. Both chemical and physical methods are available for such a study.

Anderson and co-workers[1] several years ago verified theoretical predictions[2] that the 1 and 3 positions of the azulene nucleus should be most easily attacked by electrophilic reagents.



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This is consistent with the fact that the molecule possesses a permanent dipole with the small ring slightly electron rich, the large ring corresponding electron poor. We have previously studied the azulene system by preparing the variously substituted azulenecarboxylic acids and ethyl esters thereof and measuring pK_a's and saponification rates, respectively.[3] Both relatively good and weak correlations were found between ring position of the reactive functional group and its relative reactivity (using the unperturbed azulene nucleus charge densities as a model).

Heilbronner has extensively reviewed the literature[4] dealing with preparation and physical properties of the very large number of substituted azulenes known through 1959. In sum, the review reveals a relatively widespread interest in the system from a purely synthetic standpoint, and also demonstrates conclusively from the results of several studies that the chemistry of the azulenes is in accord with theoretical predictions.

Attempts to investigate the azulenes by nuclear magnetic resonance (nmr) techniques have been somewhat limited in scope.[5,6] The complex spectrum of azulene itself has yielded to analysis.[6]

The purpose of the present investigation was to use three model compounds, azulene, 4,6,8-trimethylazulene and guaiazulene, the nmr spectra of which have previously been assigned,[5,6] in order to study the effects of acyl substitution on the ring protons in the known compounds 1-acetylazulene (2), 1,3-diacetylazulene (3), 1,1′-diguaiazulyl ketone (4), 1-formyl guaiazulene (5), and a new compound, 1,3-diacetyl-4,6,8-trimethylazulene (6).

Results and Discussion

Table I presents the ring proton assignments made in the present investigation, along with the accepted as-

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