was twice recrystallized from methanol giving 1.5 g. (21%) of 2,3,4,5-tetrachlorobiphenyl, m.p. 88–89°. On admixture with an authentic sample[8] the melting point was undepressed.

Anal. Calcd. for $C_{12}H_6Cl_4$: C, 49.30; H, 2.05; Cl, 48.70. Found: C, 49.59; H, 2.39; Cl, 48.41.

Acknowledgment.—The authors express their appreciation to the Hooker Electrochemical Co. for financial assistance during this research.

WETHERILL CHEMISTRY LABORATORY
PURDUE UNIVERSITY
WEST LAFAYETTE, INDIANA

Some Derivatives of 3-Thenaldehyde

BY W. LEWIS NOBLES[1]

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3-Thenaldehyde[2] has been condensed with acetone to yield 4-(3-thienyl)-3-butene-2-one in approximately 60% yield, and this substance has been converted to its thiosemicarbazone.

Previously, it had been demonstrated that the thiosemicarbazone of 4-(2-thienyl)-3-buten-2-one was capable of completely inhibiting the *in vitro* growth of *Mycobacterium tuberculosis* H37RV in a relatively low concentration.[3] Thus, it was thought to be of interest to prepare the corresponding 3-isomer in order that its activity might be compared with that of the 2-derivative. Preliminary results have indicated that the 3-isomer possesses significantly higher *in vitro* antitubercular activity than does the corresponding 2-substituted thiophene derivative. This may be seen from an examination of the contents of Table I.

TABLE I

Organism	Strain	γ/ml. causing complete inhibition: 2-Thienyl	3-Thienyl	Isonicotinic acid hydrazide
M. tuberculosis	H37RV	3.13	0.16	0.024
M. tuberculosis	INH-Resistant	..	.08	...
M. tuberculosis	Streptomycin resistant	..	.08	...

Acknowledgment.—We would like to take this opportunity to acknowledge the support, in part, of this work by the Cyrus M. Warren Fund of the American Academy of Arts and Sciencies and by the American Foundation for Pharmaceutical Education. Also, our appreciation is expressed to Dr. L. M. Long, Parke, Davis and Co., for arranging for the pharmacological evaluation of these compounds.

Experimental[4,5]

4-(3-Thienyl)-3-buten-2-one.—To a mixture of 3-thenaldehyde (prepared according to the modified procedure of Angyal, see footnote 2), 43.5 g. (0.75 mole) of acetone and 30 ml. of water was added slowly, with stirring, 10 ml. of 10% sodium hydroxide solution. During the addition and immediately thereafter, the temperature was maintained at 20–25° by external cooling and constant stirring. After all of the alkali had been added, the mixture was stirred for 2.5 hours at room temperature. Then, cold dilute hydrochloric acid was added until the mixture was acid to litmus. The mixture was then extracted with benzene and the benzene extract dried over anhydrous potassium carbonate. The benzene was distilled at atmospheric pressure. The residue was distilled *in vacuo*. The material which distilled at 148–152° (20–24 mm.) solidified to a yellow mass on standing; yield 24 g. (63%), m.p. 52–53°. *Anal.* Calcd. for C_8H_8OS: C, 63.13; H, 5.29. Found: C, 63.31; H, 5.46.

4-(3-Thienyl)-3-buten-2-one Thiosemicarbazone.—This compound was prepared by the general method described by Nobles and Burckhalter[6] using a few drops of hydrochloric acid to facilitate the reaction. The crude product was recrystallized from 50% ethanol, m.p. 128–129°. *Anal.* Calcd. for $C_9H_{11}N_3S_2$: C, 47.97; C, 4.92. Found: C, 48.15; H, 5.03.

(1) Gustavus A. Pfeiffer Memorial Research Fellow, 1955–1956.

(2) E. Campaigne, R. C. Bourgeois and W. C. McCarthy, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. 33, p. 93, 1955. Our sample was prepared by the procedure of S. J. Angyal, *et al.*, *J. Chem. Soc.*, 1742 (1953), developed for 2-thenaldehyde.

(3) Unpublished results, courtesy of Dr. L. M. Long, Parke, Davis and Co., Detroit, Michigan.

(4) All melting points are uncorrected.

(5) Carbon and hydrogen analyses by Weiler and Strauss, Oxford, England.

(6) W. L. Nobles and J. H. Burckhalter, *J. Am. Pharm. Assoc.*, **42**, 176 (1953).

UNIVERSITY OF MISSISSIPPI SCHOOL OF PHARMACY
UNIVERSITY, MISSISSIPPI

The Synthesis of β-Cyclopropyl-α-aminopropionic Acid

BY JOHN S. MEEK AND JOHN W. ROWE[1]

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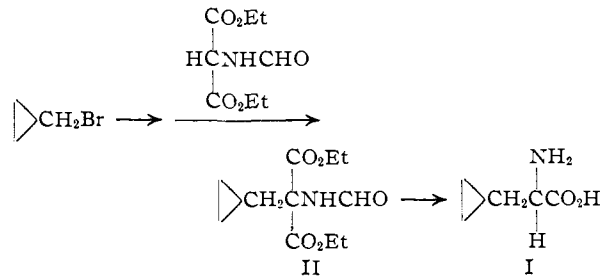
It has been shown that the interchange of a vinylene group and a sulfur atom frequently results in antimetabolitic action.[2] Similarly, it has been found that an acetylene group can also be used in place of a sulfur atom.[3]

In an extension of these exchanges, a cyclopropylene group has been introduced in place of a sulfur atom to form β-cyclopropyl-α-aminopropionic acid (I) to continue the allyl- and propargylglycine series based on cysteine. Compound (I) also may be considered a possible precursor of naturally occurring amino acids in that an organism might open the cyclopropyl ring and produce either norleucine or the essential amino acid leucine.[4]

We have now synthesized I and it has been found to be a potent antagonist to *E. coli* A.T.C.C.



(1) Taken from the Master's thesis of John W. Rowe, University of Colorado, 1952.

(2) (a) K. Dittmer, G. Ellis, H. McKennis and V. du Vigneaud, *J. Biol. Chem.*, **164**, 761 (1946); (b) R. G. Garst, E. Campaigne and H. G. Day, *ibid.*, **180**, 1013 (1949); (c) K. Dittmer, H. L. Goering, I. Goodman and S. J. Cristol, THIS JOURNAL, **70**, 2499 (1948).

(3) (a) H. Gershon, J. S. Meek and K. Dittmer, *ibid.*, **71**, 3573 (1949); (b) H. Gershon, J. Shapira, J. S. Meek and K. Dittmer, *ibid.*, **76**, 3484 (1954).

(4) α-Aminocyclopropylacetic acid likewise might be converted by an organism to the essential amino acid valine. α-Aminocyclopropylacetic acid has been synthesized and did not affect the growth of a wild type of *Neurospora crassa*. However, this amino acid was not tested with any organism as a possible substitute for valine; *cf.* P. H. Lowry, THIS JOURNAL, **74**, 1355 (1952).

strain number 9723. Further testing is in progress.[5]

β-Cyclopropyl-α-aminopropionic acid (I) was synthesized from cyclopropylcarbinyl bromide as shown.

In this synthesis the possibility of rearrangement which would lead to ethyl cyclobutylformamidomalonate or ethyl allylcarbinylformamidomalonate rather than ethyl cyclopropylcarbinylformamidomalonate (II) must be considered. It can be ruled out by the following considerations.

The bromide used in this synthesis,[6] should be mainly cyclopropylcarbinyl bromide. Roberts and Mazur, on adding cyclopropylcarbinol to ice-cooled phosphorus tribromide, obtained a mixture estimated by them to be 65% cyclopropylcarbinyl bromide, 20% cyclobutyl bromide and 6% allylcarbinyl bromide. Our bromide was prepared at about −80° and less rearrangement should have occurred.

The reaction of sodium formamidomalonate with the halides would be expected to involve no rearrangement, and that of the cyclobutyl bromide would be relatively slow.[7] The yield of II was 62% which is considerably greater than would be expected if it were derived from traces of cyclobutyl bromide or allylcarbinyl bromide. II did not show unsaturation and differed in this respect and in its melting point from ethyl allylcarbinylformamidomalonate which was synthesized by an unambiguous route. Hydrolysis of II gave an amino acid whose infrared spectrum showed an absorption band at 9.82 μ suggesting a cyclopropyl group.[8,9] There was no absorption band at 10.1 μ characteristic of monoalkylethylenes[10] and no band at 10.8–11.0 μ as reported present in seven different monosubstituted cyclobutanes.[8] This absorption band ascribed to methylene rocking appears to be shifted to longer wave lengths in certain cyclobutane derivatives where each of the four carbon atoms in the ring bears substituents[11] and also in ethylketene dimer. However, it is present in methylketene dimer.[12]

Experimental

Ethyl Cyclopropylcarbinylformamidomalonate (II).—Seventy-two grams (1 mole) of cyclopropylcarbinol[6,13] and 300 ml. of anhydrous ether were placed in a flask protected from atmospheric moisture, and the solution cooled in a Dry Ice–acetone mixture. Thirty-five ml. (0.37 mole) of phosphorus tribromide was added slowly with stirring and the mixture was allowed to come to room temperature overnight. Ten milliliters of water was added and the ether layer separated, washed with saturated sodium bicarbonate, and dried over Drierite. Fractionation gave cyclopropylcarbinyl bromide,[6] b.p. 101.5–102° (627 mm.), $d^{26.5}_4$ 1.433. Three preparations gave a total yield of 357 g. (80%, with the highest yield being 87.5%).

To a solution of 11.5 g. (0.5 gram atom) of sodium in 500 ml. of absolute alcohol was added 101.5 g. (0.5 mole) of ethyl formamidomalonate,[14] and the solution was refluxed for 5–10 minutes. Any precipitate at this point indicated the solution was not anhydrous, and if the preparation were to be continued, low yields would result. To the solution was added 70.2 g. (0.52 mole) of cyclopropylcarbinyl bromide. The reaction mixture was refluxed for 20 hours on a steam-bath. Sodium bromide precipitated and was removed and then water was added to produce a saturated solution at 50°. After the solution was decolorized, cooling produced 68.2 g. (53%) of white crystals, m.p. 64–66°. Upon recrystallization from 30% ethanol to a constant melting point the product melted at 65–66°. The product did not decolorize neutral potassium permanganate or bromine water.

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44. Found: C, 56.13; H, 7.48.[15]

Ethyl Allylcarbinylformamidomalonate (III).—Allyl chloride was converted with magnesium and paraformaldehyde to allylcarbinol and this in turn was converted with phosphorus tribromide to allylcarbinyl bromide by the method of Juvala.[16] The boiling point of our bromide was 91–92° (610 mm.), $n^{20}D$ 1.4607; lit. 98.5–99° (758 mm.), $n^{20}D$ 1.4621.

The bromide was condensed with ethyl formamidomalonate according to the procedure used to prepare II. From 9.5 g. of bromide, 10.8 g. (56%) of product (III) was obtained, m.p. 94–94.5° after recrystallization from aqueous ethanol. III rapidly decolorized bromine water and neutral potassium permanganate.[17]

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44. Found: C, 55.97; H, 7.37.

III on hydrogenation in ethanol at room temperature and pressure absorbed 97% of the theoretical amount of hydrogen and gave a product melting at 82.5–83°. When mixed with ethyl *n*-butylformamidomalonate[18] prepared from *n*-butyl bromide and ethyl formamidomalonate, m.p. 82–83°, no lowering of the m.p. was observed.

β-Cyclopropyl-α-aminopropionic Acid (I).—Twenty-five and seven-tenths grams (0.1 mole) of the malonate was hydrolyzed by refluxing with 250 ml. of 10% hydrobromic acid for 8 hours. The malonate rapidly went into solution as the formamido group hydrolyzed, but a reaction time of less than eight hours gave incomplete hydrolysis of the ester groups as shown by the fact that an oil separated upon neutralization. The solution was then evaporated to dryness on the water-bath under reduced pressure. The residual solid was taken up in 500 ml. of water and the solution was run through a Duolite A-2 anion exchange column until there was a negative test for bromide ion. Upon concentration, decolorization and crystallization from ethanol, 6.5 g. (50.4%) of amino acid, m.p. 227° dec., was obtained.

The amino acid was a sweetish tasting white solid. It gave a strong ninhydrin test, and a negative test for halogen upon sodium fusion. It did not absorb hydrogen over platinum oxide catalyst at room temperature and pressure. It slowly decolorized bromine water and neutral potassium permanganate, as does glycine due to the amino group. Upon being recrystallized to a constant melting point from ethanol, the melting point rose to 239° (dec. cor.). The Sørensen formol neutralization equivalent was 138 indicating a half mole of water of crystallization. When absolute ethanol was distilled from the amino acid and the amino acid was then dried over phosphorus pentoxide for a week at 95°, the formol titration value dropped slightly, only to immediately return to the value of 138 when recrystallized from 95% ethanol.

Anal. Calcd. for $C_6H_{11}NO_2 \cdot {}^1/_2H_2O$: C, 52.16; H, 8.75;

(5) K. Dittmer, private communication.

(6) J. D. Roberts and R. H. Mazur, THIS JOURNAL, **73**, 2509 (1951).

(7) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5035 (1951).

(8) J. M. Derfer, E. E. Pickett and C. E. Boord, *ibid.*, **71**, 2482 (1949).

(9) V. A. Slabey, *ibid.*, **76**, 3604 (1954).

(10) H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 144.

(11) E. B. Reid and M. Sack, THIS JOURNAL, **73**, 1985 (1951).

(12) E. B. Reid and S. J. Groszos, *ibid.*, **75**, 1655 (1953).

(13) C. G. Bergstrom and S. Siegel, *ibid.*, **74**, 145 (1952).

(14) A. Galat, *ibid.*, **69**, 965 (1947).

(15) Carbon and hydrogen analyses by Galbraith Labs. and Microchemicals Specialty Co.

(16) A. Juvala, *Ber.*, **63B**, 1989 (1930).

(17) III on hydrolysis with 10% hydrobromic acid gave a small amount of an impure halogen-free amino acid, m.p. 218° dec., Sørensen neut. equiv. 149.5. This was possibly allylalanine. The major product was a solid, m.p. 77.5–87.5°, having a high Sørensen neut. equiv. This possibly was impure α-amino-δ-caprolactone formed by acid-catalyzed lactonization of the expected amino acid. The similar formation of α-amino-γ-valerolactone from ethyl allylacetamidomalonate has been reported by H. L. Goering, S. J. Cristol and K. Dittmer, THIS JOURNAL, **70**, 3310 (1948).

(18) S. Minkowitz, Master's thesis, University of Colorado, 1951.

N, 10.15. Found: C, 51.99; H, 8.72; N, 10.02.[19] Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.85. Calcd. for $C_6H_{11}NO_2 \cdot H_2O$: C, 48.96; H, 8.90; N, 9.52.

The phthaloyl derivative was prepared by heating with phthalic anhydride[20] and had a melting point of 140.5–141° after recrystallizing from 50% ethanol.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05. Found: C, 64.71; H, 5.04.

The infrared absorption spectrum of I was determined in mineral oil using sodium chloride prisms and plates in a Perkin–Elmer model 12C infrared spectrometer.[1]

Cyclopropylcarbinylaminomalonic Acid.—Twenty-five and seven-tenths grams (0.1 mole) of the malonic ester was hydrolyzed by boiling with 250 ml. of 15% potassium hydroxide for 6 hours. The hydrolysate was diluted to one liter and run several times through a Duolite C-10 cation exchange column as it was very difficult to remove every trace of potassium from the compound. The solution was then concentrated under reduced pressure and crystallized from ethyl alcohol to give 14 g. of product which decomposed with the evolution of a gas at 210°. *Anal.* Calcd. for $C_7H_{11}NO_4$: N, 8.09. Found: N, 8.12.

The compound gave a weak ninhydrin test, was very soluble in water and insoluble in absolute alcohol. When refluxed with 10% hydrobromic acid, carbon dioxide was evolved and caught in a barium hydroxide trap, and upon purification of the product *via* the Duolite A-2 anion exchange column, Compound I was isolated as determined by the strong ninhydrin test, melting point and mixed melting point.

Acknowledgment.—The authors wish to thank the University of Colorado Council on Research and Creative Work for financial support of this research.

(19) Nitrogen analyses were performed by Mrs. D. E. Ramey, University of Colorado.

(20) J. H. Billman and W. F. Hartung, THIS JOURNAL, **70**, 1473 (1948).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF COLORADO
BOULDER, COLORADO

The Oximes of 9-Anthraldehyde

BY JOHN S. MEEK AND JOHN R. DANN

RECEIVED AUGUST 18, 1955

A 9-anthraldoxime was first reported by Hinkel, Ayling and Beynon[1] as being prepared "readily—by the usual methods" and melting at 187°.[2] Fieser and Hartwell prepared 9-anthraldoxime in 93% yield and obtained a melting point of 165° (I).[3]

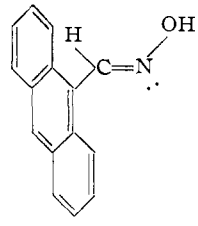
No difficulty was experienced in repeating Fieser and Hartwell's work, in which hydroxylamine hydrochloride neutralized with sodium carbonate was allowed to react with 9-anthraldehyde.

When hydroxylamine hydrochloride was used in 50% ethanolic pyridine[4] an oxime melting at 218–220° (II) was obtained. This compound could also be made by heating I in ethanol at 75° in the presence of a trace of hydrochloric acid. Compound I could be dissolved in hot 5% sodium hydroxide and reprecipitated with hydrochloric acid. Only a trace of II dissolved when heated on a steam-bath for a half-hour with 5% sodium hydroxide.

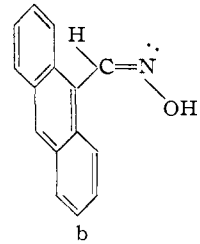
When compound I was warmed with acetic anhydride for 10 minutes the acetate was formed. Similar treatment of II gave 9-cyanoanthracene.

When I and allyl chloride were warmed with sodium hydroxide in aqueous ethanol a yellow compound presumably the O-allyl derivative (III) was formed. II upon similar treatment gave some orange colored resin and 9-cyanoanthracene.

On the basis of the above evidence I is believed to be *syn*-9-anthraldoxime (a) and II the *anti* isomer (b).



a



b

anti Forms of aldoximes upon treatment with a dehydrating agent of any kind generally lose water to yield a nitrile[5a] and it is to be noted that acetic anhydride and sodium hydroxide did convert II to a nitrile under conditions which convert I to the acetate and O-allyl derivatives. The *syn* form usually has the lower melting point and a higher ionization constant[5b] which again is in accord with our assignment of structures. The oxime with the more hindered group as in b should be more difficultly soluble in base since the resulting negative ion would be harder to solvate.

Compound I gave an allyl derivative with allyl chloride and base while II did not. This may again be due to the lack of salt formation with the less acidic oxime. The fact that the allyl derivative was yellow showed that the compound was an anthracene derivative and not an ethanoanthracene resulting from an intramolecular Diels–Alder reaction. If the O-allyl compound was derived from structure b, it should easily undergo an intramolecular Diels–Alder reaction and probably not be isolable. If III were derived from structure a, it could not give an intramolecular Diels–Alder reaction but at best an intermolecular reaction leading to a dimer, trimer or polymer. When III was heated at 200° for 10 minutes some III was recovered and an intractable oil was obtained.

(1) L. E. Hinkel, E. E. Ayling and J. H. Beynon, *J. Chem. Soc.*, 339 (1936).

(2) This melting point for an oxime of 9-anthraldehyde has not been reported again in the literature. Hinkel, Ayling and Beynon report that after crystallizing 9-anthraldehyde, m.p. 105°, in the light it melted over a range up to 135°. It is not likely that they used this material containing the photodimer to prepare their oxime, m.p. 187°. The photodimer of 9-anthraldehyde melts at 187° also according to F. D. Greene, S. L. Misrock and J. R. Wolfe, Jr., THIS JOURNAL, **77**, 3852 (1955). Greene in a private communication reported that his group has not yet made the oxime of this dimer and their preparation of the oxime of 9-anthraldehyde gave 88% of I with a trace of higher melting material, possibly our oxime, m.p. 220°.

(3) L. F. Fieser and J. L. Hartwell, THIS JOURNAL, **60**, 2555 (1938).

(4) Two usual methods for preparing oximes are given by R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202. The first of these uses sodium hydroxide instead of sodium carbonate and less alcohol, but otherwise resembles Fieser and Hartwell's method. The second procedure using pyridine and ethanol is the one leading to our oxime.

(5) (a) E. F. Degering, "An Outline of Organic Nitrogen Compounds," University Lithoprinters, Ypsilanti, Michigan, 1945, p. 182; (b) p. 175.