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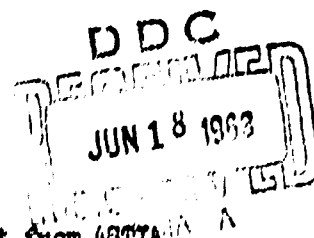
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ANNUAL PROGRESS REPORT
April 1, 1962 - March 31, 1963

By
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PROSPECTIVE ANTIRADIATION AGENTS
DA-119-193-MD-2042



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1. Washington State University
2. Prospective Antiradiation Agents
3. Gardner W. Stacy
4. 11 pages -- June 13, 1963
5. DA-P-153-MD-2049
6. Suggested by: U. S. Army Medical Research and Development Command
Department of the Army
Washington 25, D. C.

DESCRIPTIVE ABSTRACT:

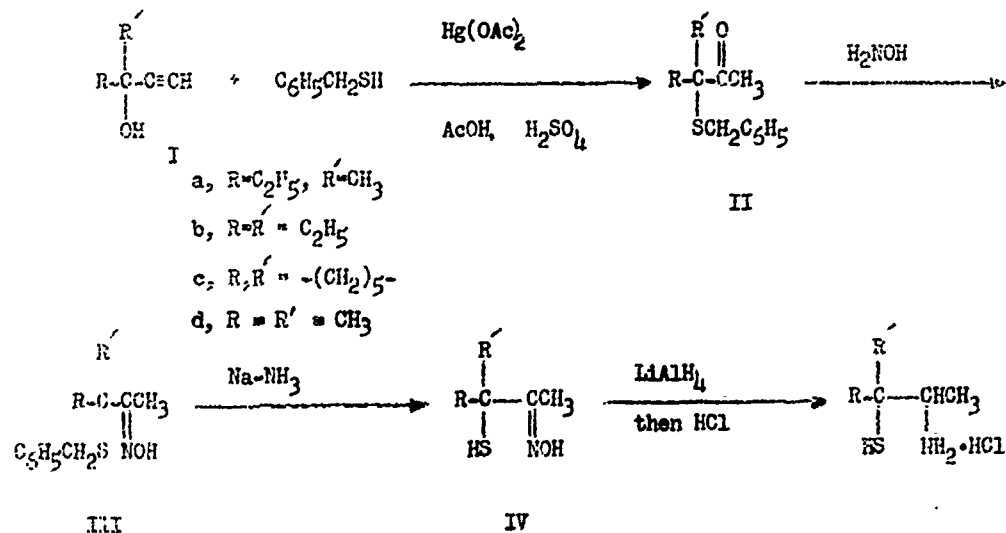
- A. Work completed during the past year involved first the extension of the five-step synthesis by means of which 3-amino-2-methyl-2-butanethiol hydrochloride (Vd) had been prepared. The synthesis showed itself to be quite general, and three additional substituted aminoalkaneethiols were synthesized. These substances and three intermediate crithethiols obtained in the process were tested as antiradiation agents but were not found to be significantly active.
- B. Investigation of possible reaction of acetylene with 1-carbethoxy-3-pyrrolidone (VI) was pursued with the hope of forming an intermediate acetylenic carbinol which would ultimately lead to an aminothiol wherein the amino group would be part of the heterocyclic five-membered ring. Although 1-carbethoxy-3-pyrrolidone was prepared by a three-step procedure, the method was tedious and complicated. Further, in several experiments, the reaction with acetylene failed to materialize; this phase of the research was, therefore, discontinued.
- C. An investigation was made of the possibilities of forming aminothiol from aminoalkenes formed from Schiff bases. Unfortunately, these

intermediates failed to react with thiols to produce the desired sulfide. Therefore, after a reasonable period of experimentation this project was discontinued.

- D. In part A, the synthesis of aminoalkanethiols has been described. These could be considered to be trialkyl-substituted about the amino and thiol functions. It was thought to be also interesting to attempt the synthesis of tetraalkyl-substituted compounds derived from trialkyl-substituted intermediates. Although the tetraethyl compound was of chief interest, the diethyl diethyl compound is being first investigated because of a quantity of the necessary starting material on hand.

Report on Work Completed or in Progress:

A. Three aminoalkanethiols (V a, b, c) similar to Vd previously prepared were obtained by the following synthetic scheme.



Since the previous report, a new catalytic mixture consisting of concentrated sulfuric acid, glacial acetic acid, and mercuric acetate has been developed for the reaction I $\rightarrow$ II and found to give superior yields of II as compared to that previously used involving boron trifluoride. 3-Benzylthio-3-methyl-2-pentanone (IIa) was prepared by reaction of 49.0 g. (0.50 mole) of Ia and 62.0 g. (0.50 mole) of 4-toluenethiol with the aid of a catalytic mixture consisting of 6.4 g. mercuric acetate, 150 ml. of glacial acetic acid, 5.0 g. of 4-toluenethiol, and 5.0 ml. of concentrated sulfuric acid. A 73% yield (78.0 g.) of IIa was obtained, b.p. 75-78° (0.01 mm.), n_D^{25} 1.5418. Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{OS}$: C, 70.23; H, 8.16; S, 11.42.

Found: C, 70.44; H, 8.25; S, 14.52. 3-Benzylthio-3-ethyl-2-pentanone (IIb) was obtained from 56.0 g. (0.50 mole) of ethynylcarbinol Ib, 62.0 g. (0.50 mole) of α -toluenethiol, and a catalytic mixture of 75 ml. of glacial acetic acid, 6.4 g. of mercuric acetate, 5.80 g. of α -toluenethiol, and 2 ml. of concentrated sulfuric acid at 70-80°. A yield of 75.0 g. (74%) resulted, b.p. 82-84° (0.03 mm.), n_{D}^{25} 1.5391, d_4^{25} 1.030. Anal. Calcd. for $C_{14}H_{20}OS$: C, 71.13; H, 8.53; S, 13.57. Found: C, 71.33; H, 8.13; S, 13.36. 1-Acetylcyclohexylbenzylsulfide (IIc) was formed from 50.0 g. (0.40 mole) of 1-ethynylcyclohexanol (Ic) and 50.0 g. (0.40 mole) of α -toluenethiol added to a catalytic mixture consisting of 150 ml. of glacial acetic acid, 6.40 g. of mercuric acetate, 3 ml. of concentrated sulfuric acid, and 5 ml. of α -toluenethiol at a reaction temperature of 70-80°; the yield was 62.5 g. (78%) of a pale yellow oil, b.p. 98° (0.03 mm.), n_{D}^{25} 1.5628, d_4^{25} 1.095. Anal. Calcd. for $C_{15}H_{20}OS$: C, 72.50; H, 8.12; S, 12.90. Found: C, 72.51; H, 8.13; S, 13.14.

Formation of the oximes III was accomplished by well established procedures.

3-Benzylthio-3-methyl-2-pentanone oxime (IIIa) was formed from 10.0 g. (0.045 mole) of IIa, 10.0 g. (0.143 mole) of hydroxylamine hydrochloride and 15.0 g. of sodium acetate in 40 ml. of water; the mixture was stirred for 12 hr. in a steam bath. The product, 9.20 g. (82%) was a thick, viscous oil, b.p. 110-115° (0.03 mm.), n_{D}^{25} 1.5728, d_4^{25} 1.225. Anal. Calcd. for $C_{13}H_{17}NOS$: C, 65.78; H, 8.07; S, 13.51. Found: C, 65.94; H, 7.99; S, 13.58. 3-Benzylthio-3-ethyl-2-pentanone oxime (IIIb) was obtained from a reaction mixture consisting of 24.0 g. (0.089 mole) of the keto sulfide (IIb) 10.0 g. (0.145 mole) of hydroxylamine hydrochloride, and 30 ml. of pyridine which was stirred overnight at room temperature and yielded 20.2 g. (82%) of a pale yellow oil, b.p. 125-128° (0.1 mm.), n_{D}^{25} 1.5552, d_4^{25} 1.225. Anal. Calcd. for $C_{14}H_{21}NOS$: C, 65.89; H, 8.42; N, 5.57. Found: C, 66.06; H, 8.26; N, 5.91. Similarly obtained was 1-Acetylcyclohexylbenzylsulfide oxime (IIIc)

from a solution of 43.0 g. (0.173 mole) of IIc, 20.0 g. (0.29 mole) of hydroxylamine hydrochloride in 50 ml. of pyridine which was stirred for 24 hr. A pale yellow oil was initially obtained but crystallized upon standing overnight; recrystallization from methanol-water yielded 40.0 g. (88%) of white, needle-like crystals, m.p. 125-127°. Anal. Calcd. for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04; S, 12.17. Found: C, 68.55; H, 7.75; S, 12.10.

Removal of the masking benzyl group succeeded by the well known hydrogenolysis procedure using sodium and liquid ammonia, resulting in the formation of α -thioloximes (IV) in good yields. 3-Methyl-3-thiol-2-pentanone oxime (IVa) was obtained by the addition of 8.00 g. (0.35 atom) of sodium metal to a solution of 31.0 g. (0.13 mole) of IIIa in 500 ml. of liquid ammonia. Extraction with ether and subsequent distillation yielded 14.2 g. (74%) of a colorless oil, b.p. 59-70° (0.05 mm.), n_D^{25} 1.4921, d_4^{25} 0.993. Anal. Calcd. for $C_5H_{13}NOS$: C, 48.94; H, 8.89; S, 21.78. Found: C, 48.75; H, 8.74; S, 21.60.

Similarly, 3-Ethyl-3-thiol-2-pentanone oxime (IVb) was obtained from 14.5 g. (0.63 atom) sodium metal added to a solution of 50.0 g. (0.20 mole) of IIb in 700 ml. of liquid ammonia. Anal. Calcd. for $C_7H_{15}NOS$: C, 52.14; H, 9.37; S, 19.88. Found: C, 52.15; H, 9.10; S, 20.10. 1-Acetylcyclohexanethiol oxime (IVc) was obtained in like manner from a solution of 46.0 g. (0.17 mole) of oxime IIc in 500 ml. of liquid ammonia to which 12.0 g. (0.45 atom) of sodium had been added; yield, 17.1 g. (57%) of white crystals, m.p. 99-100°. Anal. Calcd. for $C_8H_{15}NOS$: C, 55.46; H, 8.73; S, 18.50. Found: C, 55.57; H, 8.46; S, 18.41. The three thiol oximes, (IVa, b, c) just described were submitted for test as prospective antiradiation agents.

The reduction of the thiol oximes IV to the desired aminoalkanethiols V was carried out with lithium aluminum hydride. 2-Amino-3-methyl-3-pentanethiol (Va)

was formed by reaction of a 15.0 g. (0.10 mole) of IVa with 3.00 g. lithium aluminum hydride; yield, 6.50 g. (66%), b.p. 55-58° (0.06 mm.), n_D^{25} 1.5003, d_4^{25} 0.998. Anal. Calcd. for $C_6H_{15}NS$: C, 54.08; H, 11.35; N, 10.15. Found: C, 53.95; H, 11.61; N, 10.23.

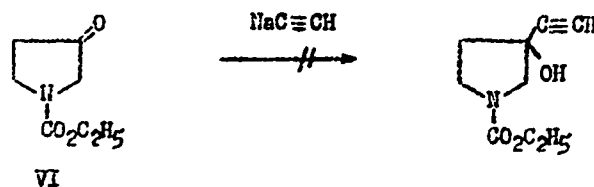
2-Amino-3-ethyl-3-pentanethiol (Vb) was prepared by the action of 2.00 g. (0.05 mole) of lithium aluminum hydride on 8.00 g. (0.05 mole) of IVb; yield, 4.50 g. (62%), b.p. 40-45° (0.03 mm.), n_D^{25} 1.5149, d_4^{25} 1.015. Anal. Calcd. for $C_7H_{17}NS$: C, 57.09; H, 11.64; S, 21.77. Found: C, 57.28; H, 11.51; S, 22.04. The corresponding hydrochloride was prepared from a solution of 1.00 g. (6.8 mmoles) of Vb in 25 ml. of anhydrous ether into which dry hydrogen chloride was introduced; yield, 990 mg. (79%), m.p. 175-176° (dec.). Anal. Calcd. for $C_7H_{18}ClNS$: C, 45.76; H, 9.87; Cl, 19.28. Found: C, 45.92; H, 9.94; Cl, 19.09.

A mixture consisting of 1.00 g. (5.40 mmoles) of Vb and 10 ml. of cyclohexanone was heated until a homogenous solution was obtained. Cooling and the addition of 20 ml. of anhydrous ether gave 5-ethyl-4,5-dimethyl-2-spirocyclohexylthiazolidine hydrochloride as a white precipitate, m.p. 232-234° (dec.). Anal. Calcd. for $C_{13}H_{26}ClNS$: C, 59.16; H, 9.57; S, 12.16. Found: C, 59.02; H, 9.46; S, 12.25.

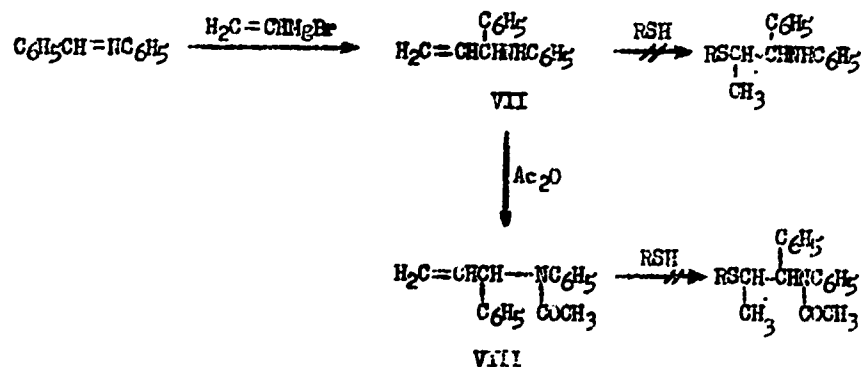
1-(1-Aminoethyl)-cyclohexanethiol hydrochloride (Vc) was formed from 35.0 g. (0.20 mole) of IVc in 100 ml. of tetrahydrofuran and 33.5 g. (0.8 mole) of lithium aluminum hydride in 400 ml. of tetrahydrofuran; yield, 22.0 g. (69%) of a colorless oil, b.p. 85-90° (0.06 mm.). A 1.00 g. (6.30 mole) sample was placed in 20 ml. of anhydrous ether and dry hydrogen chloride was introduced to yield 960 mg. (77%), m.p. 135-136°. Anal. Calcd. for $C_8H_{18}ClNS$: C, 49.11; H, 9.27; Cl, 18.11. Found: C, 48.95; H, 9.39; Cl, 17.93.

The formation of thiazolidine derivatives of these aminoalkanethiols demonstrated conclusively that the amino and thiol groups were on adjacent carbon atoms.

- B. It had been thought that there would be little difficulty in carrying out the reaction between acetylene and 1-carbethoxy-3-pyrrolidone (VI) - this derivative carrying the carbethoxy group on the nitrogen was to be employed as the free pyrrolidone is unstable. The desired intermediate VI could be synthesized in good yield but the procedures involved were unwieldy. Because of this and since reaction of this compound with acetylene failed in a number of experimental attempts, this work was discontinued.



- C. To investigate the addition of thiols to substituted allyl amines or their acyl derivatives, vinylmagnesium bromide was caused to react with N-benzylidenaniline to yield 3-phenylamino-3-phenyl-1-propene (VII)

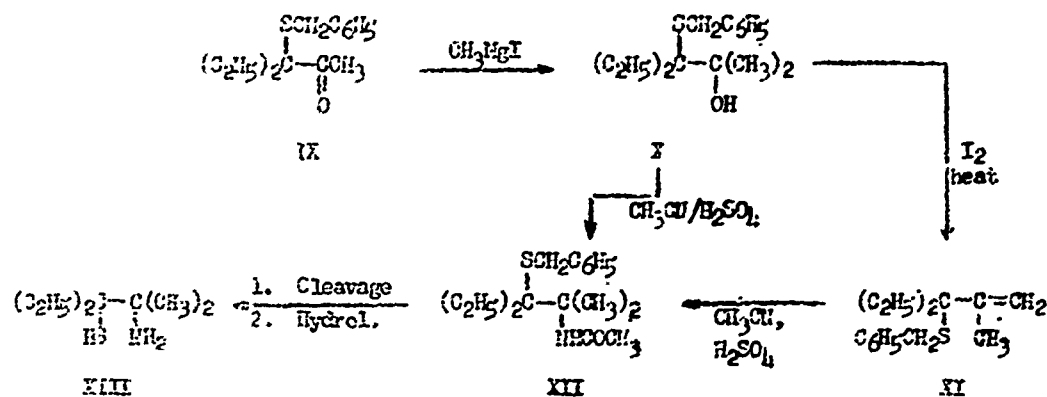


Vinylmagnesium bromide for the preparation of 3-phenylamino-3-phenyl-1-propene (VII) was obtained from 12.16 g. (0.5 g. atom) of magnesium turnings in 130 ml. of dry

tetrahydrofuran, a trace of iodine, and 53.5 g. (0.5 mole) of vinyl bromide in 65 ml. of tetrahydrofuran. To the vinylmagnesium bromide was added 90.6 g. (0.5 mole) of N-benzylideneaniline dissolved in 100 ml. of dry tetrahydrofuran. The mixture was stirred at room temperature overnight and then heated under reflux for 4 hr. The salt was decomposed by pouring it onto a mixture of ice, saturated ammonium chloride and concentrated ammonium hydroxide. After removal of ether, the residue was distilled under reduced pressure; yield 57.5 g. (55%), b.p. 100-101° (0.05 mm.), n_D^{25} 1.6045, d_4^{23} 1.0500. Anal. Calcd. for $C_{15}H_{15}N$: C, 86.09; H, 7.22; N, 6.69. Found: C, 86.45; H, 7.34; N, 6.92. The acetyl derivative VIII was prepared from 500 mg. (2.4 mmoles), 5 ml. of acetic anhydride, and 5 g. of sodium acetate in 25 ml. of water. After recrystallization from cyclohexane, 390 mg. (65%) of colorless crystals were obtained, m.p. 137.5-138°. Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.81; N, 5.57. Found: C, 81.45; H, 6.61; N, 5.40.

When the procedure of Ipatieff [V. N. Ipatieff, N. Pines, and B. S. Friedman, J. Am. Chem. Soc., 80, 2731 (1938)] for addition of thiols to alkenes was followed for either α -toluenethiol or thiolacetic acid, a complete lack of success was experienced. If addition were attempted under pressure with sulfur as a catalyst, again the results were negative. Similar negative results were obtained with the acetyl derivative. Also, neither of these substances would add the elements of water or hydrogen bromide. Further experimentation was therefore abandoned.

- D. From trialkyl-substituted mercaptoethylamines, it seemed to be a natural extension to attempt the synthesis of tetraalkyl-substituted mercaptoethylamines. The transformations contemplated are outlined as follows:



The starting material IX is a readily available intermediate from the synthesis of 2-amino-3-ethyl-3-pentanethiol (Vb). Although tetra-*n*-butylmercaptopyrimidine was of primary interest, XIII was selected as the initial objective as a quantity of IX was available to work with. Methylmagnesium iodide reacted smoothly with IX to yield the hydroxy sulfide X. The olefinic sulfide XI was obtained instead if the reaction mixture was distilled with a trace of iodine. The Ritter reaction with acetonitrile is now being studied in respect to both X and XI as the method of proceeding to the intermediate XII.

3-Benzylthio-3-ethyl-2-methyl-2-pentanol (X) was formed from methylmagnesium iodide, prepared from 10.65 g. (0.075 mole) of methyl iodide in 10 ml. of anhydrous ether added to 1.8 g. (0.075 g. atom) of magnesium turnings in 15 ml. of anhydrous ether, and 11.8 g. (0.05 mole) of 3-benzylthio-3-ethyl-2-pentanone (IX) in 12 ml. of anhydrous ether. After removal of ether, the residual oil was distilled giving 3.60 g. (70%) of a yellow liquid; b.p. 96-98° (0.025 mm.), n_D^{25} 1.5107, d_4^{25} 1.1800. Anal. Calcd. for $\text{C}_{15}\text{H}_{21}\text{OS}$: C, 71.6%; H, 9.22; S, 12.75. Found: C, 71.90; H, 9.31; S, 12.90. 3-Benzylthio-3-ethyl-2-methyl-1-pentene (XI) was produced when a reaction mixture from X was washed with saturated sodium carbonate solution and then distilled under

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reduced pressure in the presence of a trace of iodine to give a 50% yield;
b.p. 78-80° (0.025 mm.), n_D^{25} 1.5338, d_4^{25} 1.0080. Anal. Calcd. for $C_{15}H_{12}S$:
C, 76.86; H, 9.46; S, 13.68. Found: C, 77.03; H, 9.57; S, 13.78.