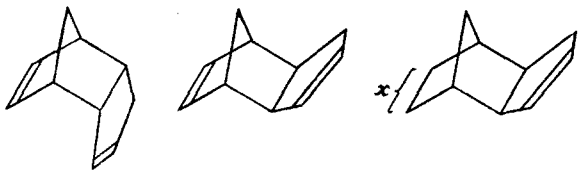
NOTES

exo-Dicyclopentadiene

By Paul D. Bartlett and Irving S. Goldstein

It was discovered by Bruson and Riener[1] that ordinary dicyclopentadiene (I) on addition of hydrogen chloride and other reagents is converted by rearrangement into a set of products (III) later shown[2] to be derived from the *exo*-isomer of dicyclopentadiene (II). The presence of this isomer in heated dicyclopentadiene was established by Alder and Stein,[3] who characterized it by means of its phenyl azide derivative and established its configuration by relating it to the well-studied isomers of the addition product of maleic anhydride to cyclopentadiene.



I II III

The isolation of *exo*-dicyclopentadiene, however, was not successfully accomplished. It was of interest to us to isolate this missing member of the series, in view of the great availability of its isomer and of the many hundreds of its derivatives made available by the method of Bruson and Riener.

exo-Dicyclopentadiene (II) was obtained in 57% yield by the reaction of alcoholic potassium hydroxide with the product of addition of hydrogen iodide to *endo*-dicyclopentadiene. The product boils at 170–172° at 763 mm. and at 51–53° under 12 mm. pressure. It has d_{20} 0.977 and $n^{25}D$ 1.5070. It does not solidify at 0°. It adds hydrogen chloride and (in the presence of sulfuric acid) water, less cleanly than the *endo*-isomer, yielding the same product as the *endo*-isomer in each case. It reacts with phenyl azide, apparently more vigorously than the *endo*-isomer, to yield a derivative melting at 123–124°.

Experimental

Iodo-dihydro-*exo*-dicyclopentadiene[1] was obtained in a yield of 97 g. (44%) from six hours of stirring on the steam-bath of 110 g. of ordinary (*endo*) dicyclopentadiene with 227 g. of 47% hydriodic acid. The product was distilled at 8–9 mm. and the fraction boiling from 120–130° was taken.

exo-Dicyclopentadiene.—To 97 g. of iodo-dihydro-*exo*-dicyclopentadiene was added a solution of 50 g. of potassium hydroxide in 200 cc. of 95% ethyl alcohol. The mixture was heated under reflux on a steam-bath for twenty-four hours, then diluted with water and extracted with ether. The ether extract was dried with calcium chloride and distilled, yielding a fraction of 28.5 g. (57% yield) boiling at 43–46° under 6–7 mm. pressure. On redistillation the fraction boiling at 51–53° at 12 mm. was retained. This boiled under atmospheric pressure (763 mm.) at 170–172° and did not solidify at 0°. It decolorized bromine water and permanganate solution. It had $n^{25}D$ 1.5070 and d_{20} 0.977. The original distillation, continued at 5 mm., yielded 16.5 g. of a light yellow oil boiling from 95 to 101° and having an odor like that of hydroxydihydro-*exo*-dicyclopentadiene.

Reaction of *exo*-Dicyclopentadiene with Sulfuric Acid.—Five grams of *exo*-dicyclopentadiene and 15 g. of 25% sulfuric acid were heated on the steam-bath with stirring for five hours. After dilution, extraction with ether, washing with alkali, drying, and distillation there was recovered about 2 g. of starting material and 2 cc. of a colorless viscous oil with a very sweet odor. This product yielded a phenylurethan which, after recrystallization from alcohol, melted at 163–165° alone and at 162–165° when mixed with the phenylurethan of authentic hydroxydihydro-*exo*-dicyclopentadiene.

Reaction with Hydrochloric Acid.—Five grams of the *exo*-dicyclopentadiene and 10 cc. of 37% hydrochloric acid were stirred for five hours on the steam-bath. The mixture turned black. The ether extract was washed with alkali, dried, and distilled, yielding almost 5 cc. of a colorless oil boiling under 10 mm. pressure at 96–98° and having $n^{25}D$ 1.5206. Chlorodihydro-*exo*-dicyclopentadiene[1] boils under 12 mm. pressure at 100–102°, with $n^{25}D$ 1.5208. The compound gave slight precipitation of potassium chloride after a day on the steam-bath with alcoholic potassium hydroxide.

Reactions of *exo*- and *endo*-Dicyclopentadienes with Phenyl Azide.—To a 3-g. sample of *exo*-dicyclopentadiene and a similar sample of the *endo* isomer, 2 cc. of phenyl azide was added. After a few minutes the solutions grew warm, the warming being more marked with the *exo* than with the *endo* form. The reaction was moderated by surrounding with water. After standing overnight the flasks both contained crystal cakes. After three recrystallizations from ethanol, in which the *exo* derivative was the more soluble of the two, and decolorization with charcoal, the phenyl azide derivative of the *endo* isomer was obtained as white needles melting at 128–129° and that of the *exo* isomer as white prisms melting at 123–124°. The mixture of the two melted at 95–105°. Alder and Stein[3] report the melting points of both the *endo* and *exo* derivatives as 127–128°.

In a second preparation of the *exo* derivative it was obtained in a yield of 80.6% from *exo*-dicyclopentadiene.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82. Found: C, 76.15; H, 6.48.

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(1) Bruson and Riener, This Journal, **67**, 723, 1178 (1945).

(2) Bartlett and Schneider, *ibid.*, **68**, 6 (1946); Bruson and Riener, *ibid.*, **68**, 8 (1946).

(3) Alder and Stein, *Ann.*, **594**, 219 (1933).

The Synthesis of Some New Pteridines

By Gertrude B. Elion and George H. Hitchings

The condensation of 4,5-diaminopyrimidines with di-carbonyl reagents, such as diketones,[1] dicarboxylic acids[2] and α-keto-esters[3] are known

(1) Kuhn and Cook, *Ber.*, **70**, 761 (1937).

(2) Purrmann, *Ann.*, **544**, 182 (1940).

(3) Purrmann, *ibid.*, **548**, 284 (1941).

methods for the synthesis of pteridines. Oxomalonic ester condenses with 2,4,5-triamino-6-hydroxypyrimidine to form isoxanthopterin-6-carboxylic acid and xanthopterin-7-carboxylic acid. In *N* acetic acid the former isomer is obtained in 85% yield; in 2 *N* sulfuric acid the yield of this isomer is only 29% and, in addition, 42% of xanthopterin-7-carboxylic acid is formed.[3]

Both 6-methylisoxanthopterin and 7-methylxanthopterin have now been prepared by condensing 2,4,5-triamino-6-hydroxypyrimidine with pyruvic acid. The formation of the xanthopterin derivative is favored both in 2 *N* sulfuric acid and in dilute acetic acid; the isoxanthopterin derivative is formed in poor yield only during the condensation in acetic acid. The two isomers are separable by their different solubilities in hot 2 *N* hydrochloric acid and are distinguishable by their ultraviolet absorption spectra.

A new pyrimidine, 2-mercapto-4,5-diaminopyrimidine, was synthesized and used as an intermediate in the preparation of 2-mercaptopteridine. Isay[4] attempted to reduce 2-chloro-4-amino-5-nitropyrimidine with hydrogen sulfide without success. However, it was found that an excess of potassium hydrosulfide reduces the nitro group and simultaneously replaces the chlorine by a sulfhydryl group. The 2-mercapto-4,5-diaminopyrimidine was condensed with glyoxal to give 2-mercaptopteridine.

2-Mercapto-4,6,7-trihydroxypteridine was synthesized by the condensation of 2-mercapto-4,5-diamino-6-hydroxypyrimidine with oxalic acid. Both mercaptopteridine derivatives were found by analysis to contain water of crystallization which is not lost at 140°. Water of crystallization which is not lost on heating is not uncommon among purine derivatives (*e. g.*, refs. 5, 9). Since the physical properties and ultraviolet absorption spectra of the mercapto compounds are consistent with the pteridine structure and differ from those of substituted pyrimidines one is justified in assuming closure of the pyrazine ring to have occurred.

Experimental

7-Methylxanthopterin.—Two and one-half grams of 2,4,5-triamino-6-hydroxypyrimidine sulfate monohydrate[7] and 2 g. of pyruvic acid were boiled in 200 ml. of 2 *N* sulfuric acid for one hour, cooled and the undissolved crystalline material filtered off (0.55 g.). The filtrate was heated to 90° and brought to about *p*H 6. The orange-brown precipitate was recrystallized twice by solution in 250 parts of hot 2 *N* hydrochloric acid, treatment with carbon and neutralization with ammonium hydroxide. On slow cooling, bunches of microscopic orange-brown crystals were formed; yield, 1.48 g. (75.8%). The compound does not melt and is insoluble in organic solvents and in hot water. The crystals contain one-half mole of water of crystallization, which is lost at 130°.

Anal. Calcd. for $C_7H_7N_5O_2 \cdot {}^1/_2H_2O$: C, 41.58; H, 3.96; H_2O, 4.45. Found: C, 42.07; H, 4.14; H_2O, 4.49.

6-Methylisoxanthopterin.—Two and one-half grams of 2,4,5-triamino-6-hydroxypyrimidine were dissolved in 200 ml. of hot 5% aqueous acetic acid containing 2 ml. of pyruvic acid. The solution was brought to a boil and then permitted to stand at room temperature for several hours. A copious orange precipitate began to form in a few minutes. After standing overnight at 10°, the precipitate was filtered off, washed with water and alcohol and dried *in vacuo*. The crude product (2.38 g.) was dissolved in 150 ml. of 0.25 *N* sodium hydroxide solution, treated with carbon and filtered into 250 cc. of boiling 2 *N* hydrochloric acid. A light-colored amorphous precipitate formed, leaving an orange-colored supernatant liquid. Re-solution and precipitation in the same way resulted in a pale pink product, weighing 0.35 g. (10%), and having no melting point. This compound closely resembles isoxanthopterin in color and insolubility in hot mineral acids.

Anal. Calcd. for $C_7H_7N_5O_2$: C, 43.52; H, 3.63. Found: C, 43.42; H, 3.35.

By neutralization of the orange-colored acidic filtrates from the purification of 6-methylisoxanthopterin, 1.43 g. (42%) of 7-methylxanthopterin was obtained.

2-Mercapto-4,5-diaminopyrimidine.—A mixture of 5 g. of 2-chloro-4-amino-5-nitropyrimidine[4] and 150 ml. of *N* potassium hydrosulfide solution was heated on the steam-bath for two and one-half hours. The solution was filtered hot to remove a small amount of sulfur and the filtrate was acidified with acetic acid. The crude yellow precipitate was recrystallized from 700 ml. of hot water. After cooling, fluffy yellow needles formed slowly (1.9 g.). Evaporation of the mother liquors to 200 ml. yielded another 0.65 g. of product. Recrystallization from 250 parts of hot water, using carbon, gave white needles, darkening at 230° and decomposing at 250°.

Anal. Calcd. for $C_4H_6N_4S$: C, 33.80; H, 4.22. Found: C, 33.84; H, 4.27.

2-Mercaptopteridine.—A solution of 1.42 g. of 2-mercapto-4,5-diaminopyrimidine in 400 ml. of hot water and 1 g. of glyoxal (as 35% commercial solution) was boiled for fifteen minutes; orange prisms precipitated on cooling. After recrystallization from 400 ml. of water, the yield was 0.95 g. (52%), dec. 200°–205°. The product crystallizes with 1 mole of water, which is not lost at 140° after four hours.

Anal. Calcd. for $C_6H_4N_4S \cdot H_2O$: C, 39.60; H, 3.26. Found: C, 39.61; H, 3.23.

2-Mercapto-4,6,7-trihydroxypteridine.—A finely divided mixture of 0.5 g. of 2-mercapto-4,5-diamino-6-hydroxypyrimidine[8] and 2.5 g. of oxalic acid was heated to 140°. A slight vacuum was applied and the temperature was raised gradually to 260°, where it was maintained for ten minutes. The reaction mixture was dissolved in 85 ml. of 0.3 *N* sodium hydroxide solution, treated with carbon and filtered into 50 ml. of hot 2 *N* hydrochloric acid. The yellow precipitate was recrystallized by the same procedure. Yield was 0.4 g. (60%). The compound crystallizes with 1 mole of water, which is not lost at 140° after eight hours; it has no melting point.

Anal. Calcd. for $C_6H_4N_4O_3S \cdot H_2O$: C, 31.30; H, 2.60. Found: C, 31.51; H, 2.64.

Ultraviolet Absorption Spectra.—The spectra of the new pteridines were determined in 0.1 *N* hydrochloric acid

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA AT *p*H 1.0

Compound	Absorption maxima in Å.	
Xanthopterin	2300, 2600	3520
7-Methylxanthopterin	2320, 2700	3580
Isoxanthopterin	2880	3420
6-Methylisoxanthopterin	2900	3360
2-Mercaptopteridine	2700	3150
2-Mercapto-4,6,7-trihydroxypteridine	2400	3140

(4) Isay, *Ber.*, **39**, 250 (1906).
(5) Fischer, *ibid.*, **30**, 2246 (1897).
(6) Kenner, Lythgoe and Todd, *J. Chem. Soc.*, 656 (1944).
(7) Traube and Dudley, *Ber.*, **46**, 3839 (1913).
(8) Traube, *Ann.*, **331**, 64 (1904).

with the Beckmann spectrophotometer. The absorption maxima are given in Table I, together with those of xanthopterin and isoxanthopterin determined in the same way.

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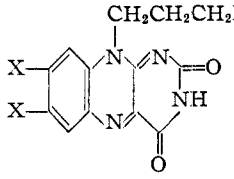
Basically-substituted Isoalloxazines

BY HOWARD BURKETT

The structural similarity of atebrin to riboflavin suggested the synthesis of basically-substituted isoalloxazine derivatives, such as I, II and III, as possible antimalarials.



I, X = CH_3—
II, X = CH_3O—
III, X = Cl—

After this work was begun, other series of compounds very closely related to these were reported.[1,2,3] As a result the preparation of related compounds which had been planned was not carried out. The synthesis of compound III was attempted using a procedure similar to that employed for I and II and also according to the method of Kuhn and Weygand,[4] in which acetic acid served as the solvent and boric acid as the catalyst. That the product in very dilute solution gave a yellow-green fluorescence, typical of isoalloxazines, would indicate that the desired product was present, but the analyses indicated considerable contamination and cast some doubt that the expected compound was obtained. Consequently, this product was not submitted for biological testing and it is not reported in this note.

Compounds I and II were devoid of antimalarial activity, when tested on ducks infected with *Plasmodium lophurae*.

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Experimental

7,8-Dimethoxy-10-(γ-diethylaminopropyl)-isoalloxazine Hydrochloride.—Four grams of 4,5-dinitroveratrole[5] was mixed with 4 ml. of γ-diethylaminopropylamine and 5 ml. of ethanol. After the mixture had refluxed for twenty hours, it was poured into water and acidified with hydrochloric acid. This solution was extracted with ether. The aqueous solution was made basic with sodium hydroxide and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered and saturated with anhydrous hydrogen chloride, forming an oily precipitate of crude 4-nitro-5-(γ-diethylaminopropylamino)-veratrole hydrochloride,[6] which could not be made to crystallize. The hydrobromide, sulfate and free-base could not be obtained in solid form and the base could not be distilled. Consequently, the oily hydrochloride was dissolved in 40 ml. of methanol and hydrogenated at atmospheric pressure and room temperature, using 0.10 g. of Adams platinum oxide catalyst. After the catalyst had been removed by filtration, the methanol was evaporated under reduced pressure with slight warming. Twenty milliliters of methanol was added and again evaporated. Ether was added to the residue and the mixture was saturated with anhydrous hydrogen chloride. After the ether had been decanted, the oil which remained was dissolved in 40 ml. of boiling methanol and 2.5 g. of alloxan monohydrate in 15 ml. of methanol was added. After refluxing for thirty minutes, the mixture was cooled and filtered. Recrystallization of the yellow solid from a water–acetone solution gave 1.04 g. (13.1%) of product melting at 220–222° with decomposition.

Anal. Calcd. for $C_{19}H_{25}N_5O_4 \cdot HCl \cdot 2H_2O$: C, 49.70; H, 6.58; N, 15.25. Found: C, 49.76; H, 6.22; N, 15.70.

4-Nitro-5-(γ-diethylaminopropylamino)-*o*-xylene.—Three grams of 4,5-dinitro-*o*-xylene,[7] 4 ml. of γ-diethylaminopropylamine and 8 ml. of ethanol were refluxed on the steam-bath for four days. The reaction mixture was cooled, poured into water, acidified with concentrated hydrochloric acid and extracted with ether. In a short time, as the dissolved ether evaporated spontaneously from the aqueous solution, yellow needles precipitated. Filtering and washing with a small amount of water yielded 2.89 g. of product melting at 211–212.5°.

Anal. Calcd. for $C_{15}H_{25}N_3O_2$: C, 57.00; H, 7.99; N, 13.33. Found: C, 56.73; H, 8.03; N, 13.17.

Evaporation of the filtrate to two-thirds of its original volume and cooling yielded an additional 0.4 g. of slightly less pure product, making the total yield 3.29 g. (77%).

7,8-Dimethyl-10-(γ-diethylaminopropyl)-isoalloxazine Hydrochloride.—Treatment of the 4-nitro-5-(γ-diethylaminopropylamino)-*o*-xylene in the same way as the 4-nitro-5-(γ-diethylaminopropylamino)-veratrole hydrochloride was treated above, yielded 37.5% of a yellow, crystalline product melting at 289–289.5° with decomposition.

Anal. Calcd. for $C_{19}H_{25}N_5O_2 \cdot HCl \cdot 2.5H_2O$: C, 52.20; H, 6.86; N, 16.01. Found: C, 52.26; H, 6.66; N, 16.23.

(1) Adams, Weisel and Mosher, THIS JOURNAL, **68**, 883 (1946).
(2) King and Acheson, *J. Chem. Soc.*, 681 (1946).
(3) Kipnis, Weiner and Spoerri, THIS JOURNAL, **69**, 799 (1947).
(4) Kuhn and Weygand, *Ber.*, **68**, 1282 (1935).
(5) Prepared according to the method of Vermeulen, *Rec. trav. chim.*, **48**, 969 (1929).
(6) The procedure for the synthesis of this compound has been discussed by Parijs, *Rec. trav. chim.*, **49**, 45 (1930), and by Kipnis, Weiner and Spoerri, THIS JOURNAL, **66**, 1446 (1944). The latter authors give other references to applications of this reaction.
(7) Prepared according to the method of Crossley and Renouf, *J. Chem. Soc.*, **95**, 212 (1909).

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The Reduction of Allylic Quaternary Ammonium Bromides

BY DAVID R. HOWTON

In connection with other work, we have studied the reduction of 2-cyclohexenyltrimethylammonium bromide (I). The catalytic hydrogenation of I at room temperature and atmospheric pressure over Adams platinum, Raney nickel, palladium-on-barium-sulfate, or palladium-on-charcoal proceeds with the uptake of more than one molecular equivalent of hydrogen and the forma-