[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, GEORGETOWN UNIVERSITY MEDICAL CENTER, THE CELANESE CORPORATION OF AMERICA AND THE WYETH INSTITUTE FOR MEDICAL RESEARCH][1,2]

Spiranes. II. Spiro[3.3]heptane Derivatives

LEONARD M. RICE AND CHARLES H. GROGAN

Received March 17, 1960

Derivatives of spiro[3.3]heptane have been prepared from the basic Fecht acid, *dl*-spiro[3.3]heptane-2,5-dicarboxylic acid. Spiro[3.3]heptane-2,2,5,5-tetracarboxylic acid tetraamyl ester has been isolated and shown to be a major intermediate in the preparation of Fecht acid. Improved syntheses of the corresponding diacid chloride, amide, glycol, and methyl ester have been developed. From these materials new dialkylaminoalkyl esters, alkyl and dialkylamides, a dinitrile, and the corresponding amines obtained by reduction of the alkyl and dialkylamides, and the dinitrile have been prepared. Spiro[3.3]-heptane-2,5-diacetic acid has been obtained in low yield.

Compounds possessing the spirane carbon nucleus attracted our attention several years ago because of the lack of information on pharmacological activity of compounds with this type of structure. Spiroheptanedicarboxylic acid was first obtained in small yield in 1907 by Fecht[3] by the sodium-alcohol condensation of pentaerythritol tetrabromide and dimethyl malonate. Interest in this basic structure was aroused when it was reported that weak optical activity was present even though no asymmetric carbon atom is involved. Backer and Schurink[4] succeeded in partially resolving Fecht acid, spiro[3.3]heptane-2,5-dicarboxylic acid, into its *d* and *l* isomers.

The study of the chemistry of Fecht acid (in the older literature the name 4-spiroheptane-2,6-dicarboxylic acid is used) was facilitated when in 1931 Backer and Schurink[5] improved the laborious synthesis of this acid. They used ethyl malonate instead of methyl malonate previously employed. Ester exchange takes place between the amyl alcohol and ethyl malonate in the presence of sodium but does not occur appreciably with methyl malonate; the resulting ethanol can be readily distilled.

We have improved and increased by five times the preparation of the starting material, Fecht acid (I). We have likewise improved the preparation of derivatives of Fecht acid containing functional groups suitable for further transformations. Among these are included the diacid chloride (II), previously reported by Janson and Pope[6] and Backer and Kemper,[7] the dimethyl ester (IX),[7] the diamide (XV),[6,7] and the diglycol (X).[7]

For the sake of completion of the literature at this point, it should be stated that spiro[3.3]heptane-2,5-diamine was prepared by Janson and Pope[6] and resolved into its *d* and *l* isomers. Backer and Kemper[8] studied 2,5-dibromospiro[3.3]heptane-2,5-dicarboxylic acid and prepared several derivatives involving the carboxyl group as well as the replacement of bromine by the sulfonate group.

Our studies branched out in several directions from the basic Fecht acid. First, we isolated the tetraamyl ester of the intermediate spiro[3.3]-heptane-2,2,5,5-tetracarboxylic acid (III), which proved to be a major intermediate in the preparation of Fecht acid by condensation of pentaerythritol tetrabromide with ethyl malonate. The tetracarboxylic acid had been isolated by Backer and Schurink.[7] This tetraamyl ester was reduced to the new interesting bis-*gem*-glycol (IV), which was further characterized as the dibenzal derivative (V).

The second series of synthetic transformations involved the formation of the known diamide (XV) and its efficient conversion to the new dinitrile (XVI). This dinitrile was converted by reduction to the next higher homologous diamine (XVII), which was characterized by five derivatives.

A third type of transformation involved formation of bisalkyl and bisdialkylamides (VI), and their reduction to the corresponding bisalkylaminomethyl and dialkylaminomethyl spiro[3.3]-heptanes (VII). The amine (VIIb) was converted to the bismethonium salt (VIII) which was compared with hexamethonium for hypotensive activity. Its hypotensive activity was slight and of short duration. It likewise had a weak curarimimetic activity.

A fourth series of new derivatives was obtained by preparing representative dialkylaminoalkyl esters (XVIII) from the acid chloride (II) and dialkylaminoalkanols.

(1) This project was begun at Georgetown University Medical Center several years ago. It was continued by one of us (L. M. R.) at The Celanese Corporation of America, Summit, N. J., and at the Wyeth Institute for Medical Research, Radnor, Pa.

(2) The project was brought to its present stage of completion with the support of the Geschickter Fund for Medical Research, Inc. The support of these organizations is hereby gratefully acknowledged.

(3) H. Fecht, *Ber.*, **40**, 3883 (1907).

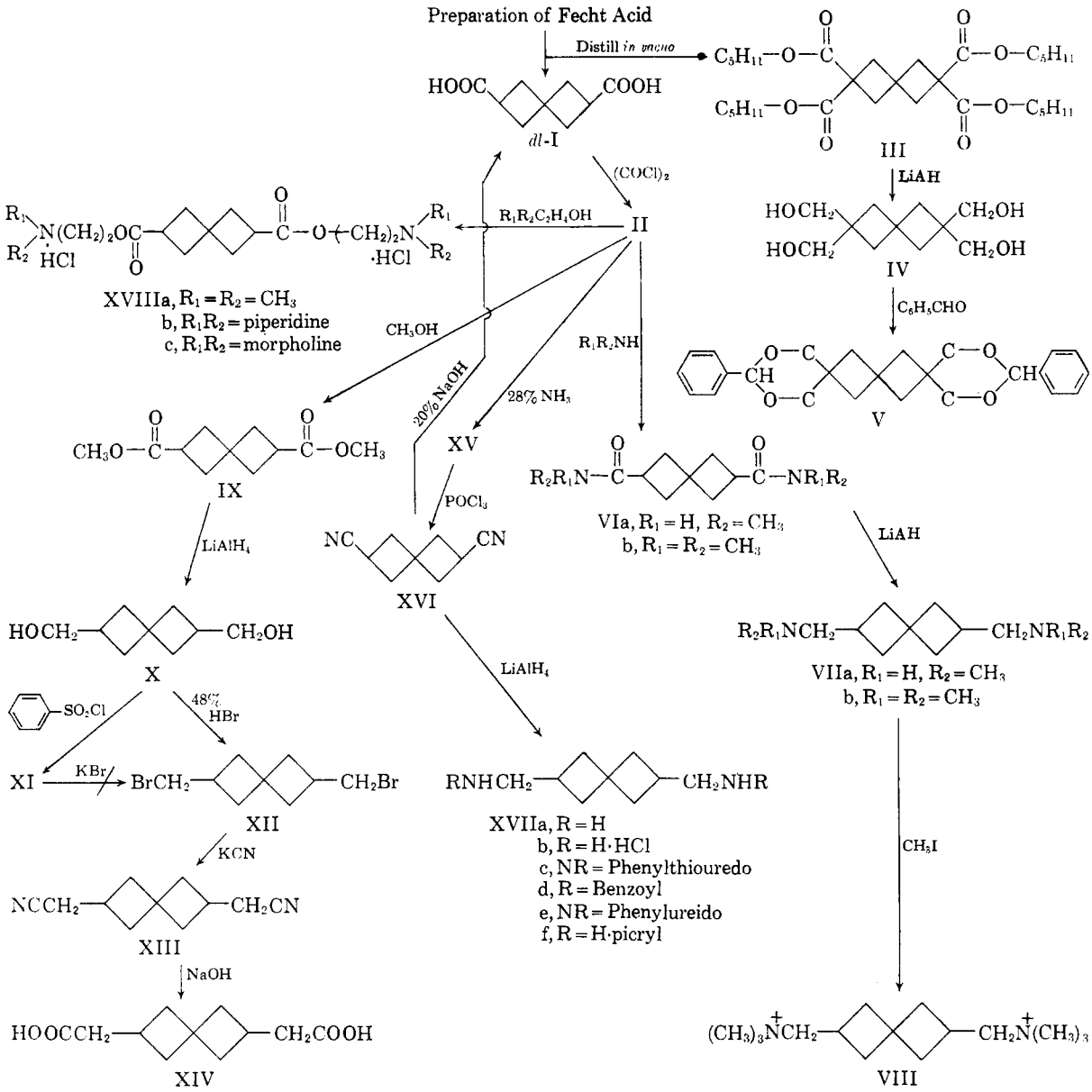
(4) H. J. Backer and H. B. J. Schurink, *Proc. Acad. Wetenschoppen (Amsterdam)*, **31**, 370, April 28 (1928).

(5) H. J. Backer and H. B. J. Schurink, *Rec. trav. chim.*, **50**, 921 (1931).

(6) S. E. Janson and Sir W. J. Pope, *Proc. Roy. Soc. (London)*, **A-154**, 53 (1936).

(7) H. J. Backer and H. G. Kemper, *Rec. trav. chim.*, **57**, 1249 (1938).

(8) H. J. Backer and H. G. Kemper, *Rec. trav. chim.*, **57**, 761 (1938).



The final type of transformation was aimed at the next higher aliphatic acid homolog, spiro[3.3]-heptane-2,5-diacetic acid. The dimethyl ester of Fecht acid (IX) was obtained in excellent yield by treating the acid chloride with absolute methanol. This was reduced in excellent yield with lithium aluminum hydride to the corresponding diglycol (X). The conversion of the diglycol to the required dibromide (XII) proved to be very difficult. The dibromide was finally obtained in low yield by direct repeated treatment of the glycol with 48% aqueous hydrobromic acid. Other methods failed entirely to give isolable amounts of the dibromide.

Two other methods that might be of value in this conversion are: (1) the use of lithium bromide instead of potassium bromide in the dibenzenesulfonate (XI) process and (2) direct esterification with anhydrous phosphoric acid and potassium bromide. We did not have sufficient quantity of the necessary glycol (X) to try these possible alternative methods. Since the dibromide (XII) is a key intermediate for the preparation of higher homologs, a practicable synthesis is still to be desired.

In view of the difficulty encountered in obtaining the dibromide (XII), a detailed study of its conversion into the dinitrile (XIII) was not possible. However, the standard conversion with potassium cyanide takes place in low yield and sufficient crude dinitrile (XIII) was obtained to prepare and characterize the spiro[3.3]heptane-2,5-diacetic acid (XIV).

It should be pointed out that no attempt was made to resolve those derivatives of the spiro nucleus which are capable of optical resolution.

EXPERIMENTAL

dl-Spiro[3.3]heptane-2,5-dicarboxylic acid (Fecht acid) (I). A modification of the improved synthesis of Backer and

Schurink[5] was used. Four separate runs were made using 0.5*M* quantities of pentaerythritol tetrabromide. One run was modified so as to isolate the tetraamyl ester of spiro-[3.3]heptane-2,2,5,5-tetracarbocylic acid. The procedure was as follows: Sodium, 2.5 moles, 57.5 g., was dissolved in 2.5 l. of absolute amyl alcohol. When solution of the sodium was complete, 400 g. (2.5 moles) of ethyl malonate was added with stirring and warming until the sodium compound was dissolved. Then 200 g. (0.5 mole) of pentaerythritol tetrabromide was added. The mixture was distilled until the vapor temperature reached 130°, near the boiling point of amyl alcohol. Most of the ethanol, formed by ester exchange between the ethyl malonate and amyl alcohol in the presence of sodium, was contained in the distillate. The reflux condenser was replaced, a volume of amyl alcohol equal to the distillate added, and the mixture refluxed for 40–50 hr.

Most of the amyl alcohol was then distilled, some water added, and the remainder of the amyl alcohol removed by distillation. The upper layer was extracted several times with ether to remove the ester salt, the ether stripped, and the ester salt saponified by adding a solution of 450 g. of potassium hydroxide (7.5 moles) in 3.75 l. of ethanol and letting the mixture stand at room temperature for 48 hr. The potassium salt was filtered, dissolved in water, decolorized with charcoal, and acidified with concd. hydrochloric acid. The acid was extracted out with ether in the Eykman continuous ether extractor.

The ether extract was dried over sodium sulfate and the ether stripped, leaving a solid residue which consisted of a mixture of spiro[3.3]heptane tetra- and dicarboxylic acids. The former is present in greater amount. The solid mixture of carboxylic acids, on being heated slowly to 200–212°, melted, lost carbon dioxide, and solidified on cooling. The resultant brown mass was dissolved in 1 l. of boiling water, decolorized with charcoal, and recrystallized from water. After a further recrystallization from water or ethyl acetate, the desired *dl*-spiro[3.3]heptane-2,5-dicarboxylic acid was obtained as colorless needles, m.p. 212°, 70–75 g., 75–80%.

Tetraamylspiro[3.3]heptane-2,2,5,5-tetracarboxylate (III). If during the preparation of Fecht acid (I), the distillation, prior to the saponification step and after removal of solvents, was continued *in vacuo*, a total of 153 g. of material boiling under 200°/0.2 mm. was obtained. There was a clean break in the temperature at this point and the pressure fell to 0.05–0.06 mm. Continued distillation yielded a 185 g. of a fraction, b.p. 218–225°/0.05–0.06 mm., which proved to be the tetraamyl ester of the intermediate tetracarboxylic acid. No attempt was made to identify components of the fraction boiling up to 200°, which was probably a mixture of esters of the di- and tetracarboxylic acids.

Anal. Calcd. for $C_{31}H_{52}O_8$: C, 67.36· H, 9.48. Found: C, 67.10; H, 9.52. n_D^{25} 1.4541.

2,2,5,5-Tetrahydroxymethylspiro[3.3]heptane (IV). This glycol was prepared in good yield from the tetraamyl ester (III) by reduction with lithium aluminum hydride in anhydrous ether. Two runs were made using 25 g. of lithium aluminum hydride and 100 g. and 76 g., respectively, of the ester. The reduction was standard procedure except that after the decomposition of the reaction mixture with water, drying the ether over anhydrous sodium sulfate and stripping the ether, *very little product was found in the ether*. The glycol is only slightly soluble in ether and most of it was found with the inorganic salt residue. The residue from the lithium aluminum hydride reduction was extracted in a Soxhlet overnight with absolute ethanol. On cooling the extract, the glycol crystallized. The solution was concentrated and the glycol crystallized from ethanol. The crude product melted at 185–187.5°. Two additional recrystallizations from ethanol gave the analytically pure material, m.p. 187.5–188.5°. The two runs gave 25.2 and 20.6 g. of glycol, respectively, for an average yield of 67%.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.30; H, 9.41.

2,2,5,5-Tetrahydromethylspiro[3.3]heptane dibenzal acetal (2,5-bis(4′-phenyldioxolane)-spiro[3.3]heptane). The glycol was further characterized by conversion into the dibenzal derivative. The glycol, 3.92 g. (0.01 mole) and 2.2 g. (0.02 mole) of chlorine-free benzaldehyde were dissolved in 50 ml. of toluene and 50 ml. of acetic acid. A crystal of *p*-toluenesulfonic acid was added and the mixture refluxed for 3 hr. while fitted with a trap to remove water vapor. The reaction mixture was evaporated to dryness on a steam bath and the crude product recrystallized from methanol, m.p. 122–124°. An additional crystallization from absolute methanol gave a constant melting product, m.p. 128–129°.

Anal. Calcd. for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.41; H, 7.50.

Spiro[3.3]heptane-2,5-dicarboxylic acid chloride (II). The acid chloride of Fecht acid has been prepared by other workers (Backer and Kemper[7] and Janson and Pope[6]) by older methods employing phosphorus chlorides and thionyl chloride. Since this was one of the key intermediates in our conversions, and in view of the laborious preparation of the Fecht acid, the more elegant reagent, oxalyl chloride, has been investigated. The conversion with oxalyl chloride was clean-cut and gave a high yield, 80–90%, of pure product, b.p. 154°/15 mm.

Spiro[3.3]heptane-2,5-dicarboxamide (XV). Fecht acid chloride, 31 g. (0.14 mole), was added dropwise with rapid stirring to 40 g. of 28% ammonia in 200 ml. of water maintained at or below 10°. The mixture was stirred for 1 hr., filtered, and the crude amide washed with cold ethanol and then water, m.p. 246–247°, 20.5 g., 80%. Recrystallization from water gave a m.p. of 247–248°, ethanol-water mixture, 248.5–249°. Janson and Pope[6] give m.p. 249–250°. The crude amide is suitable for other transformations. Recrystallization of 18 g. of the amide from 200 ml. of water resulted in recovery of 12.6 g. of product, m.p. 248.5–249°. The diamide is nearly insoluble in ethanol, ethyl acetate, and acetone at room temperature.

Dimethylspiro[3.3]heptane-2,5-dicarboxylate (IX). The known dimethyl ester of Fecht acid was prepared in 95% yield by reaction of the acid chloride with excess absolute methanol. It was isolated by vacuum distillation, b.p. 117–118°/3 mm. Backer and Kemper[7] report b.p. 141°/11 mm.

2,5-Dihydroxymethylspiro[3.3]heptane (X). The known glycol of Fecht acid was prepared by Backer and Kemper[7] by sodium-alcohol reduction of the diphenyl ester in only 46% yield. The glycol has been prepared in excellent yield and purity by reduction of the methyl ester (IX) with lithium aluminum hydride. From 87 g. (0.41 mole) of the ester and 22 g. (excess) of lithium aluminum hydride in anhydrous ether there was obtained 52 g., 81%, of the glycol, b.p. 112–113°/0.1 mm. Backer and Kemper[7] report b.p. 167°/16 mm.

2,5-Dihydroxymethylspiro[3.3]heptane dibenzenesulfonate (XI). The glycol, 15.6 g. (0.1 mole), and 20 ml. of pyridine were cooled to 0° in an ice bath and 35.2 g. (0.2 mole) of benzenesulfonyl chloride slowly added. The mixture was allowed to stand overnight. The product was washed successively with water, dilute hydrochloric acid, sodium bicarbonate solution, and copiously with water. It was dried *in vacuo* and cooled at −25° but could not be induced to crystallize.

Anal. Calcd. for $C_{21}H_{24}S_2O_6$: C, 57.78· H, 5.54. Found: C, 57.77; H, 5.80.

2,5-Dibromomethylspiro[3.3]heptane (XII). This dibromide proved most difficult to prepare. The method of Kamm and Marvel[9] was first tried. The reaction, carried out with 87.2 g. of 48% aqueous hydrobromic acid, 12.4 ml. of concd. sulfuric acid and 15.6 g. (0.1 mole) of the glycol, yielded a tarry mass from which none of the desired product could be isolated. The usual methods employing phosphorus bromides or benzenesulfonamide also yielded intractable

(9) O. Kamm and C. S. Marvel, *Org. Syntheses*, Coll. Vol. I, 25 (1941).

tarry residues. Refluxing the glycol bisbenzenesulfonate with potassium bromide in ethanol for several hours gave only traces of the dibromide. The desired dibromide was finally obtained under forcing conditions in poor yield as follows: The glycol, 40 g. (0.26 mole), was refluxed with 3 molar equivalents of 48% aqueous hydrobromic acid for 8 hr. on a steam bath. The reaction mixture was poured into a large volume of water. A blue oil separated. The water was extracted three times with ether, the ethereal solution dried over calcium chloride, the ether stripped, and the product distilled. The material boiling between 85–100°/0.4–0.5 mm. was collected. This product had a low bromine content, 45% as compared to 56.73% theory, and a correspondingly high carbon content. The entire product was recycled through the entire procedure *three* more times. The bromine content gradually increased until, on the fourth cycle, 11.50 g. (16%), of product b.p. 90–92°/0.4 mm., was collected.

Anal. Calcd. for $C_9H_{14}Br_2$: C, 38.33; H, 5.00; Br, 56.67. Found: C, 38.70; H, 5.08; Br, 56.53.

Spiro[3.3]heptane-2,5-diacetic acid (XIV). The dibromide (XII), 11.50 g. (0.041 mole), was dissolved in 50 ml. of absolute ethanol together with 7.6 g. (0.082 mole corrected to 100%) of potassium cyanide and a crystal of potassium iodide and the mixture refluxed for 8 hr. The mixture was evaporated to dryness, the oily residual solid extracted with ether, the ether extract dried over sodium sulfate, and the ether stripped. Attempted vacuum distillation of the residue showed it to be a mixture of unchanged bromide and the desired dinitrile; but the quantity of material was too small to permit isolation of the nitrile in analytical purity. The crude dinitrile was mixed with an excess of 20% aqueous sodium hydroxide and the mixture allowed to stand overnight. The mixture was strongly acidified with concd. hydrochloric acid and extracted with ether in a continuous extractor overnight. On evaporation of the ether to dryness, 3.5 g. (40% based on the dibromide), of crude material was obtained. Two recrystallizations from ethyl acetate gave the acid with constant melting point, 134–135°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.42; H, 7.61.

Molecular weight from neutralization equivalent: Calcd. 212.2. Found: 213. The same acid was obtained in poor yield by Arndt-Eistert conversion from the acyl chloride (II) with diazomethane.

2,5-Bis(N,N-dimethylamido)spiro[3.3]heptane (VIb). An excess (80 g. of a 25% aqueous solution) of dimethylamine was placed in a three necked reaction flask equipped with stirrer, reflux condenser, and dropping funnel and cooled to near 0° in an ice bath. Fecht acid chloride, 22.1 g. (0.1 mole), was added dropwise with rapid stirring keeping the temperature below 10°. The clear solution was evaporated to dryness, the residue dissolved in a minimum of water, and the water solution extracted overnight in a continuous ether extractor. The ether solution was evaporated to dryness yielding 19.5 g. (82%) of crude product, m.p. 105–110°. Recrystallization from isopropyl alcohol–petroleum ether (b.p. 30–60°) sharpened the m.p. to 111–112°. An additional recrystallization from the same system gave a m.p. of 111.5–112°.

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.45; H, 9.30; N, 11.65.

2,5-Bis(N-methylamido)spiro[3.3]heptane (VIa). This compound was prepared in a manner analogous to the *N,N*-dimethylamide. From 22.1 g. (0.1 mole) of the acid chloride and an excess of 25% aqueous methylamine, 17 g. (81%) of crude product, m.p. 171–176°, was obtained. Recrystallization from isopropyl alcohol raised the m.p. to 188–190°. Further recrystallization from water gave a constant melting product, m.p. 192–193°.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.00; H, 8.63; N, 13.49.

2,5-Bis(N,N-dimethylaminomethyl)spiro[3.3]heptane (VIIb). The *N,N*-dimethylamide (VIb), 12 g. (0.05 mole), was reduced in the usual manner with an excess of lithium aluminum hydride in absolute ether and yielded 7.5 g., 71%, of the amine, b.p. 142–144°/30 mm. It was converted directly to the *dihydrochloride* by adding an excess of saturated alcoholic hydrogen chloride to the amine dissolved in isopropyl alcohol and precipitating with ether, m.p. 292°. Recrystallization from isopropyl alcohol–methanol gave the salt with m.p. 295–296° dec.

Anal. Calcd. for $C_{13}H_{28}Cl_2N_2$: C, 55.11; H, 9.96; N, 9.89; Cl, 25.05. Found: C, 55.29; H, 10.12; N, 9.82; Cl, 25.00.

The *picrate* was formed in ethanol water and melted at 209–210°.

Anal. Calcd. for $C_{25}H_{32}N_8O_{14}$: N, 16.76. Found: N, 16.47.

2,5-Bis(N-methylaminomethyl)spiro[3.3]heptane (VIIa). This amine was prepared in a similar manner by reduction of 8 g. of the amide (VIa) and obtained in 85% yield as the *dihydrochloride*, m.p. 286–287° after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_{11}H_{24}Cl_2N_2$: C, 51.76; H, 9.48; N, 10.98; Cl, 27.78. Found: C, 51.64; H, 9.25; N, 11.00; Cl, 27.80.

The *picrate* was prepared from 0.5 g. of the amine liberated from the hydrochloride in methanol water, and recrystallized from methanol water, m.p. 211–212°.

Anal. Calcd. for $C_{23}H_{28}N_8O_{14}$: C, 43.13; H, 4.41; N, 17.50. Found: C, 43.32; H, 4.37; N, 17.46.

2,5-Bis(trimethylaminomethyl)spiro[3.3]heptane diiodide (VIII). The bismethonium quaternary salt of the amine (VIIb) was prepared from 5 g. of the amine and a 10% excess of methyl iodide in isopropyl alcohol. On standing overnight, the product crystallized. It was washed with ethanol and ether and melted at 302°. Recrystallization from methanol–isopropyl alcohol gave white crystals, m.p. 302–303°.

Anal. Calcd. for $C_{15}H_{32}I_2N_2$: C, 36.45; H, 6.52; N, 5.67; I, 51.36. Found: C, 36.44; H, 6.78; N, 5.42; I, 51.30.

2,5-Dicyanospiro[3.3]heptane (XVI). This dicyanide proved almost as difficult to prepare as the dibromide (XII). Several trials using phosphorus pentoxide, thionyl chloride, and phosphorus pentachloride as dehydrating agents yielded little or none of the desired product. The desired dinitrile was finally prepared in good yield as follows: When 20 g. (0.11 mole) of the diamide was heated under reflux for 1 hr. in a mixture of 90 ml. of benzene and 90 ml. of phosphorus oxychloride, the amide all dissolved giving a clear solution. On cooling, the mixture was slowly poured with stirring over 1 l. of crushed ice. The benzene layer was separated and the aqueous phase extracted twice with benzene. The benzene solution was dried over anhydrous sodium sulfate, the benzene stripped, and the product distilled *in vacuo*, b.p. 122–127°/0.3 mm., yield 14.2 g. (88%). The product solidified in the receiver and melted at 45° and was not changed by recrystallization from hexane.

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.93; H, 6.89; N, 19.10. Found: C, 73.79; H, 6.56; N, 19.09.

Proof that this was the desired 2,5-dinitrile was afforded by hydrolysis to Fecht acid. One gram of the nitrile was dissolved in 8 ml. of concd. sulfuric acid by swirling. After standing for 5 min., 20 ml. of water was added and the mixture refluxed for 2 hr. On cooling, crystals were deposited which were removed by filtration. The aqueous phase was extracted three times with ether. A total of 1.1 g. of material was obtained from the residue and ether extract, m.p. 205°. Recrystallization from ethyl acetate raised the m.p. to 211–211.5°. A mixed melting point with authentic Fecht acid (I) gave no depression. The infrared absorption spectra were identical.

2,5-Aminomethylspiro[3.3]heptane (XVIIa). When 11 g. of the nitrile (XVI) was reduced with lithium aluminum hydride in anhydrous ether, 7.5 g. (64%) of the desired amine was obtained, b.p. 66–72°/0.35 mm.

Anal. Calcd. for $C_9H_{18}N_2$: C, 70.07· H, 11.76; N, 18.17. Found: C, 70.53; H, 12.02; N, 18.09.

The dihydrochloride was formed in the usual manner in

isopropyl alcohol, m.p. over 360°, and recrystallized from isopropyl alcohol–ether, m.p. over 360°.

Anal. Calcd. for $C_9H_{20}Cl_2N_2$: C, 47.58; H, 8.87; N, 12.33; Cl, 31.22. Found: C, 47.84; H, 8.85; N, 12.49; Cl, 31.30.

The picrate was formed in the usual manner in methanol, m.p. 236°, not changed on recrystallization.

Anal. Calcd. for $C_{21}H_{24}N_8O_{14}$: C, 41.16; H, 3.95. Found: C, 41.33; H, 4.21.

The *phenylurea* was formed from 0.5 g. of the amine and a slight excess of phenylisocyanate in benzene, m.p. 200–201°. On recrystallization from methanol, the m.p. was raised to 204°.

Anal. Calcd. for $C_{23}H_{28}N_4O_2$: C, 70.38; H, 7.19; N, 14.28. Found: C, 70.53; H, 7.44; N, 14.14.

The *phenylthiourea* was formed from 0.5 g. of the amine and phenylisothiocyanate in benzene, m.p. 185°. On recrystallization from methanol the m.p. was raised to 186°.

Anal. Calcd. for $C_{23}H_{28}N_4S_2$: C, 65.06; H, 6.65; N, 13.28. Found: C, 65.05; H, 6.90; N, 13.40.

The *dibenzamide* was formed from 0.5 g. of the amine and benzoyl chloride by the Schotten-Bauman procedure, m.p. 168–170°, increased to 170–170.5° on recrystallization from methanol.

Anal. Calcd. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.24; H, 7.20; N, 7.83.

2,5-Bismorpholinoethylspiro[3.3]heptane dicarboxylate dihydrochloride (XVIIIc). The bismorpholinoethyl ester of Fecht acid was prepared by adding 4.42 g. (0.02 mole) of the acid chloride in 50 ml. of benzene to 5.24 g. (0.04 mole) of morpholinoethyl alcohol dissolved in 50 ml. of benzene and refluxing several hours. On cooling, the crude product crystallized. It was filtered, washed with benzene and ether, and dried, m.p. 199–201°, 8 g. (83%). Two recrystallizations from isopropyl alcohol–ether gave a constant melting product, m.p. 207–208°.

Anal. Calcd. for $C_{21}H_{36}Cl_2N_2O_6$: C, 52.17; H, 7.51; N, 5.80; Cl, 14.67. Found: C, 52.33; H, 7.66; N, 5.99; Cl, 14.70.

2,5-Bispiperidinoethylspiro[3.3]heptane dicarboxylate dihydrochloride (XVIIIb) was prepared in an analogous manner from 4.42 g. (0.02 mole) of the acid chloride and 5.17 g. (0.04 mole) of piperidinoethyl alcohol. There was obtained 7.8 g. (81%) of product which melted after two recrystallizations from isopropyl alcohol–ether, at 228–229°.

Anal. Calcd. for $C_{23}H_{40}Cl_2N_2O_4$: C, 57.60; H, 8.41; N, 5.84; Cl, 14.79. Found: C, 57.48; H, 8.76; N, 5.90; Cl, 14.97.

2,5-Bis(2-dimethylaminoethyl)spiro[3.3]heptane dicarboxylate dihydrochloride (XVIIIa) was prepared in an analogous manner from 6.63 g. (0.03 mole) of the acid chloride and 5.35 g. (0.06 mole) of 2-dimethylaminoethanol in 150 ml. of benzene and refluxed for 1 hr. There was obtained 11.55 g. crude product, m.p. 209–212° (94%). Recrystallization from methanol–ether raised the m.p. to 234–235° and from isopropyl alcohol–ethanol to 234.5–235°.

Anal. Calcd. for $C_{17}H_{32}Cl_2N_2O_4$: C, 51.13; H, 8.08; N, 7.02; Cl, 17.75. Found: C, 50.81; H, 8.02; N, 7.22; Cl, 17.60.

908 Lincoln Ave.
Falls Church, Va.

[Contribution from The Department of Chemistry, Kansas State College and Strosacker's Laboratory, The Dow Chemical Company]

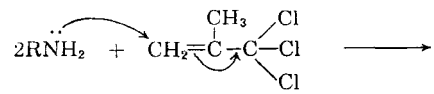
Dichloromethylallyl Compounds. III. N-(3,3-Dichloro-2-methylallyl)amines

D. G. KUNDIGER,[1] H. PLEDGER, Jr.,[2] and R. L. SOULEN[3]

Received April 28, 1960

A new series of new amines were prepared by the reaction of 3,3,3-trichloro-2-methyl-1-propene and 1,1,3-trichloro-2-methyl-1-propene with *N*-substituted amines, ammonia, and hydrazine. The physical constants and the preparation of these compounds and some of their derivatives are reported.

In continuation of earlier studies[4] on the chemistry of 3,3,3-trichloro-2-methyl-1-propene (I) and 1,1,3-trichloro-2-methyl-1-propene (II) with nucleophilic reagents, this paper reports the results of a study of the reactions of these chlorides with *N*-substituted amines, ammonia, and hydrazines. Previous work[4,5] has indicated that these isomeric chlorides are highly reactive. The same compound results when either chloride reacts with the same nucleophile. For example, the reaction of aqueous sodium hydroxide with chloride I or II yields 3,3-dichloro-2-methyl-2-propen-1-ol.[6] The reactions of chlorides I and II with amino compounds has further substantiated the earlier indications. The highly exothermic reaction between amino compounds and chloride I probably proceeds by an SN2′ reaction.



$$RNHCH_2C(CH_3)=CCl_2 + \overset{+}{R}N\overset{-}{H_3}Cl \qquad SN2'$$

The expected inductive withdrawal of electrons from nitrogen by the γ-chlorine atoms in the dichloromethylallyl group is greatly facilitated by the double bond in the allylic system. This base weakening effect leads to interesting results. This

(1) Deceased.

(2) Present address, Organic Process Development Laboratory, The Dow Chemical Company, Freeport, Tex. To whom requests for reprints should be sent.

(3) Portions of this paper represent part of a dissertation submitted by Robert L. Soulen in partial fulfillment of the requirements for the Ph.D. degree at Kansas State University.

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