AMINO ACIDS

X. PREPARATION AND CHEMISTRY OF 2-(ω-CARBOXYALKYLAMINO)-DIHYDROTHIAZINES, -TETRAHYDROPYRIMIDINES, AND -IMIDAZOLINES[1,2]

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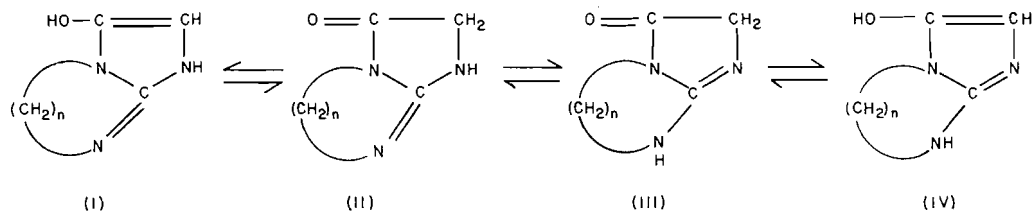
ABSTRACT

The preparation and properties of 3-keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole, 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine, and 4-keto-2,3,6,7,8,9-hexahydro-4(H)-pyrimido(1,2-*a*)pyrimidine are described. The first two bicyclic systems possess active methylene groups in position 2 and they are oxidized to indigo-type dyes.

INTRODUCTION

The bicyclic compounds 3-keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole* and 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine* were previously described (1). It has now been found that the original melting points given for these bicyclic compounds and their picrates are in error. Both of these compounds are readily oxidized and the presence of oxidation products in the original preparations is undoubtedly responsible for the high melting points previously reported. Both 3-keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole and 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine may exist in the tautomeric forms I–IV. The presence of the pentad



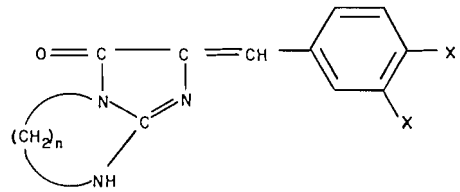
(I) (II) (III) (IV)

n = 2 or 3

system —C=N—CH_2—C=O is responsible for the mobility of the hydrogens at C_2. Further proof of the presence of an active methylene group was obtained by condensing these bicyclic compounds (I, n = 2 and 3) with benzaldehydes to form the corresponding 2-benzylidene derivatives (V).

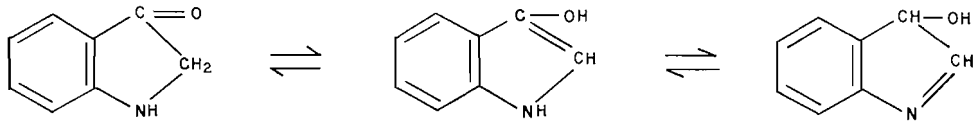
A comparison of the tautomeric structures I–IV with indoxyl tautomeric structures VI–VIII indicates that the bicyclic compounds (I–IV, n = 2 and 3) would be expected to oxidize to indigo-type dyes, and the residues from the sublimation of the crude preparations of these bicyclic compounds did have typical dye properties. The dark blue residue from 3-keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole gave a deep blue solution

[1]*Contribution No. 34.*
[2]*Amino Acids. IX, J. Org. Chem.* **23**, *1973 (1958).*
**Named in accordance with the rules on nomenclature of fused ring compounds, The Ring Index, Am. Chem. Soc. 2nd ed. 1960. These compounds were referred to as 3-keto-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole and 3-keto-Δ⁵-hexahydro-1,4,8-pyrimidazole respectively in reference 1.*



(V)

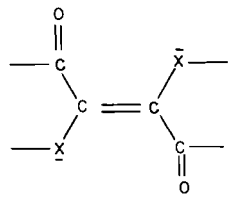
n = 2 or 3
X = H or Cl



(VI) (VII) (VIII)

on dissolving in concentrated hydrochloric acid while the residue from 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine gave a wine-red acid solution. These highly colored materials possess high melting points and are very insoluble in the common organic solvents.

Lüttke's (2) molecular orbital calculations and studies on indigo, selenoindigo, thioindigo, etc., have demonstrated that the benzene nucleus is not necessary for the development of indigoid characteristics such as light absorption. The ring-free chromophore IX

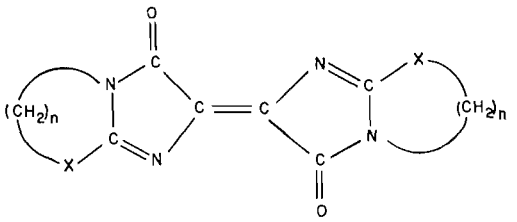


(IX)

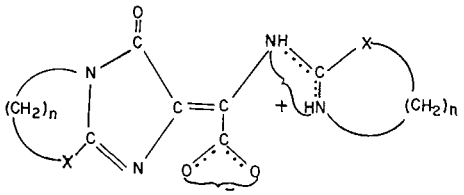
X = NH or S

with the double, crossed auxochrome–antiauxochrome groups on a common —C=C— group is considered to be the simplest system which will exhibit the characteristic properties of indigo-type dyes. Thus the formation of dyes from the above bicyclic systems II is understandable.

When 2-carboxymethylamino-Δ^2-dihydro-1,3-thiazine was prepared by refluxing glycine and 2-methylmercapto-Δ^2-dihydro-1,3-thiazine in aqueous methanol, a deep blue-black metallic dye was formed as a by-product. It might be expected that this dye as well as those from compounds II, $n = 2$, and II, $n = 3$, would possess a structure X similar to indigo. However, the analytical values agree with structure XI. This problem of structure is still under investigation.



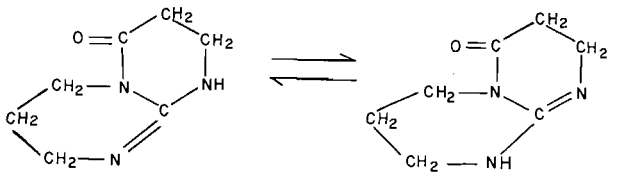
(X)



(XI)

DISCUSSION

The three bicyclic derivatives, 3-keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole (II, $n = 2$), 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine (II, $n = 3$), and 4-keto-2,3,6,7,8,9-hexahydro-4(H)-pyrimido(1,2-*a*)pyrimidine (XII), have been prepared by an improved procedure. These compounds were finally purified by sublimation *in vacuo* under nitrogen. Special care was required in the isolation of compound XII,

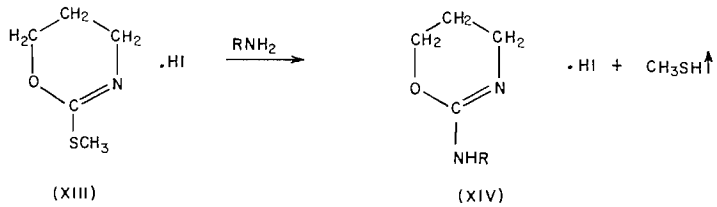


(XII)

which hydrolyzed extremely rapidly to the parent acid, 2-(2-carboxyethylamino)-Δ^2-tetrahydropyrimidine.

An attempt to prepare an analogous bicyclic compound from 2-methylmercapto-5,6-dihydro-4(H)-1,3-oxazine (XIII) and glycine was unsuccessful. This oxazine derivative was not very reactive in comparison with 2-methylmercapto-2-imidazolines (3) and 2-methylmercapto-2-thiazolines (4). After prolonged heating of compound XIII with benzylamine and α-naphthylmethylamine only small yields (10–13%) of the respective 2-benzylamino- (X, R = C_7H_7) and 2-α-naphthylmethylamino-5,6-dihydro-4(H)-1,3-oxazine (X, R = $C_{11}H_9$) were obtained.

Several methods were investigated for the preparation of 3,4,5,6-tetrahydro-2(H)-1,3-oxazine-2-thione. Two of these gave the desired compound in approximately 34% yield.



(XIII) (XIV)

On the other hand the procedure used by Fisher (5) for the preparation of 4,4,6-trimethyl-2-thio-tetrahydro-1,3-oxazine gave a 77% yield of 1,3-di-(3-hydroxypropyl)-thiourea and a 20.5% yield of potassium 3-hydroxypropyldithiocarbamate. 1,3-Di-(3-hydroxypropyl)-thiourea was also obtained when 3-amino-1-propanol was heated with carbon disulphide in ethanol for several hours.

3-Keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole (II, $n = 2$), on being heated under reflux with absolute ethanolic hydrogen chloride for 17 hours, gave a 66% yield of 2-carbethoxymethylamino-2-imidazoline. The other bicyclic compounds II, $n = 3$, and XII were much more stable towards ethanolic hydrogen chloride solution. After 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine was heated in this reagent for 6 days, 72.3% was recovered unchanged. Compound XII, on being heated with ethanolic hydrogen chloride for 7.5 days, gave 30% of 2-(2-carbethoxyethylamino)-Δ^2-tetrahydropyrimidine and 18% unchanged starting material.

2-(N-3,4-Dichlorobenzylcarbamyl)-methylamino-2-imidazoline was prepared by heating bicyclic compound II, $n = 2$, with ethanolic benzylamine solution.

EXPERIMENTAL*

2-Carboxymethylamino-2-imidazoline

2-Carboxymethylamino-2-imidazoline (m.p. 283° decomp.) was prepared in 86% yield as previously described (1) from 2-methylmercapto-2-imidazolinium iodide, aqueous sodium hydroxide solution, and glycine. The reported (1) melting point is 293° with decomposition.

3-Keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-a)imidazole

2-Carboxymethylamino-2-imidazoline (15 g, 0.105 mole) was heated under reflux with hydrogen chloride (11.5 g, 0.315 mole) in absolute ethanol (250 ml) for 3 hours. Benzene (50 ml) was added and the solution was heated for an additional hour. The benzene–water–ethanol azeotrope was distilled and the remaining ethanol solution was again treated with benzene. The removal of benzene–water–ethanol was repeated three times, after which the ethanolic solution was taken to dryness *in vacuo*.

The crude, oily ester hydrochloride in absolute methanol (400 ml) was passed through a column of IRA 400 resin (300 ml in hydroxyl form) which had been previously washed thoroughly with absolute methanol. The column was washed with methanol (300 ml) until the methanol washings were neutral and the combined eluate and washings were evaporated *in vacuo* to dryness. The yellowish crystalline solid melted at 165–170°, yield 9.5 g (72.6%). Crystallization from a minimum amount of ethanol in the presence of Norite gave colorless crystals melting at 168–170°, yield 5.56 g (42.4%). A sample was sublimed at 145–155° *in vacuo* (0.2 mm). The white crystalline sublimate melted at 169–170°. Anal. calc. for $C_5H_7N_3O$: C 48.00, H 5.64, N 33.59%; found: C 47.80, H 5.68, N 33.59%.

The picrate (m.p. 180–181°) was prepared in 86.2% yield in the usual manner with ethanolic picric acid solution. One crystallization from absolute ethanol raised the melting point to 180.5–181.5°. Anal. calc. for $C_{11}H_{10}N_6O_8$: C 37.30, H 2.85, N 23.73%; found: C 37.29, H 2.94, N 23.60%.

Opening One Ring of 3-Keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-a)imidazole

A. With Ethanolic Hydrogen Chloride

A solution of 3-keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole (0.2 g, 0.0016 mole) in ethanolic hydrogen chloride (0.063 g, 0.0017 mole) was refluxed for 17 hours. This solution on treatment with ethanolic picric acid solution gave a 66% yield of 2-carbethoxymethylamino-2-imidazoline picrate (m.p. 190.5–191.5°). The reported (1) melting point is 193–195°.

**All melting points are uncorrected. Microanalyses were determined by Micro-Tech Laboratories, Skokie, Ill.*

B. With 3,4-Dichlorobenzylamine

3,4-Dichlorobenzylamine (0.35 g, 0.002 mole) and 3-keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)-imidazole (0.25 g, 0.002 mole) in absolute ethanol (6 ml) was refluxed for 2 hours. The reaction mixture was evaporated to dryness and the solid product was crystallized from water in the presence of Norite, yield 0.26 g (43.3%). Two crystallizations from water raised the melting point of the 2-(N-(N'-3,4-dichlorobenzylcarbamylmethyl)amino)-2-imidazoline from 155° to 156–157°. Anal. calc. for $C_{12}H_{14}Cl_2N_4O$: C 47.84, H 4.69, Cl 23.54, N 18.60%; found: C 47.80, H 4.89, Cl 23.10, N 18.41%.

A sample in ethanol, on treatment with ethanolic picric acid, gave a 98% yield of a crystalline picrate (m.p. 195–196°). The melting point remained unchanged after crystallization from absolute ethanol. Anal. calc. for $C_{18}H_{17}Cl_2N_7O_8$: C 40.77, H 3.23, Cl 13.37, N 18.49%; found: C 40.60, H 3.48, Cl 13.47, N 18.11%.

2-Methylmercapto-Δ^2-tetrahydropyrimidine

2-Methylmercapto-Δ^2-tetrahydropyrimidinium iodide (6.45 g, 0.025 mole) in water (10 ml) at 0° was treated with an aqueous solution of potassium hydroxide (1.4 g, 0.025 mole in 5 ml water). This solution was extracted with ether (10×100 ml) and the combined ether extracts were dried over anhydrous sodium sulphate. Evaporation of the ether gave a 82.4% yield of the free base (m.p. 89–90°). The melting point of 2-methylmercapto-Δ^2-tetrahydropyrimidine was not changed by crystallization from acetone–hexane solution. Anal. calc. for $C_5H_{10}N_2S$: C 46.13, H 7.74, N 21.53, S 24.63%; found: C 46.35, H 7.74, N 21.94, S 24.78%.

The picrate (m.p. 179.5–180.5°) was formed in the usual manner from water, yield 94%. Anal. calc. for $C_{11}H_{13}N_5O_7S$: C 36.76, H 3.65%; found: C 36.88, H 3.81%.

2-Carboxymethylamino-Δ^2-tetrahydropyrimidine

The original procedure (1) for the preparation of 2-carboxymethylamino-Δ^2-tetrahydropyrimidine was modified because the product was difficult to isolate and purify.

An intimate mixture of 2-methylmercapto-Δ^2-tetrahydropyrimidine (19.53 g, 0.15 mole) and glycine (11.26 g, 0.15 mole) was heated in an oil bath at 90° for 50 minutes. After the mixture melted, white crystals began to form. The heating was continued for 35 minutes at 130°. After the crystalline product had cooled, *n*-amyl alcohol (20 ml) was added and the mixture was refluxed for 60 minutes. The crystalline solid (m.p. 212–214°) was removed by filtration, yield 71.6%. Two crystallizations from aqueous ethanol raised the melting point to 219–220° (reported (1) m.p. 211.5–212°).

2-Carbethoxymethylamino-Δ^2-tetrahydropyrimidine Hydrochloride

This compound was prepared in quantitative yield by the procedure given (1) for the esterification of 2-carboxymethylamino-2-imidazoline. The crude 2-carbethoxymethylamino-Δ^2-tetrahydropyrimidine hydrochloride (m.p. 162–168°) was used to prepare 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)-pyrimidine.

3-Keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-a)pyrimidine

A solution of 2-carbethoxymethylamino-Δ^2-tetrahydropyrimidine hydrochloride (18.6 g, 0.084 mole) in absolute methanol (370 ml) was passed through a column of IRA 400 resin (300 ml in hydroxyl form) which had been previously washed with methanol. The column was washed with absolute methanol (450 ml) and the eluate and washings were combined. The elution and washing procedures were carried out under nitrogen. The crude product from the evaporation of eluate and washings was dissolved in absolute ethanol (60 ml). A mixture of yellow, red, and white crystals separated from the solution on cooling to −10°, yield 5.85 g (50.2%). This crude mixture melted at 157–168°. Concentration of the mother liquors to a small volume gave an orange-colored microcrystalline powder (m.p. >350°), yield 0.15 g.

The first crop of mixed crystals (3.28 g) was sublimed *in vacuo* (0.2 mm) at a bath temperature of 150–160°. The white crystalline sublimate melted at 179.5–180° in an evacuated capillary tube, yield 2.92 g (89%). Resublimation did not change the melting point. Anal. calc. for $C_6H_9N_3O$: C 51.78, H 6.52, N 30.20%; found: C 51.73, H 6.51, N 30.18%.

The picrate (m.p. 193.8–194.8°) was prepared in 97.2% yield from ethanol solution. Anal. calc. for $C_{12}H_{12}N_6O_8$: C 39.14, H 3.29, N 22.82%; found: C 39.36, H 3.55, N 22.39%.

Treatment of 3-Keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-a)pyrimidine with Ethanolic Hydrogen Chloride

3-Keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine (0.35 g, 0.0025 mole) was heated under reflux in absolute ethanol containing hydrogen chloride (0.006 mole) for 6 days. Evaporation of the solvent left a semicrystalline hygroscopic mass (0.43 g). A portion (0.15 g) of the crude product in absolute ethanol was converted to its picrate (m.p. 189°) in the usual manner, yield 0.23 g (72.3%). This picrate did not depress the melting point of a known sample of 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)-pyrimidine picrate (m.p. 193°).

The original crude product was crystallized twice from ethanol–ether solution to give crystals (m.p. 209–210° (block), 214–215° (evac. cap.)) of the hydrochloride of the original bicyclic compound. Anal. calc. for $C_6H_{10}ClN_3O$: C 41.04, H 5.74, Cl 20.19, N 23.93%; found: C 40.87, H 5.68, Cl 20.28, N 23.80%.

2-(2-Carboxyethylamino)-Δ²-tetrahydropyrimidine

2-Methylmercapto-Δ²-tetrahydropyrimidine (28 g, 0.215 mole) and β-alanine (19.15 g, 0.215 mole) were mixed thoroughly and heated at 90° for 20 minutes. After the reaction mixture had melted, crystals began to sublime onto the cooler sides of the reaction flask. The temperature was raised to 105° and held at this temperature for 1 hour after which it was heated at 130° for 30 minutes. Ethanol (35 ml) was added to the solidified mass after it had cooled and the reaction mixture was refluxed for 4.6 hours. The white solid (m.p. 209.5–210°) was removed by filtration, yield 21.6 g (58.9%). This acid was very difficult to free from solvent and the melting point varied considerably on recrystallization from aqueous or anhydrous solvents. Thus the picrate (m.p. 164–165°) was formed in 60.6% yield in the usual manner from absolute ethanol. Crystallization from ethanol did not change the melting point. Anal. calc. for $C_{13}H_{16}N_6O_9$: C 39.00, H 4.03, N 21.00%; found: C 39.02, H 4.10, N 20.82%.

An attempt to purify a sample of 2-β-carboxyethylamino-Δ²-tetrahydropyrimidine by sublimation *in vacuo* at 170° gave a sublimate which melted at 120–123°. This sublimate in ethanol yielded a picrate in 39.1% yield melting at 212–213°. Two crystallizations from absolute ethanol raised the melting point to 214–215°. This picrate did not depress the melting point (214–215°) of 4-keto-2,3,6,7,8,9-hexahydro-4(H)-pyrimido(1,2-*a*)pyrimidine picrate (*vide infra*).

4-Keto-2,3,6,7,8,9-hexahydro-4(H)-pyrimido(1,2-a)pyrimidine

2-(2-Carboxyethylamino)-Δ²-tetrahydropyrimidine (10.01 g, 0.058 mole) was converted in quantitative yield into the hydrochloride salt of its ethyl ester by the procedure previously (1) described. A portion of the colorless oil in alcohol was converted into its picrate (m.p. 117°, resolidified and remelted at 128°) in 76.7% yield. Two crystallizations from absolute ethanol raised the melting point to 121° with resolidification and remelting at 136°. Anal. calc. for $C_{15}H_{20}N_6O_9$: C 42.06, H 4.71, N 19.62%; found: C 42.39, H 4.69, N 19.71%.

2-(2-Carbethoxyethylamino)-Δ²-tetrahydropyrimidine hydrochloride (13.8 g, 0.58 mole) in absolute methanol (250 ml) was passed through IRA 400 resin and the product was recovered. The procedure was the same as described above for the cyclization of 2-carbethoxymethylamino-Δ²-tetrahydropyrimidine hydrochloride to 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine. The crude product sintered at 110° and melted at 176–188°, yield 8.7 g.

The crude product was sublimed *in vacuo* (0.2 mm) at 120–130°, yield 3.34 g (38.4%). The sublimate of 4-keto-2,3,6,7,8,9-hexahydro-4(H)-pyrimido(1,2-*a*)pyrimidine melted at 127°. Two further sublimations did not change the melting point. This bicyclic compound hydrolyzed extremely rapidly and it was not possible to obtain an analytical sample free from traces of the parent acid, 2-(β-carboxyethylamino)-Δ²-tetrahydropyrimidine. Anal. calc. for $C_9H_{11}N_3O$: N 27.43%; found: N 26.60%. The sublimate in absolute ethanol gave a crystalline picrate (m.p. 214–215°) of 4-keto-2,3,6,7,8,9-hexahydro-4(H)-pyrimido(1,2-*a*)pyrimidine in 91.4% yield. Anal. calc. for $C_{13}H_{14}N_6O_8$: C 40.84, H 3.69, N 21.98%; found: C 40.73, H 3.70, N 22.08%.

Treatment of 4-Keto-2,3,6,7,8,9-hexahydro-4(H)-pyrimido(1,2-a)pyrimidine with Ethanolic Hydrogen Chloride

The bicyclic compound (0.17 g, 0.001 mole) in absolute ethanol containing hydrogen chloride (0.003 mole) was heated under reflux for 7.5 days. Evaporation of the solvent gave a viscous colorless oil which partially crystallized on standing in an evacuated desiccator for several days. A portion (0.09 g) of the product on treatment with ethanolic picric acid solution gave a crystalline picrate (m.p. 208–213°), yield 18.2%. One crystallization from ethanol raised the melting point to 214–215°. It did not depress the melting point of a known sample of 4-keto-2,3,6,7,8,9-hexahydro-4(H)-pyrimido(1,2-*a*)pyrimidine picrate (m.p. 214–215°) on admixture.

The mother liquor from the bicyclic picrate on concentration and cooling gave a second picrate (m.p. 121°, resolidification with remelting at 136–137°), yield 0.05 g (30.6%). This picrate was identified as the picrate of 2-(2-carbethoxyethylamino)-Δ²-tetrahydropyrimidine (m.p. 121° and 136–137°).

Benzylidene Derivative of 3-Keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-a)imidazole

3-Keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole (0.5 g, 0.004 mole), fused sodium acetate (0.58 g), and benzaldehyde (0.6 ml, 0.006 mole) in glacial acetic acid were heated in an oil bath at 140° for 75 minutes. The solution became dark orange in color and after 15 minutes yellow crystals separated. The mixture was allowed to cool to room temperature and the crystals (m.p. 266–274°) were collected by filtration, yield 0.45 g. A second crop (75 mg) of crystals was obtained from the mother liquors on further cooling, total yield 61.2%. Two crystallizations from absolute ethanol raised the melting point to 283.5–284.2°. Anal. calc. for $C_{12}H_{11}N_3O$: C 67.60, H 5.20, N 19.71%; found: C 67.33, H 5.37, N 20.17%. Ultraviolet absorption spectrum (in ethanol): λ_{max} 237 mμ, ε 11,350; λ_{max} 242 mμ (sh), ε 10,650; λ_{max} 347 mμ, ε 27,250.

The picrate (215–217° decomp.) was formed in the usual manner in ethanol solution, yield 38%. Two crystallizations from absolute ethanol raised the melting point to 217.4–218.2° decomp. Anal. calc. for $C_{18}H_{14}N_6O_8$: C 48.88, H 3.19, N 19.00%; found: C 48.94, H 3.33, N 18.51%.

Benzylidene Derivative of 3-Keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-a)pyrimidine

Freshly sublimed 3-keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-*a*)pyrimidine (0.51 g, 0.0037 mole), fused sodium acetate (0.61 g), and benzaldehyde (0.6 ml, 0.006 mole) in glacial acetic acid (4.5 ml) were refluxed for 75 minutes. After the solution was cooled in freezing mixture, crystals of sodium acetate separated, yield 0.27 g. The filtrate was taken to dryness *in vacuo* and the residue was extracted with water

to remove the remaining sodium acetate. The residue melted at 227–232°, yield 0.54 g (63.6%). Two crystallizations from absolute ethanol raised the melting point to 239.2–239.8°. Anal. calc. for $C_{13}H_{13}N_3O$: C 68.70, H 5.77, N 18.49%; found: C 68.21, H 5.83, N 18.50%. Ultraviolet absorption spectrum (in ethanol): λ_{max} 241 mμ, ε 13,600; λ_{max} 247 mμ (sh), ε 12,680; λ_{max} 365 mμ, ε 25,340.

The picrate (m.p. 217–219°) was prepared from ethanol solution in 90.6% yield. Two crystallizations from absolute ethanol raised the melting point to 223.4–224.2°. Anal. calc. for $C_{19}H_{16}N_6O_8$: C 49.99, H 3.53, N 18.42%; found: C 50.01, H 3.55, N 18.34%.

3,4-Dichlorobenzylidene Derivative of 3-Keto-1,2,6,7-tetrahydro-3(H),5(H)-imidazo(1,2-a)pyrimidine

This compound (m.p. 248–256° decomp.) was prepared in 91% yield by the procedure given above for the preparation of 2-benzylidene-3-keto-1,2,5,6-tetrahydro-3(H)-imidazo(1,2-*a*)imidazole. Two crystallizations from absolute ethanol raised the melting point to 265–266° decomp. Anal. calc. for $C_{13}H_{11}Cl_2N_3O$: C 52.73, H 3.74, Cl 23.94, N 14.19%; found: C 52.58, H 3.87, Cl 24.15, N 14.10%.

A crystalline picrate (m.p. 237–240° decomp.) was obtained in quantitative yield from ethanol solution. Two crystallizations from absolute ethanol raised the melting point to 246.2–246.6° decomp. Anal. calc. for $C_{19}H_{14}Cl_2N_6O_8$: C 43.44, H 2.69, Cl 13.50, N 16.00%; found: C 43.45, H 2.89, Cl 12.96, N 16.25%.

2-Carboxymethylamino-Δ^2-dihydro-1,3-thiazine

2-Methylmercapto-Δ^2-dihydro-1,3-thiazine (4) (17.68 g, 0.12 mole) and glycine (9.01 g, 0.12 mole) in methanol–water (1:1) solution (200 ml) were refluxed for 19 hours. The reaction mixture turned a deep blue color after the first few hours of heating. A dark blue crystalline solid (m.p. >360°) separated from the cooled solution, yield 3.53 g. This dye was virtually insoluble in all the common organic solvents. A dilute solution in hydrochloric acid was deep blue in color. Anal. calc. for $C_{12}H_{14}N_4O_3S_2$: C 44.25, H 4.33, N 16.67, S 19.65%; found: C 44.73, H 4.52, N 16.61, S 19.47%.

The filtrate, from which the dye had been removed, was evaporated to dryness. The residue was dissolved in hot methanol with the exception of a small amount (0.37 g) of blue dye. The filtrate from the blue dye, on cooling, gave a mixture of blue and white crystals (m.p. 170–173°), yield 6.49 g. The mother liquors yielded a second crop of crystals (m.p. 169–173°). The total yield of crude 2-carboxymethylamino-Δ^2-dihydro-1,3-thiazine was 9.87 g (46.8%). Two crystallizations from ethanol in the presence of Norite gave grey crystals melting at 174–175° (blue melt). Anal. calc. for $C_6H_{10}N_2O_2S.H_2O$: C 37.48, H 6.30, N 14.58, S 16.68%; found: C 37.29, H 6.41, N 14.82, S 16.42%.

The picrate (m.p. 159–160°, dark blue melt) was prepared in 82% yield in the usual manner from water. Anal. calc. for $C_{12}H_{13}N_5O_9S$: C 35.73, H 3.25, N 17.37, S 9.95%; found: C 36.01, H 3.33, N 17.28, S 7.72%.

3,4,5,6-Tetrahydro-2(H)-1,3-oxazine-2-thione

Method A

3,4,5,6-Tetrahydro-2(H)-1,3-oxazine-2-thione (m.p. 124–125°) was prepared in 34% yield by the method of Menard *et al.* (6).

Method B

A solution of carbon disulphide (31.2 g, 0.4 mole) in chloroform (80 ml) was added dropwise over a period of 40 minutes to a stirred solution of 3-amino-1-propanol (30 g, 0.4 mole) and triethylamine (40.4 g, 0.4 mole) in chloroform (80 ml) at 0°. This reaction mixture was stirred for 5 minutes at 25° and then cooled again to 0°. After ethyl chloroformate (43.2 g, 0.4 mole) was added over a period of 50 minutes, stirring was continued for 20 minutes. A solution of triethylamine (44.4 g, 0.44 mole) in chloroform (150 ml) was added during the next 50 minutes after which stirring was continued for 15 minutes. Then the chloroform solution was washed with 5% aqueous sodium hydroxide (2×150 ml), 5% hydrochloric acid (2×150 ml), and water (5×200 ml). After the chloroform solution was dried over anhydrous sodium sulphate and allowed to stand in the refrigerator for 15 minutes, it was evaporated to dryness. The crude yield of 3,4,5,6-tetrahydro-2(H)-1,3-oxazine-2-thione (m.p. 124–125°) was 15.6 g (33.3%). The structure of this compound was confirmed by its infrared spectrum, analyses, and molecular weight determination. The infrared spectrum of the compound dispersed in Nujol mull gave the following absorption bands: 3195 cm^{-1} (N—H stretching mode), 1573 cm^{-1} (N—H bending mode), and 1376 cm^{-1} (—N—C=S stretching mode (provisional assignment)). One crystallization from acetone raised the melting point to 126.5–127.5°. Anal. calc. for C_4H_7NOS: C 41.00, H 6.01, N 11.95, S 27.36%, mol. wt. 117.05; found: C 41.11, H 6.18, N 11.67, S 27.26%, mol. wt. (Rast) 119.

2-Methylmercapto-5,6-dihydro-4(H)-1,3-oxazine Hydroiodide

Methyl iodide (24.8 g, 0.17 mole) was added portionwise to a suspension of 3,4,5,6-tetrahydro-2(H)-1,3-oxazine-2-thione (15.8 g, 0.13 mole) in absolute ethanol (35 ml). The reaction mixture was heated under reflux for 45 minutes and then the clear solution was evaporated to dryness *in vacuo*. The crystalline residue was treated with cold absolute methanol (50 ml) and the insoluble residue was removed by filtration. Addition of water (20–25 ml) to the methanolic filtrate gave the crystalline product (m.p. 64.5–65.5°), yield 31.84 g (91.4%). Infrared spectrum of the compound in Nujol mull gave the following absorption bands: 3290 cm^{-1} (=N—H^+ stretching mode), 1638 cm^{-1} (C=NH^+ stretching mode), and 1536 cm^{-1} (=NH^+ bending mode). Anal. calc. for $C_5H_{10}INOS$: C 23.18, H 3.89, N 5.41, S 12.38%; found: C 23.15, H 3.78, N 5.08, S 11.94%.

2-Benzylamino-5,6-dihydro-4(H)-1,3-oxazine Picrate

2-Methylmercapto-5,6-dihydro-4(H)-1,3-oxazine hydroiodide (3.9 g, 0.015 mole) and benzylamine (1.6 g, 0.015 mole) in ethanol were refluxed for 17 hours. The solvent was removed *in vacuo* and the residual oil was dissolved in ethanol and treated with aqueous picric acid solution. The solvent was decanted from the oily picrate (yield 10.2%), which crystallized (m.p. 168–170°) on heating with fresh ethanol. Three crystallizations from ethanol raised the melting point to 172.5–173.5. Anal. calc. for $C_{17}H_{17}N_5O_8$: C 48.69, H 4.09, N 16.70%; found: C 48.33, H 4.13, N 16.73%.

A paper chromatogram of the residual oil from this reaction showed that very little reaction had taken place after the prolonged heating period.

2-(α-Naphthylmethylamino)-5,6-dihydro-4(H)-1,3-oxazine Picrate

A solution of α-naphthylmethylamine (2.3 g, 0.015 mole) and 2-methylmercapto-5,6-dihydro-4(H)-1,3-oxazine hydroiodide (3.9 g, 0.015 mole) in ethanol (12 ml) was heated under reflux for 26 hours. Evaporation of the solvent gave 5.53 g of a glasslike, solid mass. A sample (1.1 g) of this product in methanol was treated with aqueous picric acid solution. A mixture of oily and crystalline picrates formed. The crystals were collected by filtration and identified by a mixed melting point determination as α-naphthylmethylamine picrate (m.p. 226–228° decomp.). Treatment of the remaining oily picrate with boiling water (100 ml) and boiling methanol caused partial crystallization to occur. The crystals (m.p. 215–217°) were removed by filtration, yield 0.18 g (12.8%). Several crystallizations from methanol raised the melting point to 219–219.5°. Anal. calc. for $C_{21}H_{19}N_5O_8$: C 53.73, H 4.08, N 14.92%; found: C 53.80, H 4.34, N 14.85%.

1,3-Di-(2-hydroxypropyl)-thiourea

Method A

Carbon disulphide (22.84 g, 0.3 mole) in absolute ethanol (15 ml) was added to a cooled (5–10°) solution of 3-amino-1-propanol (22.53 g, 0.3 mole) in absolute ethanol (35 ml) over a period of 1 hour. The reaction mixture was heated at reflux for 7 hours and then the solvent was removed *in vacuo*. After the oily product had been heated at 110° for 8 hours, it was dissolved in absolute ethanol (50 ml) and heated under reflux for an additional 8 hours. The alcohol was removed *in vacuo* and the waxy solid (30 g, 85.5% yield) was crystallized from ethanol–ether solution. This crystalline product melted at 90.4–91°, yield 20.3 g. Anal. calc. for $C_7H_{16}N_2O_2S$: C 43.71, H 8.39, N 14.57, S 16.67%; found: C 43.58, H 8.33, N 14.19, S 16.68%.

Method B

3-Amino-1-propanol (62.7 g, 0.836 mole) was added to a solution of potassium hydroxide (16 g, 0.28 mole) in absolute ethanol (200 ml). Carbon disulphide (69.9 g, 0.92 mole) was added dropwise to this solution at 30° over a period of 1 hour. After standing at room temperature for 1.5 hours, the reaction mixture was heated under reflux (48°) for 3 hours. A small amount of unreacted carbon disulphide (6 ml) was removed by distillation and the residue was heated under reflux (72–76°) for 6 hours. The solution on standing at room temperature overnight deposited large prisms. The crystals (m.p. 148–152° decomp.) were recovered by filtration, yield 20.23 g. Evaporation of the ethanol filtrate *in vacuo* gave a yellow, mobile oil (95.5 g). Addition of acetone to this oil gave a second crop of the high-melting (150° decomp.) product. Careful fractional crystallization of the remainder with acetone and then hexane gave a total yield of 32.43 g (20.5% based on 3-amino-1-propanol) of the potassium salt of 3-hydroxypropyldithiocarbamic acid and 63.8 g (76.9%) of 1,3-di-(3-hydroxypropyl)-thiourea (m.p. 88–90°). The thiourea gave no depression in melting point on admixture with a sample of the 1,3-di-(3-hydroxypropyl)-thiourea (m.p. 90.4–91°) described above under Method A.

A portion of the crude potassium salt of 3-hydroxypropyldithiocarbamic acid was crystallized twice from warm ethanol–ether solution. The final melting point was 149.5–150.5° with decomposition. Anal. calc. for $C_4H_8KNOS_2$: C 25.37, H 4.26, N 7.40, S 33.87%; found: C 25.76, H 4.35, N 7.13, S 33.71%.

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