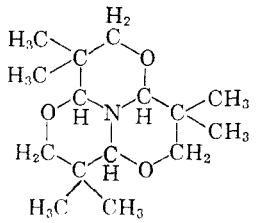
lated. The properties of this material matched those described by Cavalla[6] and by Lynn.[7] The NMR spectrum of IV was quite simple, indicative of a highly symmetrical structure (Table I).

TABLE I

NMR SPECTRUM OF IV[8]

Peak Position, C.P.S. (Relative to Water)	Proton Structure	Relative Area
50	CH	1
59	CH_2	2
141	CH_3	3
155	CH_3	3

Peak positions and their relative areas were in accord with structure IV, but also indicated two distinct types of methyl protons. If the two methyl group peaks arose from spin-spin interaction of the adjacent tertiary proton, a multiplet structure would be required for the tertiary proton resonance from the spin-spin interaction with the methyl protons. However, the tertiary proton resonance was a single, sharp peak. A Fischer-Taylor-Hirschfelder model of IV showed that the rings are coplanar. One methyl group of each ring lies in the plane of the rings, while the other methyl group projects from the plane. This structure undoubtedly is the basis for the doublet in the methyl proton resonance.



IV

EXPERIMENTAL

5,6-Dihydro-β,β,5,5-tetramethyl-2H-1,3-oxazine-2-ethanol (III). Ammonia was passed into a solution of 102 g. of 5-hydroxy-β,β,4,4-tetramethyl-2-*m*-dioxaneethanol[9] (hydroxypivalaldehyde dimer, I) in 120 ml. of methanol. The temperature of the strongly exothermic reaction was kept at 15–20° by means of an ice bath. Ammonia was added until no further reaction took place, and the solution was then heated under a reflux condenser by a steam bath to remove excess ammonia. Distillation of the reaction solution through a 6-in. Vigreux column gave 72 g. (79%) of III, b.p. 92–94° (2 mm.). The product solidified rapidly and was recrystallized from hexane to give 63 g., m.p. 72–73°.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3; N, 7.6; neut. equiv., 185. Found: C, 64.7; H, 10.3; N, 7.5; neut. equiv., 183. Infrared maxima: 3.1, 3.35, 3.5, 6.1, 6.8, 7.25, 7.35, 7.5, 7.6, 7.7, 7.85, 8.1, 8.2, 8.6, 9.2, 9.4, 9.7, 9.9, 10.3, 10.65, 10.8, 10.9, 12.6 μ.

The phenylurethane of III was prepared by refluxing a solution of 5.5 g. of III and 3.5 g. of phenyl isocyanate in 50 ml. of hexane for 2 hr. When the mixture was cooled, an oil separated and rapidly crystallized. The solvent was decanted, and the residue was pulverized and recrystallized twice from a hexane-benzene mixture to give 7.2 g. of the phenylurethane of 5,6-dihydro-β,β,5,5-tetramethyl-2H-1,3-oxazine-2-ethanol, m.p. 112–113°.

Anal. Calcd. for $C_{17}H_{23}N_2O_3$: C, 67.4; H, 7.6; N, 9.3. Found: C, 67.2; H, 8.0; N, 9.2. Infrared maxima: 3.0, 3.35, 3.5, 5.8, 6.1, 6.25, 6.45, 6.65, 6.75, 6.9, 7.3, 7.6, 8.1, 8.25, 8.5, 9.2, 9.4, 9.7, 10.1, 10.8, 13.2, 14.4 μ.

Decomposition of 5,6-Dihydro-β,β,5,5-tetramethyl-2H-1,3-oxazine-2-ethanol (III). Forty-five grams of 5,6-dihydro-β,β,5,5-tetramethyl-2H-1,3-oxazine-2-ethanol was distilled at atmospheric pressure through a 6-in. Vigreux column. A strong evolution of formaldehyde occurred. About 5 ml. of isobutyraldehyde and 2.0 ml. of a liquid, b.p. 130–148°, were obtained. When the base temperature reached 210°, the distillation was stopped because of excessive foaming. The residue was a viscous, black tar with a highly crystalline material dispersed in it. This tar was triturated with acetone, and the solid residue was recrystallized from ethyl alcohol to give 4.8 g. of 4,4,8,8,12,12-hexamethyl-2,6,10-trioxa-13-azatricyclo[7.3.1.$0^{5,13}$]tridecane (IV), m.p. 185–187°.

Anal. Calcd. for $C_{15}H_{27}NO_3$: C, 67.0; H, 10.0; N, 5.2. Found: C, 67.0; H, 10.2; N, 5.2.

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(6) J. F. Cavalla, *J. Chem. Soc.*, 4672 (1956).
(7) J. W. Lynn, *J. Am. Chem. Soc.*, **77**, 6067 (1955).
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(9) E. Späth and I. V. Szilagyi, *Ber.*, **76**, 949 (1943).

Synthesis of 1-Methyl-1-azaspiro[5.5]-undecan-5-one

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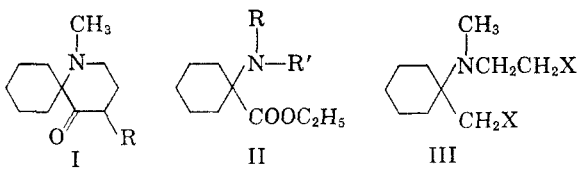
As part of a program dealing with the investigation of muscle relaxant agents the preparation of derivatives of 1-azaspiro[5.5]undecane was considered. This system constitutes rings A and C[1] of the erythrina alkaloids—a group of substances possessing strong curarizing activity.

In recent years Hill and Conley[2] developed a number of methods for the synthesis of 1-azaspiro-[5.5]undecan-2-one. For our work, however, we desired a derivative which would lend itself more readily to chemical modifications than Hill's spirolactam. As basic piperidones can be readily obtained by the Dieckmann closure of appropriately

(1) V. Boekelheide and V. Prelog, *Progress in Organic Chemistry*, Vol. 3, J. W. Cook, ed., Academic Press, New York, 1955, p. 243.
(2) (a) R. K. Hill and R. T. Conley, *Chem. & Ind.*, 1314 (1956); (b) R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957).

substituted amino diesters,[3] the synthesis of 1-methyl-1-azaspiro[5,5]undecan-5-one (I. R=H) was undertaken.

1-(Methylamino)cyclohexanecarboxamide[4] was converted *via* the corresponding acid to ethyl 1-(methylamino)cyclohexanecarboxylate (II. R=H; R′=CH_3); similarly, the 1-(benzylamino)- and 1-(2-diethylaminoethylamino)cyclohexanecarboxylates II[R=H; R′=$CH_2C_6H_5$ and $CH_2CH_2N(C_2H_5)_2$] were prepared from their respective amino carboxamides.[4] Ethyl 1-(methylamino)cyclohexanecarboxylate was alkylated in the presence of anhydrous potassium carbonate with 4-bromobutyronitrile as well as with ethyl 4-bromobutyrate to give ethyl 1-(3-cyanopropylmethylamino)cyclohexanecarboxylate (II. R=CH_3; R′=$(CH_2)_3CN$) and ethyl 1-(3-carbethoxypropylmethylamino)-cyclohexanecarboxylate II (R=CH_3; R′=$(CH_2)_3COOC_2H_5$), respectively. When the amino diester II (R=CH_3; R′=$(CH_2)_3COOC_2H_5$) was subjected to the action of sodium hydride in boiling benzene, ring closure took place as expected and ethyl 1-methyl-1-azaspiro[5.5]-undecan-5-one-4-carboxylate (I. R=$COOC_2H_5$) was isolated in good yield. Conversion of the keto ester to the desired spiro ketone I(R=H) was effected by treatment with hydrochloric acid. Quaternization of the keto ester with methyl iodide resulted in the loss of the ester grouping, yielding as the reaction product the methiodide of the spiro ketone I (R=H).



Parallel experiments were carried out with ethyl 1-aminocyclohexanecarboxylate II (R=R′=H); alkylation with ethyl 4-bromobutyrate resulted in the amino diester II[R=$(CH_2)_3COOC_2H_5$; R′=H] which was converted to its benzoyl derivative II [R=COC_6H_5; R′=$(CH_2)_3COOC_2H_5$]. This compound, however, resisted the usual Dieckmann ring closure conditions and attempts to obtain the *N*-unsubstituted spiro ketone were abandoned.

Another pathway leading to piperidines of potential pharmaceutical usefulness involves the condensation between nitrogen mustards and phenylacetonitrile.[5] Ethyl 1-(carbethoxymethylmethylamino)cyclohexanecarboxylate (II. R=CH_3, R′ = $CH_2COOC_2H_5$)—obtained by the alkylation of the amino ester II (R=H; R′=CH_3) with ethyl bromoacetate—was converted to the diol III (X=OH) by lithium aluminum hydride reduction. Treatment of the diol with thionyl chloride provided the desired nitrogen mustard derivative III (X=Cl), but its condensation with phenylacetonitrile did not lead to the desired piperidine derivative.

Preliminary pharmacological tests showed that the spiropiperidines I (R=H and $COOC_2H_3$) were devoid of curariform activity but exhibited antispasmodic properties as measured by the charcoal meal method.[6]

EXPERIMENTAL[7]

Ethyl 1-(methylamino)cyclohexanecarboxylate (II. R=H; R′=CH_3). A solution containing 300 g. of 1-(methylamino)-cyclohexanecarboxamide[4] and 1.5 l. of cond. hydrochloric acid was stirred and refluxed for 8 hr. The mixture was evaporated to dryness under reduced pressure and the residue was suspended in 1.5 l. of absolute ethanol saturated at 0° with gaseous hydrogen chloride. The mixture was refluxed for 24 hr., cooled to 0° and resaturated with hydrogen chloride. Refluxing was continued for another 24 hr. The solution was evaporated to dryness and the residue was taken up in 100 ml. of water. The solution was made basic with 20% potassium hydroxide and the oil was extracted with several portions of chloroform. The extract was dried and distilled, b.p. 108–109°/18 mm., n_D^{27} 1.4548, yield 118 g. (33%).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.57. Found: C, 64.64; H, 10.60; N, 7.48.

Ethyl 1-(benzylamino)cyclohexanecarboxylate (II. R=H; R′=$CH_2C_6H_5$). The preceding reaction conditions were applied to 69.6 g. of 1-(benzylamino)cyclohexanecarboxamide.[4] The amino ester was obtained in a yield of 24.2 g. (28%), b.p. 109–114°/0.6 mm. It was converted to its hydrochloride, m.p. 176–178° (recrystallized from ethyl acetate).

Anal. Calcd. for $C_{16}H_{24}ClNO_2$: C, 64.68; H, 8.07; N, 4.70. Found: C, 64.64; H, 8.22; N, 4.50.

Ethyl 1-(2-diethylaminoethylamino)cyclohexanecarboxylate (II. R=H; R′=$CH_2CH_2N(C_2H_5)_2$). Prepared by the above method from 24.1 g. of 1-(2-diethylaminoethylamino)cyclohexanecarboxamide,[4] the product was obtained in a yield of 6.5 g. (24%), b.p. 90–94°/0.05 mm. The material was converted to its dihydrochloride, m.p. 182–184° (from ethanol and ethyl acetate).

Anal. Calcd. for $C_{16}H_{32}Cl_2N_2O_2$: C, 52.62; H, 9.37; N, 8.19. Found: C, 52.81; H, 9.36; N, 7.95.

Ethyl 1-[2-(4-pyridyl)ethylamino]cyclohexanecarboxylate (II. R=H; R′=CH_2CH_2-4-pyridyl.) A mixture consisting of 34.2 g. of ethyl 1-aminocyclohexanecarboxylate,[8] 21.6 g. of 4-vinylpyridine, 12 g. of glacial acetic acid, and 78 ml. of methanol was refluxed for 12 hr. After removal of the solvent under reduced pressure the residue was dissolved in 50 ml. of water and the solution was made basic with 10% potassium hydroxide. The mixture was extracted with chloroform (200 ml.) and the extract was diluted with twice its volume of ether. A small amount of solid was filtered off and the filtrate was distilled. The portion, b.p. 145–160°/0.07 mm., was collected and coverted to a dihydrochloride. After several recrystallizations from ethanol–ethyl acetate, the material melted at 194–195°, yield 29.7 g. (42%).

(3) (a) H. S. Mosher, *Heterocyclic Compounds*, R. C. Elderfield, ed., Vol. 1, Wiley, New York, 1950, p. 655. (b) N. J. Leonard and E. Barthel, Jr., *J. Am. Chem. Soc.*, 72, 3632 (1950).

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(5) O. Eisleb, *Ber.*, 74, 1433 (1941).

(6) J. W. Miller and H. H. Anderson, *J. Pharmacol. Exptl. Therap.*, 112, 191 (1954).

(7) (a) All melting points are uncorrected. (b) Analyses performed by Mr. E. Hoffmann and staff.

(8) H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, 70, 3121 (1948).

Anal. Calcd. for $C_{16}H_{26}Cl_2N_2O_2$: C, 55.00; H, 7.50; N, 8.02. Found: C, 54.73; H, 7.37; N, 8.08.

Ethyl 1-(N-methylbenzamido)cyclohexanecarboxylate (II. R = COC_6H_5; R′ = CH_3). To a stirred solution containing 9.2 g. of ethyl 1-(methylamino)cyclohexanecarboxylate, 50 ml. of chloroform, and 10 ml. of pyridine was added dropwise a solution of 10 g. of benzoyl chloride in 10 ml. of chloroform while the temperature was maintained at 10° by means of an ice bath. The solution was refluxed for 2 hr., the solvents were evaporated and the residue was taken up in benzene. The benzene solution was washed with successive portions of 3*N* hydrochloric acid, 20% potassium carbonate and water. The solvent was evaporated and the residue recrystallized from pentane, m.p. 62–63°, yield 6.8 g. (47%).

Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.86; H, 8.01; N, 4.84. Found: C, 70.64; H, 7.97; N, 4.69.

General procedure for the preparation of aminocyclohexane cyano esters and aminocyclohexane diesters. A mixture consisting of molar quantities of II (R = H; R′ = H or CH_3), powdered anhydrous potassium carbonate and a cyano- or carbethoxyalkyl bromide was stirred and heated at 105° over a period of 3 days. Ice water (500 ml.) was added and the two layers were separated. The aqueous layer was extracted with three 500-ml. portions of ether and the extracts were combined with the original organic layer. The solution was dried and distilled. The following compounds were prepared by this method:

Ethyl 1-(3-cyanopropylamino)cyclohexanecarboxylate (II. R = H; R′ = $(CH_2)_3CN$), b.p. 136–139°/0.8 mm., n_D^{28} 1.4668, yield 76%.

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.40; H, 9.35; N, 11.47.

Ethyl 1-(3-carbethoxypropylamino)cyclohexanecarboxylate (II. R = H; R′ = $(CH_2)_3COOC_2H_5$), b.p. 104–106°/0.05 mm., n_D^{29} 1.4581, yield 87%. The base was converted into a hydrochloride, melting after a recrystallization from absolute ether at 140–142°.

Anal. Calcd. for $C_{15}H_{28}ClNO_4$: C, 55.97; H, 8.77; N, 4.35. Found: C, 55.87; H, 8.77; N, 4.32.

Ethyl 1-(3-cyanopropylmethylamino)cyclohexanecarboxylate (II. R = CH_3; R′ = $(CH_2)_3CN$), b.p. 122–125°/0.05 mm., n_D^{27} 1.4732, yield 65%.

Anal. Calcd. for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.37; H, 9.46; N, 11.13.

Ethyl 1-(carbethoxymethylmethylamino)cyclohexanecarboxylate (II. R = CH_3; R′ = $CH_2COOC_2H_5$), b.p. 108–109°/0.06 mm., n_D^{26} 1.4605, yield 93%.

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29; N, 5.16. Found: C, 62.25; H, 9.31; N, 5.34.

Ethyl 1-(3-carbethoxypropylmethylamino)cyclohexanecarboxylate (II. R = CH_3, R′ = $(CH_2)_3COOC_2H_5$), b.p. 125–130°/0.05 mm., n_D^{28} 1.4636, yield 97%.

Anal. Calcd. for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.00; H, 9.92; N, 4.52.

Ethyl 1-(N-3-carbethoxypropylbenzamido)cyclohexanecarboxylate (II. R = COC_6H_5; R′ = $(CH_2)_3COOC_2H_5$). A mixture consisting of 28.5 g. of ethyl 1-(3-carbethoxypropylamino)cyclohexanecarboxylate, 17 g. of benzoyl chloride, and 100 ml. of dry benzene was refluxed for 2 hr. Ethanol (20 ml.) was added and refluxing was continued for another 2 hr. The solution was washed with successive portions of 10% potassium hydroxide, 3*N* hydrochloric acid, and saturated potassium bicarbonate solution. After drying and removal of the solvent the residual viscous oil was distilled, b.p. 200–205°/0.05 mm., n_D^{30} 1.5122, yield 34 g. (78%).

Anal. Calcd. for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.88; H, 7.90; N, 3.72.

Ethyl 1-methyl-1-azaspiro[5.5]undecan-5-one-4-carboxylate (I, R = $COOC_2H_5$) *hydrochloride.* A suspension of 2.45 g. of sodium hydride in 35 ml. of dry benzene was flushed with nitrogen and a solution containing 13.5 g. of ethyl 1-(3-carbethoxypropylmethylamino)cyclohexanecarboxylate, 10 ml. of dry benzene, and 0.2 ml. of anhydrous ethanol was added. The reaction mixture was stirred and refluxed for 10 hr., cooled to 5°, and 6 ml. of glacial acetic acid and 5.5 ml. of water were added successively.

The suspension was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 200 ml. of ether and the solution was dried and saturated with gaseous hydrogen chloride. The precipitate was collected and recrystallized from ether-acetone (4:1), m.p. 177–178°, yield 11 g. (84%).

Anal. Calcd. for $C_{14}H_{24}ClNO_3$: C, 58.02; H, 8.35; N, 4.83. Found: C, 58.22; H, 8.32; N, 4.81.

1-Methyl-1-azaspiro[5.5]undecan-5-one (I. R = H) *hydrochloride.* A solution of 7.2 g. of ethyl 1-methyl-1-azaspiro [5.5]undecan-5-one-4-carboxylate hydrochloride in 40 ml. of 6*N* hydrochloric acid was refluxed for 2 hr. After cooling the solution was made basic with 20% potassium hydroxide. The resulting oil was extracted with several portions of ether and the extract was dried and distilled, b.p. 68–69°/0.06 mm., yield 3.8 g. (84%). The base was converted into its hydrochloride which melted after a recrystallization from ether-ethanol at 217–218°.

Anal. Calcd. for $C_{11}H_{20}ClNO$: C, 60.67; H, 9.26; N, 6.43. Found: C, 60.80; H, 9.11; N, 6.67.

1-Methyl-1-azaspiro[5.5]undecan-5-one (I. R = H) *methiodide.* A solution consisting of 8.4 g. of ethyl 1-methyl-1-azaspiro[5.5]undecan-5-one-4-carboxylate, 50 ml. of absolute ethanol, and 5 ml. of methyl iodide was refluxed for 2 hr. The solution was condensed to one-third of its original volume and 100 ml. of ether was added. The precipitate was filtered and recrystallized from acetone-ether, m.p. 99–102° dec., yield 4.6 g. (33%).

Anal. Calcd. for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.72; H, 7.15; N, 4.36.

1-(2-Hydroxyethylmethylamino)cyclohexanemethanol (III. X = OH). To a stirred suspension of 13.7 g. of lithium aluminum hydride in 600 ml. of ether was added dropwise a solution of 48 g. of ethyl 1-(carbethoxymethylmethylamino)-cyclohexanecarboxylate in 200 ml. of ether. The reaction mixture was refluxed for 12 hr. and the excess hydride destroyed by dropwise addition of 20% sodium hydroxide. The solution was filtered and distilled, b.p. 105–106°/0.03 mm., n_D^{26} 1.5013, yield 23.5 g. (71%).

Anal. Calcd. for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 63.93; H, 11.34; N, 7.66.

1-(2-Chloroethylmethylamino)-1-chloromethylcyclohexane (III. X = Cl) *hydrochloride.* A solution of 14 g. of the diol III (X = OH) in 25 ml. of dry benzene was saturated with gaseous hydrogen chloride, 23 g. of thionyl chloride was added and the mixture was stirred and heated at 55° over a period of 3 hr. The solvent was evaporated under reduced pressure and the residue was dissolved in 20 ml. of absolute ethanol. The solution was refluxed briefly and the solvent was evaporated. The solid residue was recrystallized from ethyl acetate and from benzene, m.p. 118–122°, yield 16.5 g. (85%).

Anal. Calcd. for $C_{10}H_{20}Cl_2N$: C, 46.08; H, 7.72; N, 5.38. Found: C, 45.95; H, 7.65; N, 5.64.

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Synthesis of 3,3′-Thiobis(6-methylphenol)

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In the course of the synthesis of certain inhibitors and polymer stabilizers, we became interested in making diaryl sulfides with phenolic groups *meta* to