droxide trap. Removal of the acetic anhydride *in vacuo* at 50–60° yielded a brown solid which was triturated with 10 ml of ether, dried *in vacuo* over potassium hydroxide at room temperature, and then extracted with nine 40-ml portions of *n*-hexane to give 0.66 g (57%) of crude product, mp 98–99° dec. Recrystallization twice from dry *n*-hexane gave the analytical sample: mp 104–106°; infrared spectrum, carbonyl absorption at 1720 cm^{-1}; pmr spectrum, τ_{max} at 8.49 (doublet 3 H), 7.69 (singlet 3 H), 7.09 (singlet 3 H), 5.08 (quartet 1 H), 1.19 (singlet 1 H), 1.12 (singlet 1 H); λ_{max} ($\epsilon \times 10^{-3}$) in *n*-hexane 283 (14.90).

Anal. Calcd for $C_{11}H_{12}N_4O_2S$: C, 50.00; H, 4.55; N, 21.30; S, 12.10. Found: C, 50.43; H, 4.76; N, 21.12; S, 12.19.

Compound **2** was obtained in 90% yield by acetylation of 6-[2-(3-oxobutylthio)]purine (**3**). A suspension of 0.5 g of **3** in 10 ml of benzene and 2 ml of acetic anhydride gave a clear solution after refluxing for 30–40 min. The product, isolated by the procedure above, was identical with **2**, as shown by mixture melting point and analyses.

6-[2-(3-Oxobutylthio)]purine (3).—To a solution of sodium hydroxide (0.24 g, 6 mmoles) in 40 ml of water, was added 9-acetyl-6-[2-(3-oxobutylthio)]purine (**2**) (1.4 g, 5.3 mmoles). The solid gradually dissolved on heating and stirring for 20 min. The cooled solution was adjusted to a pH of 5 with glacial acetic acid. On refrigeration, a white solid precipitated, 0.9 g (76%), mp 180–183°. Recrystallization from water gave colorless needles: mp 187–189° dec; pmr spectrum, τ_{max} at 8.45 (doublet 3 H), 7.65 (singlet 3 H), 5.02 (quartet 1 H), 1.45 (singlet 1 H), 1.39 (singlet 1 H); λ_{max} ($\epsilon \times 10^{-3}$) in pH 1 304 (15.0), MeOH 284 (11.4), in pH 11 290 (12.2); R_{Ad} 1.69.

Anal. Calcd for $C_9H_{10}N_4OS$: C, 48.63; H, 4.53; N, 25.20. Found: C, 48.64; H, 4.85; N, 24.99.

Compound **3** was also obtained by alkylation of purine-6-thione. A suspension of 2.0 g (11.7 mmoles) of purine-6-thione and 1.18 g (1.64 ml, 11.7 mmoles) of triethylamine in 10 ml of anhydrous dimethylformamide was stirred for 10 min at room temperature under anhydrous conditions. 3-Chloro-2-butanone (1.25 g, 1.21 ml, 11.7 mmoles) was added all at once and the mixture stirred for 15 hr. The mixture was then poured into 40 ml of ice water, and the pH adjusted to 5 with glacial acetic acid. The solid (1.2 g) was collected by filtration and dried at 70°; a second crop (0.6 g) was obtained from the mother liquor (total yield 69%). Recrystallization from water gave the product, mp 186–187° dec, which did not depress the melting point of compound **3**. Compound **3** was also obtained in a poorer yield (42%) by alkylation with potassium carbonate as the base.

6-[2-(3-Oxopentylthio)]purine (4).—A solution of compound **1** (2.0 g, 8.95 mmoles) and propionic anhydride (60 ml) was refluxed under anhydrous conditions for 6 hr. The propionic anhydride was removed *in vacuo* at 60°. The brown residue was triturated with two 10-ml portions of *n*-hexane and dried *in vacuo* over potassium hydroxide at room temperature. Extraction of the tan solid with three 100-ml portions of ether yielded 1.1 g (44%) of the crude acylated material which was not purified further. To a solution of 0.151 g of sodium hydroxide in 25 ml of water was added 0.86 g (2.9 mmoles) of the crude acylated material and the mixture was heated with stirring for 20 min. The resulting solution was cooled, the pH adjusted to 5 with glacial acetic acid, and the precipitate collected and dried *in vacuo* at 80° to give 0.60 g of the product (36% over-all yield, based on **1**). Recrystallization from water yielded the analytical sample: mp 195–196°; λ_{max} ($\epsilon \times 10^{-3}$) in pH 1 304 (13.5), in MeOH 282 (17.6), in pH 11 291 (12.10); R_{Ad} 1.82.

Anal. Calcd for $C_{10}H_{12}N_4OS$: C, 50.82; H, 5.12; N, 23.71. Found: C, 50.82; H, 5.26; N, 23.62.

9-*p*-Nitrobenzyl-6-[2-(2-carboxyethylthio)]purine (5).—To a rapidly stirred suspension of 6-mercapto-9-*p*-nitrobenzylpurine[13] (1.0 g, 3.49 mmoles) and anhydrous potassium carbonate in 30 ml of anhydrous dimethylformamide (dried over 4 Å molecular sieves) was added dropwise 0.534 g (0.314 ml, 3.49 mmoles) of 2-bromopropanoic acid. The mixture was stirred 5 hr under anhydrous conditions at room temperature. The solvent was removed *in vacuo* at 40–50° and the oily brown residue triturated with 20–30 ml of water. The pH was adjusted to 2–3 with 6 *N* HCl and the solid filtered, washed with three 5-ml portions of water, and dried *in vacuo* at room temperature to yield 1.23 g (98%). Recrystallization from ethanol gave the pure product, melting at 165–168° dec when placed on the hot stage at 125°; in the infrared spectrum a C=O absorption appeared at 1720 cm^{-1}; ultraviolet exhibited λ_{max} ($\epsilon \times 10^{-3}$) in pH 1 290 (20.6), in MeOH 286 (22.7), in pH 11 292 (24.8); R_{Ad} was 1.58.

Anal. Calcd for $C_{15}H_{13}N_5O_4S$: C, 50.13; H, 3.64; N, 19.49. Found: C, 49.69; H, 3.90; N, 19.41.

9-*p*-Nitrobenzyl-6-[2-(3-oxobutylthio)purine] (6).—A solution of 9-*p*-nitrobenzyl-6-[2-(2-carboxyethylthio)]purine (**5**) (1.0 g, 2.79 mmoles) in acetic anhydride (40 ml) was refluxed for 15 hr under anhydrous conditions. The acetic anhydride was removed *in vacuo* and the resulting brown oil was extracted with four 60-ml portions of ether. The dried ether extract yielded 0.4 g (41%) of crude product, mp 150–153°. Recrystallization from ethanol gave yellow plates: mp 157–159° dec; λ_{max} ($\epsilon \times 10^{-3}$) in MeOH 284 (26.3); R_{Ad} 1.58.

Anal. Calcd for $C_{16}H_{15}N_5O_3S$: C, 53.76; H, 4.23; N, 19.59. Found: C, 53.99; H, 4.20; N, 19.61.

Dakin–West Reactions on Phenoxy- and Thiophenoxyacetic Acid.—A mixture of thiophenoxyacetic acid (3.0 g, 17.9 mmoles), 30 ml of acetic anhydride, and 30 ml of anhydrous 2,6-lutidine was refluxed for 12 hr. The acetic anhydride and lutidine were removed *in vacuo* and the thiophenoxyacetone was distilled at 144° at 15 mm (bath temperature 160°) to yield 0.6 g (21%). The ketone was converted into its phenylhydrazone, mp 82.5 (lit.[14] 82.5). A mixture melting point with an authentic sample showed no depression.

A similar procedure was used for phenoxyacetic acid except that pyridine was used as the base. The phenoxyacetone, bp 118–120° at 20 mm (lit.[15] 110–112° at 12 mm), was obtained in a yield of 17%: semicarbazone, mp 173–174° (lit.[16] mp 173°).

Registry No.—**1**, 15268-84-5; **2**, 15260-05-6; **3**, 15260-06-7; **4**, 15260-07-8; **5**, 15260-08-9; **6**, 15260-09-0; thiophenoxyacetic acid, 103-04-8; phenoxyacetic acid, 122-59-8.

(13) H. J. Schaeffer and E. Odin, *J. Med. Chem.*, **9**, 576 (1966).

(14) A. Delisle, *Ann.*, **260**, 252 (1890).

(15) W. B. Whitney and H. R. Henze, *J. Am. Chem. Soc.*, **60**, 1148 (1938).

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Synthesis and Stereochemistry of Hydrophenanthrenes. VI. A Special Case of the Semmler–Wolff Rearrangement[1,2]

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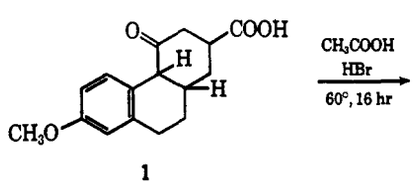
The aromatization of ring B in 1,2,3,4,4aβ,9,10,10aβ-octahydro-7-methoxy-4-oxo-2β-phenanthrenecarboxylic



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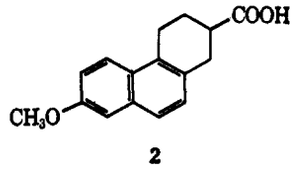

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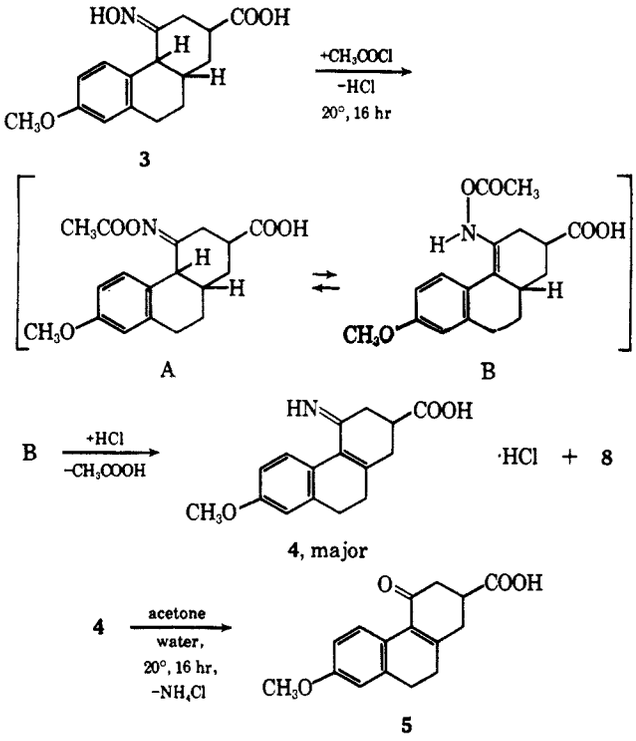
(1) Part V: Z. G. Hajos, C. P. Parios, and M. W. Goldberg, *J. Org. Chem.*, **31**, 1360 (1966).

(2) All compounds described are racemates. As a matter of convenience only one enantiomeric series (10aβ hydrogen) has been pictured.

(3) Deceased Feb 17, 1964.

SCHEME I

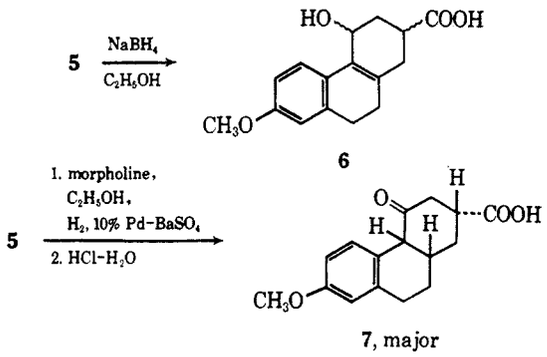


acid (1) by a new scheme has been described in a previous paper of this series.[4]

In view of this result, it seemed of interest to investigate the reaction of the corresponding oxime (3)[4] with acetyl chloride (Scheme I).

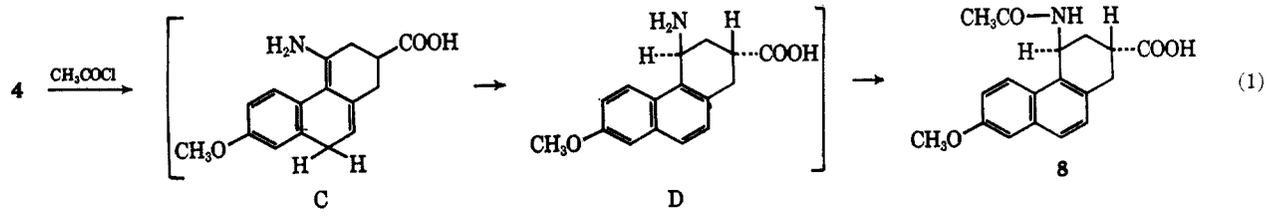
The reaction proceeded at 20° within 16 hr to give a crystalline intermediate 4 as the major reaction product. The compound was contaminated with 8, the minor reaction product, and its instability prevented further purification. However, ultraviolet and infrared spectroscopy of a freshly prepared sample of crude 4 suggests that it is the hydrochloride of an unsaturated γ-iminocarboxylic acid, which was probably formed *via* intermediates A and B. The net result in the conversion of 3 into 4 (Scheme I) is the loss of one molecule of water. The conversion of the β,γ-unsaturated oxime 3 into enimine 4 constitutes a special case of the Semmler–Wolff rearrangement, which normally involves oximes of α,β-unsaturated ketones. Intermediates of type 4 have been postulated in the rearrangement.[5]

The structure of intermediate 4 could be further substantiated by its conversion into the unsaturated keto acid 5 upon standing in acetone and water at 20° for 16 hr. The already mentioned instability of the compound is most probably due to partial hydrolysis of the α,β-unsaturated imine. The unsaturated keto acid 5 was identified by the following means. (a) Ultraviolet spectroscopy was in agreement with data of the literature[6] on 1,2,3,4,9,10-hexahydro-4-oxo-7-methoxyphenanthrene. (b) Nuclear magnetic resonance spectroscopy showed no vinylic proton. (c) Reduction with sodium borohydride gave a mixture of hydroxy acids. The ultraviolet spectrum of this mixture was similar to that of 2-acetyl-1,2,3,4,9,10-hexahydro-7-methoxyphenanthrene described in a previous paper of this series.[7] (d) Catalytic hydrogenation of the morpholine salt of 5 gave the known[4] B/C *cis* keto acid 7 as the major reduction product. This was identical with an authentic sample of 7 by comparison of their infrared spectra and by mixture melting point determination.



The catalytic hydrogenation involves *cis* addition of hydrogen to the double bond of the morpholine salt of 5 from the opposite side of the bulky carboxylate group.

It should be mentioned that from the mother liquor of crystallization of the unsaturated keto acid 5 a second crystalline compound 8 could be isolated in minute quantities. Microanalysis revealed an empirical formula of $C_{18}H_{19}NO_4$. Ultraviolet spectroscopy indicated the methoxynaphthalene chromophore, which was found previously[4] in the acid 2. Infrared spectroscopy showed the presence of the secondary amide and carboxylic acid functions. Nuclear magnetic resonance spectroscopy and mass spectrometry confirmed structure 8. The 4β-axial configuration of the acetamido group was proven by a quartet at 5.98 ppm (collapsible to a rough triplet after deuterium exchange) indicating an equatorial C-4 proton α to an exchangeable proton. The 2α-equatorial configuration seems to be the most likely arrangement for the carboxyl group. A 2β-axial configuration would most probably have led to spontaneous lactam formation in the intermediate D. Spontaneous lactonization with 2β,4β-diaxial substituents has been described in a previous paper of this series.[8]



(1)

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The minor reaction product **8** was present as an impurity in the crude eniminocarboxylic acid **4**, as shown by ultraviolet spectroscopy (*cf.* Experimental Section); **8** was most probably formed by the rearrangement of **4** to intermediate D, followed by acetylation of the latter by acetyl chloride (eq 1). The rearrangement bears some resemblance to the conversion of **1** into **2** and adds further support to the postulated structure of intermediate **4**.

Experimental Section[9]

1,2,3,4,9,10-Hexahydro-7-oxo-7-methoxy-2-phenanthrenecarboxylic Acid (5).—To 42 ml of acetyl chloride was added with stirring 4.05 g of the oxime acid (**3**).[4] The flask was stoppered and the reaction mixture was stirred at 20° for 16 hr. A small sample (0.2 ml) was taken to dryness *in vacuo*, and the residual solid was suspended in petroleum ether (bp 30–60°). Filtration gave 31 mg (98%) of the crude imine hydrochloride **4**: mp 72–75° dec; λ_{max} 209 mμ (ε 17,300), 233 (10,150),[10] and 254 (10,070); ν_{max}^{KBr} 2940 (very broad, salt band), 1700 (carboxyl carbonyl), and 1620 cm^{-1} (α,β-unsaturated imine).

The remaining portion of the reaction mixture was poured on ice without the isolation of the intermediate **4**. Enough acetone was added to dissolve the precipitate, and it was stirred under nitrogen at 20° for 16 hr. About one-third of the solvent was then removed *in vacuo*. After standing for 2 hr at 20° a crystalline precipitate formed. It was filtered to give 2.55 g (66.8%) of the crude unsaturated keto acid **5**, mp 208–210°. Recrystallization from acetone gave analytically pure **5**: mp 210–211.5°; λ_{max} 246 mμ (ε 17,400), 292 (4840), and 311 (4320); ν_{max}^{KBr} 1705 (carboxyl carbonyl) and 1663 cm^{-1} (α,β-unsaturated ketone); nmr (C_5D_5N) multiplet at δ 2.25 and 2.57 ($-CH_2CH_2-$, J = 7 cps), multiplet at 2.85 ($-CH_2CHCH_2CO-$), singlet at 3.65 (CH_3O) multiplet at 6.70 (3 H, aromatic), and broad singlet at 11.0 (COOH)

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.59; H, 5.76.

4β-Acetamido-1,2,3,4-tetrahydro-7-methoxy-2α-phenanthrenecarboxylic Acid (8).—Filtration of the 2.55 g of crude **5** gave an acetone and water-containing mother liquor. The acetone was evaporated *in vacuo*, and the water was extracted with ethyl acetate. The extract was washed free of mineral acid, dried with sodium sulfate, and evaporated *in vacuo* to yield 1.24 g of an amorphous powder. Crystallization from acetone and petroleum ether (bp 30–60°) gave 0.76 g of a solid, which was recrystallized from chloroform, to give 131 mg of analytically pure **8**: mp 232–3°; λ_{max} 231 mμ (ε 61,500), 263.5 (5380), 273 (5750), 283 (4040), 320 (2120) and 334.5 (2600); ν_{max}^{KBr} 1720 (carboxyl carbonyl), 1630 cm^{-1} (amide carbonyl); nmr (C_5D_5N) singlet at δ 1.94 (CH_3CON), multiplet at 2.60–3.50 ($-CH_2CHCH_2-$), singlet at 3.77 (CH_3O), quartet at 5.98 (C-4 proton, $J_{4H,NH}$ = 7.5 cps and $J_{3H,4H}$ = 5.5 cps), broad multiplet at 7.10–7.75 (four aromatic protons, and COOH), multiplet at 8.05 (1 H, aromatic), and doublet at 8.25 (HN–CO). The high resolution mass spectrum showed a molecular ion at m/e 313 ($C_{18}H_{19}NO_4$). The major fragment ions were observed at m/e 295 ($C_{18}H_{17}NO_3$), 254 ($C_{16}H_{14}O_3$), 209 ($C_{15}H_{13}O$), 194 ($C_{14}H_{10}O$), 178 ($C_{14}H_{10}$), and 165 ($C_{13}H_9$).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.06; H, 6.16; N, 4.55.

Sodium Borohydride Reduction of the Unsaturated Keto Acid 5.—To 8.4 mg of **5** in 2 ml of absolute ethyl alcohol was added 2 mg of sodium borohydride. After stirring for 2 hr at 20° it was poured into 2 ml of ice water. Most of the alcohol was evaporated *in vacuo*, and the water solution was extracted with ethyl acetate. The extract was dried over sodium sulfate, and evaporated *in vacuo* to give 6.1 mg of an amorphous solid (**6**), λ_{max} 271 mμ (ε 17,070).

1,2,3,4,4aβ,9,10,10aβ-Octahydro-7-methoxy-4-oxo-2α-phenanthrenecarboxylic Acid (7).—To 54.5 mg of the unsaturated keto acid **5** in 3.8 ml of absolute ethyl alcohol was added 17.4 mg of morpholine in 1.7 ml of absolute ethyl alcohol. The morpholine salt of **5** formed was hydrogenated at 20° and atmospheric pressure in the presence of 11.0 mg of 10% palladium on barium sulfate catalyst. After the uptake of 1 mole of hydrogen, the catalyst was filtered and the alcohol solution was evaporated to dryness *in vacuo* to give 75 mg of an amorphous solid. Crystallization from a small amount of absolute ethyl alcohol gave 36.1 mg of the morpholine salt of **7**, mp 153.5–154°. This salt was dissolved in 0.5 ml of water, and 1 drop of 2 *N* hydrochloric acid was added. The crystalline precipitate was filtered and dried *in vacuo* at 40° for 6 hr. Recrystallization from a small amount of acetone gave 20 mg of the *cis* keto acid **7**, mp 171–173°.

Registry No.—**4**, 15378-22-0; **5**, 15378-23-1; **7**, 1987-81-1; **8**, 15378-25-3.

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(8) Z. G. Hajos, D. R. Parrish, and M. W. Goldberg, *J. Org. Chem.*, **31**, 713 (1966).

(9) All melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. All ultraviolet spectra were taken in ethyl alcohol with a Cary 14M spectrophotometer. Infrared spectra were taken with a Beckman IR-9 spectrophotometer. Nmr spectra were taken with a Varian HA-100 spectrometer at 100 Mc/sec and tetramethylsilane as an internal standard.

(10) The band at 233 mμ indicates approximately 19% of **8** as an impurity.

2-Amino-2-thiazoline. IV.[1] The Ring Opening of 2-Amino-2-thiazolines and 2-Amino-2-selenazoline with Hydrogen Sulfide to Form Thiourea Derivatives

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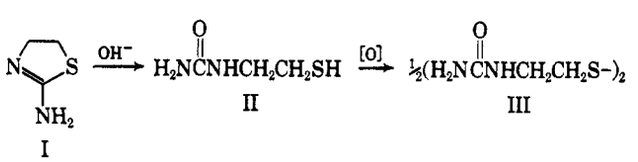
Schöberl, *et al.*,[2] reported that 2-amino-2-thiazoline (I), when heated for 0.5 hr with 2 *N* sodium hydroxide solution, ring opened to give 2-(mercaptoethyl)urea



I II III

(II). Oxidation of the latter compound with 3% hydrogen peroxide solution gave the corresponding disulfide (III). This alkali treatment followed by peroxide oxidation has been applied also to 2-amino-5,6-dihydro-4H-1,3-thiazine (IV, 2-aminopentathiazoline)[3] and to 2-amino-2-selenazoline[4] to give 1,1′-[dithiobis(trimethylene)]diurea and 1,1′-(diselenodiethylene)-diurea, respectively. Resistance to the action of aqueous alkali was encountered, however, in attempts

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(2) A. Schöberl and M. Kawohl, *Monatsh.*, **88**, 478 (1957); A. Schöberl and G. Hansen, *Chem. Ber.*, **91**, 1055 (1958).

(3) A. Schöberl, M. Kawohl, and G. Hansen, *Ann.*, **614**, 83 (1958).

(4) L. V. Pavlova and F. Yu. Rachinskii, *Zh. Obshch. Khim.*, **35**, 492 (1965).