was obtained. For analysis, a sample was dried at 100° and 0.05 mm.; pK'_a 6.3 (80% DMF) and 6.6 (60% DMF); $\lambda_{max}^{CHCl_3}$ 5.77 μ; λ_{max}^{EtOH} 247 and 295 mμ, ϵ 9150 and 3020 as compared to λ_{max}^{EtOH} 247 and 295 mμ, ϵ 8730 and 3070 for ajmaline.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64; mol. wt., 324.4. Found: C, 73.76, 74.01; H, 7.64, 7.65; N, 8.22; mol. wt. (electrometric titration), 317 ± 20.

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The Identity of Heilpern's "Pinacolylthiourea" and the Preparation of Authentic 2-Thiono-4,4,5,5-tetramethylimidazolidine

BY RALPH SAYRE

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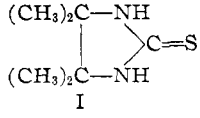
The reaction of aqueous ammonia with a mixture of acetone and carbon disulfide was investigated by Heilpern,[1] who isolated the principal product (his so-called "pinacolylthiourea") as crystals which melted with decomposition at 240–243°. As possible structures for the presumed new compound, to which he erroneously assigned the empirical formula $C_7H_{14}N_2S$, he considered the saturated cyclic thioureas I and II, deciding in favor of the former because permanganate oxidation of the thiourea gave 5,5-dimethylhydantoin (III) as the only product he could isolate and identify. The subsequent literature contains four brief and uninformative references[2] to the compound.



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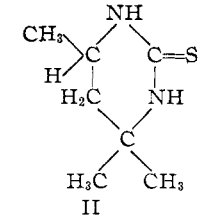

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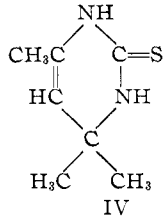

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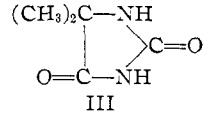
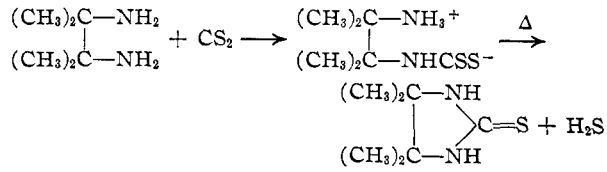


III

In 1946, repetition of Heilpern's preparation of the thiourea gave a product which, after six recrystallizations, melted with decomposition at 254–255°. Its infrared spectrum[3] showed fairly strong absorption at 1700 cm.$^{-1}$, interpreted by Dr. Fred Halverson of these laboratories as showing the presence of a C=C linkage and indicating that the thiourea was probably the tetrahydropyrimidine derivative IV. In verification of this conjecture, an almost identical curve was obtained in measuring the infrared absorption of an unsaturated cyclic thiourea $C_7H_{12}N_2S$, to which structure IV had been assigned by Traube[4] two years prior to Heilpern's publication. This compound, made by Traube's procedure from diacetonamine acid oxalate by reaction with potassium thiocyanate, was also prepared by various other published methods.[5]

Using the procedure by which Heilpern convinced himself of the structure of his "pinacolylthiourea," a pure specimen of 2-thiono-4,4,6-trimethyl-1,2,3,4-tetrahydropyrimidine, prepared by the method of Mathes[5b] and melting with decomposition at 254–255°, was subjected to permanganate oxidation; ring contraction occurred, giving 5,5-dimethylhydantoin as the only crystalline product. Conversely, in order to show the fallacy of Heilpern's assumption that one of the *gem*-dimethyl groups of the postulated symmetrical imidazolidine derivative I undergoes complete oxidation while the other remains intact, authentic 2-thiono-4,4,5,5-tetramethylimidazolidine was made by treating 2,3-dimethylbutane-2,3-diamine with carbon disulfide:



Its infrared spectrum showed no absorption band at 1700 cm.$^{-1}$. Permanganate oxidation of the new compound left both *gem*-dimethyl groups intact, giving a high yield of 4,4,5,5-tetramethyl-2-imidazolidone, which was also prepared by phosgenation of 2,3-dimethylbutane-2,3-diamine. The infrared spectrum of the imidazolidone showed extremely strong absorption at 1700 cm.$^{-1}$, attributable to the carbonyl group.

Experimental[6]

Permanganate Oxidation of IV.—To a well-stirred suspension of 4.69 g. (0.03 mole) of authentic 2-thiono-4,4,6-trimethyl-1,2,3,4-tetrahydropyrimidine in 100 ml. of water, 100-ml. portions of 0.125 *M* potassium permanganate were added at intervals ranging from 10 to 30 minutes, depending on the rate of consumption. After 1200 ml. had been added, it became necessary to heat the mixture and to add the permanganate in smaller portions. A total of 1740 ml. was required to complete the oxidation. The precipitated manganese dioxide was filtered off, and the strongly alkaline filtrate was slightly acidified with sulfuric acid, concentrated by vacuum distillation at about 40°, and finally evaporated

(1) J. Heilpern, *Monatsh. Chem.*, **17**, 229–244 (1896).

(2) W. Herzog, *Oesterr. Chem.-Ztg.*, **24**, 76 (1921); P. C. Ray and R. Das, *J. Chem. Soc.*, **121**, 326 (1922); F. G. Moses, R. W. Hess and R. L. Perkins, U. S. Patent 1,801,319 (1931); W. G. Bywater, D. A. McGinty and N. D. Jenesel, *J. Pharmacol. Expl. Therap.*, **85**, 14 (1945). The thiourea is listed in Beilstein (4th Ed.) as a thioimidazolidone (Vol. XXIV, 12); and a poorly characterized derivative which Heilpern obtained is listed as an imidazoline (Vol. XXIII, 351).

(3) The infrared curves referred to in this paper were obtained in these laboratories under the direction of Dr. R. C. Gore and have been deposited as Document number 4687 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints, or $1.25 for 35 mm. microfilm payable to: Chief, Photoduplication Service, Library of Congress.

(4) W. Traube, *Ber.*, **27**, 277 (1894).

(5) (a) W. P. ter Horst, U. S. Patents 2,131,790 (1938) and 2,234,848 (1941); (b) R. A. Mathes, F. D. Stewart and F. Swedish, Jr., THIS JOURNAL, **70**, 1452 (1948); (c) K. C. Roberts and R. J. Moualim, British Patent 654,609 (1951). Without adducing any evidence that the compound possesses mercaptan-like properties, these chemists have generally formulated it as a 2-mercapto-1,4(or 3,4)-dihydropyrimidine derivative. The present work, besides confirming Traube's statement that it is almost insoluble in aqueous alkali, showed that it does not react with iodine to give a disulfide.

(6) Melting points by capillary method, corrected for stem emergence.

to dryness. The residue was extracted with boiling ethanol, and the filtrate from the insoluble potassium sulfate was evaporated at room temperature, leaving 3.8 g. of colorless semi-crystalline residue. This was taken up in 10 ml. of hot water, which deposited 0.77 g. of well-formed crystals melting at 177–178°. Evaporation of the water from the mother liquor left a transparent gum which could not be induced to crystallize. The infrared absorption curve of the crystalline product was identical with that of an authentic specimen of 5,5-dimethylhydantoin.

2,3-Dimethyl-2,3-dinitrobutane.—This intermediate was prepared from 2-bromo-2-nitropropane and the sodium salt of 2-nitropropane by the method of Seigle and Hass.[7] In a later preparation, this method was modified as follows, so as to combine in a single operation the bromination of 2-nitropropane[8] and the Seigle and Hass condensation. A stirred and cooled mixture of 44.5 g. (0.5 mole) of 2-nitropropane and 84 ml. of 6 *N* sodium hydroxide was half brominated by the dropwise addition of 40.0 g. (0.25 mole) of bromine, and 165 ml. of ethanol was then added. The stirred solution was boiled gently under a reflux condenser for 3 hours, toward the end of which the product began to crystallize. The slurry was poured into 500 ml. of ice-water and filtered, yielding 24.7 g. of 2,3-dimethyl-2,3-dinitrobutane (56% of theoretical).

2,3-Dimethylbutane-2,3-diamine.—The dinitro compound was reduced by the method of Bewad.[9] A slurry of 17.6 g. (0.1 mole) of 2,3-dimethyl-2,3-dinitrobutane in 150 ml. of concentrated hydrochloric acid was vigorously stirred at 50–60° during the gradual addition of 75 g. of 20-mesh granular tin. The solution was boiled for 15 minutes under a reflux condenser, made strongly alkaline by the addition of sodium hydroxide, and steam distilled. All of the diamine came over in the first 350 ml. of distillate, from which the new imidazolidine derivatives could be obtained directly by treatment with carbon disulfide or with phosgene, as described below. In order to isolate the diamine as the free base, the addition of about 100 g. of solid sodium hydroxide to the distillate resulted in the separation of most of it in fairly pure form as a liquid layer. The diamine could also be isolated as its oxalate by neutralizing the distillate with 1 *N* oxalic acid, which caused the rapid formation of fine colorless crystals melting at 323–324°. The yield of oxalate, which was nearly insoluble in alcohol as well as in water, was 15.7 g. (76%). *Anal.*[10] Calcd. for $C_8H_{18}N_2O_4$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.79; H, 9.10; N, 13.44.

2-Thiono-4,4,5,5-tetramethylimidazolidine (I).—The distillate from the reduction of 17.6 g. of 2,3-dimethyl-2,3-dinitrobutane was treated with 10 g. of carbon disulfide, and the mixture was boiled under a reflux condenser for 2 hours, during which hydrogen sulfide was eliminated and a crystalline product began to separate. The resulting slurry was evaporated to about half its initial volume, cooled, and filtered, yielding 9.8 g. of colorless 2-thiono-4,4,5,5-tetramethylimidazolidine (62% of theoretical based on the dinitro compound). The product, recrystallized from ethanol, melted at 252–253°; no decomposition occurred, as shown by the fact that the melt was allowed to solidify several times and could be remelted without change in appearance or behavior. *Anal.* Calcd. for $C_7H_{14}N_2S$: C, 53.12; H, 8.92; N, 17.70; S, 20.26. Found: C, 53.05, 53.17; H, 8.83, 8.81; N, 17.63, 17.50; S, 20.04, 20.33.

It is of interest to note that melting point depressions of only 2–4° were observed when 2-thiono-4,4,6-trimethyl-1,2,3,4-tetrahydropyrimidine melting at 254–255° was mixed in proportions varying from 1:3 to 3:1 with the new compound. 2-Thiono-4,4,5,5-tetramethylimidazolidine appears to be devoid of mercaptan-like properties, as shown by its insolubility in alkali and its failure to undergo oxidation with iodine.

4,4,5,5-Tetramethyl-2-imidazolidone.—A total of 1140 ml. of 0.125 *M* potassium permanganate, added in small portions with stirring and toward the end with heating, was required to oxidize 9.5 g. (0.06 mole) of 2-thiono-4,4,5,5-tetramethylimidazolidine. The colorless filtrate from the precipitated manganese dioxide was neutralized with sulfuric acid and evaporated to incipient crystallization. The slurry was cooled and filtered, yielding 7.23 g. of colorless 4,4,5,5-tetramethyl-2-imidazolidone (84% of theoretical). The compound melted at 288–289°, unchanged after recrystallization from 110 ml. of ethanol. *Anal.* Calcd. for $C_7H_{14}N_2O$: C, 59.12; H, 9.93; N, 19.70. Found: C, 59.19, 59.12; H, 9.94, 9.86; N, 19.68, 19.97.

As confirmation of the structure of this compound, one-half of the distillate from the reduction of 17.6 g. of 2,3-dimethyl-2,3-dinitrobutane was treated with 20 ml. of 5 *N* sodium hydroxide and brought to slight acidity by bubbling phosgene into the stirred solution at a moderate rate. After evaporation to dryness, the residual solid was extracted with 100 ml. of boiling ethanol. Evaporation of the extract left a crystalline residue weighing 3.57 g. (50%). Recrystallization from water gave pure 4,4,5,5-tetramethyl-2-imidazolidone melting at 288–289°.

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(7) L. W. Seigle and H. B. Hass, *J. Org. Chem.*, **5**, 100 (1940). These authors reported a 29% yield of product melting at 208–209°. In the present work, their procedure gave a 59% yield of pure dinitro compound melting at 211–212°.

(8) V. Meyer and J. Tscherniak, *Ann.*, **180**, 116 (1876).

(9) J. Bewad, *Ber.*, **39**, 1232 (1906).

(10) The microanalyses reported were carried out in these laboratories under the direction of Dr. J. A. Kuck.

Application of the Japp–Klingemann Reaction.[1] A New Synthesis of Ornithine

BY D. SHAPIRO AND R. A. ABRAMOVITCH

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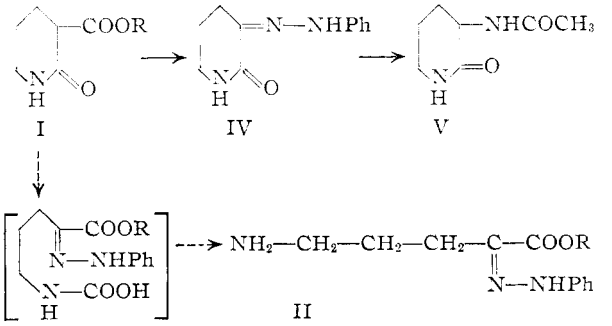
Manske and Robinson[2] showed that the reaction of ethyl cyclopentanone-2-carboxylate with diazotized aniline led to a ring opening with consequent formation of the half ester phenylhydrazone of α-ketoadipic acid. In the course of a study of the Japp–Klingemann reaction with compounds of this type it occurred to us that a similar reaction with 3-carbethoxy-2-piperidone(I)[3] might cause an analogous ring opening, thus giving rise to the phenylhydrazone (II). In fact, the Japp–Klingemann reaction of the ester (I, R = Et) with diazotized aniline gave a tar which did not contain any II or the possible corresponding lactam IV, neither was any carbon dioxide evolution observed. If, however, the ester was first hydrolyzed to the acid (I, R = H), then coupling with benzenediazonium chloride took place readily giving IV in moderate yields, and this, in turn, gave 3-acetamido-2-piperidone (V) on reductive acetylation. Since V has already been hydrolyzed to ornithine[4] these reactions provide a new approach to the latter amino acid.



(1) R. Japp and F. Klingemann, *Ber.*, **20**, 2942, 3284 (1887).

(2) R. H. F. Manske and R. Robinson, *J. Chem. Soc.*, 240 (1927).

(3) N. F. Albertson and J. L. Fillman, THIS JOURNAL, **71**, 2819 (1949).

(4) M. Bergmann and H. Koster, *Z. physiol. Chem.*, **159**, 179 (1926).