be an ideal intermediate for the preparation of **5**. Indeed, reaction of **8** with triethyl orthoformate gave 5-(ethoxymethylenamino)pyrazole-3,4-dicarbonitrile (**9**), which upon treatment with alcoholic ammonia was converted to the desired aglycone analog, 3-cyano-4-aminopyrazolo[3,4-*d*]pyrimidine (**5**). An attempt to purify **9** by crystallization led to rapid and complete hydrolysis to 5-formamidopyrazole-3,4-dicarbonitrile (**10**); in fact, **9** reverted slowly to **10** even upon standing in the presence of air.

The structure of **5** was confirmed by alkaline hydrolysis to the carboxylic acid **6**, which upon decarboxylation (effected by vacuum sublimation) gave 4-aminopyrazolo[3,4-*d*]pyrimidine (**7**), identical (ultraviolet and infrared) with an authentic sample. The ease of decarboxylation of **6** contrasts with the difficulty experienced in attempts to decarboxylate the corresponding acid in the naturally occurring pyrrolo[2,3-*d*]pyrimidine series.[2] Nitrous acid readily converted **5** to 3-cyano-4(5H)-pyrazolo[3,4-*d*]pyrimidinone (**11**).

Attempts to convert the aglycone **1** and its azalog **5** to their respective ribosides are in progress.

Experimental Section

3-Cyano-4-aminopyrazolo[3,4-*d*]pyrimidine (5).—A mixture of 6.45 g. (0.05 mole) of 5-aminopyrazole-3,4-dicarbonitrile[5] and 70 ml. of triethyl orthoformate was heated under reflux for 7 hr., with precautions to protect the reaction mixture against atmospheric moisture. Excess triethyl orthoformate was removed by evaporation under reduced pressure and the residual, crude ethoxymethylenamino derivative **9** dissolved in 100 ml. of absolute ethanol and added to 50 ml. of ethanolic ammonia (saturated at 0°). After 24 hr. at room temperature, the solid which had separated was collected by filtration; a second crop of product was obtained by concentration of the filtrate; the total yield was 6.40 g. (83%). The analytical sample was prepared by crystallization from water. The product slowly decomposed upon heating above 200°. It showed bands at $\lambda_{max}^{C_2H_5OH}$ 233 and 282 mμ (ε 9630 and 10,010).

Anal. Calcd. for $C_6H_4N_6$: C, 45.04; H, 2.52; N, 52.53. Found: C, 44.86; H, 2.44; N, 52.44.

5-Formamidopyrazole-3,4-dicarbonitrile (10).—Crude 5-(ethoxymethylenamino)pyrazole-3,4-dicarbonitrile (**9**), prepared by evaporation of the triethyl orthoformate reaction mixture as described above, was recrystallized from pyridine–petroleum ether (30–60°), with no special precautions to use scrupulously dry solvents. The product so obtained decomposed slowly upon heating above 200°; it exhibited a strong amide carbonyl band at 1700 cm.$^{-1}$ (infrared) and $\lambda_{max}^{C_2H_5OH}$ 216 and 245 mμ (ε 14,300 and 11,500).

Anal. Calcd. for $C_6H_3N_5O$: C, 44.76; H, 1.88; N, 43.52. Found: C, 44.73; H, 1.88; N, 43.46.

Conversion of 3-Cyano-4-aminopyrazolo[3,4-*d*]pyrimidine (5) to 4-Aminopyrazolo[3,4-*d*]pyrimidine (7).—A mixture of 2.0 g. of 3-cyano-4-aminopyrazolo[3,4-*d*]pyrimidine and 50 ml. of 10% aqueous sodium hydroxide was heated under reflux for 24 hr., cooled and acidified with 9% aqueous hydrochloric acid. Filtration gave 1.60 g. (72%) of a product whose infrared spectrum indicated the presence of bands characteristic of a carboxylic acid and the loss of the nitrile band (2235 cm.$^{-1}$) characteristic of the starting material. Vacuum sublimation of this crude carboxylic acid resulted in smooth decarboxylation to give 4-aminopyrazolo[3,4-*d*]pyrimidine, identical in every respect (ultraviolet and infrared) with an authentic sample.[7]

3-Cyano-4(5H)-pyrazolo[3,4-*d*]pyrimidinone (11).—A suspension of 1.25 g. of 3-cyano-4-aminopyrazolo[3,4-*d*]pyrimidine in 40 ml. of 8% aqueous hydrochloric acid was stirred at 0° while a solution of 5 g. of sodium nitrite in 10 ml. of water was added slowly over the course of 1 hr. An additional 1 g. of sodium nitrite was then added and the reaction mixture was brought to boiling. Cooling resulted in the separation of 0.75 g. (60%) of a white, crystalline solid which was recrystallized from water: m.p. 348° dec.; $\lambda_{max}^{C_2H_5OH}$ 225, 232, and 261 mμ (ε 9660, 12,268, and 14,000).

Anal. Calcd. for $C_6H_3N_5O$: C, 44.76; H, 1.88; N, 43.52. Found: C, 44.56; H, 1.92; N, 43.42.

(7) We are indebted to Dr. Harry B. Wood, Jr., Cancer Chemotherapy National Service Center, National Institutes of Health, for supplying us with this material.

Indolothiopyrylium Compounds. II. 1,2,3,4-Tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]-thiopyran and -thiopyrylium Salts[1,2]

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In a recent article[2] we described the preparation of benz[*b*]indolo[2,3-*d*]thiopyrylium perchlorate, as well as a number of substituted derivatives, and presented n.m.r. spectral data which favored the electronic distribution of the thiopyrylium formulation of this new aromatic ring system. We now wish to report the synthesis of 1,2,3,4-tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyrylium perchlorate (**6a**) and the corresponding chloride **6b** (see Scheme I), which, except for the location of the positive charge, are analogous to and essentially iso-π-electronic with salts of the indole alkaloid sempervirine.[4] The free base, 1,2,3,4-tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyran (**7**), is also of interest as a new pseudoazulene,[5] formally derived from cyclopenta[*c*]thiopyran (**8**)[6,7] by aza replacement of the 5-methine group and fusion of additional carbocyclic rings at the c and g (3,4 and 6,7) bonds.

The 6,7,8,9-tetrahydrobenzo[*g*]thiochroman-4-one (**2**) required as starting material was prepared by ring closure of 3-(tetralyl-*ar*-2-thio)propionic acid (**1**) with concentrated sulfuric acid, and separated from the isomeric ketone **3** *via* fractional crystallization and subsequent hydrolysis of the semicarbazones as already described.[8] The structure of ketone **2**, although assigned but not unambiguously established by the original authors,[8] was corroborated by its n.m.r. spectrum (in deuteriochloroform), which, in addition to a series of three multiplets centered at[9] δ 3.04, 2.71, and 1.75, representing the 12 aliphatic protons, exhibited two singlets (integration for one proton each) at δ 7.80 and 6.94, corresponding to the two aromatic protons. The δ value of the low-field singlet

(1) Abstracted from the Ph.D. Dissertation of P. H. Scott, Lehigh University, 1965.

(2) Part I: T. E. Young and P. H. Scott, *J. Org. Chem.*, **30**, 3613 (1965).

(3) Warner-Lambert Research Fellow, 1963–1965.

(4) R. B. Woodward and W. M. McLamore, *J. Am. Chem. Soc.*, **71**, 379 (1949); R. B. Woodward and B. Witkop, *ibid.*, **71**, 379 (1949).

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(6) A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *J. Am. Chem. Soc.*, **85**, 3448 (1963); A. G. Anderson, Jr., W. F. Harrison, R. G. Anderson, and A. G. Osborne, *ibid.*, **81**, 1255 (1959).

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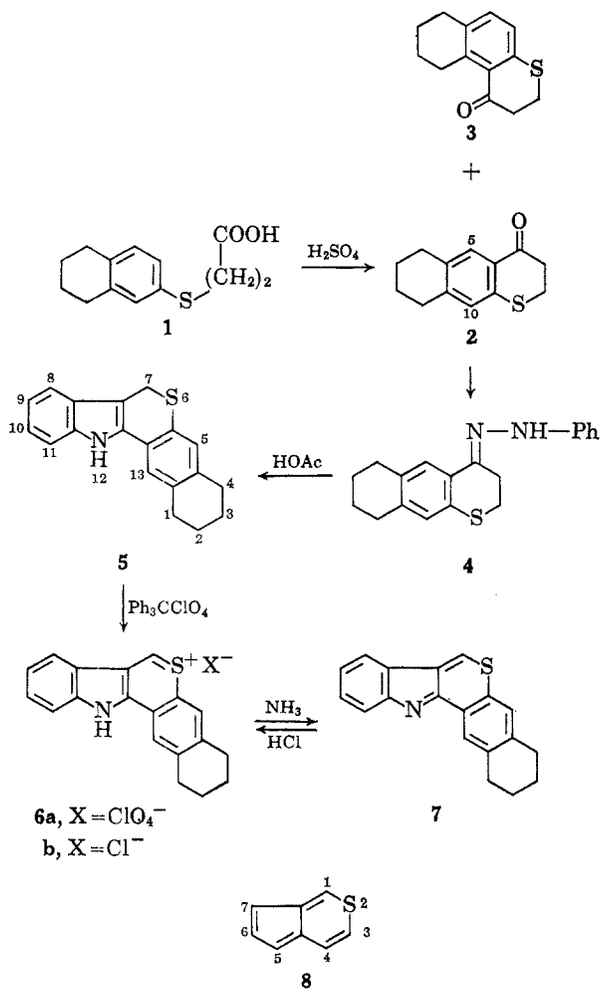
(8) F. Krollpfeiffer and H. Schultze, *Ber.*, **56**, 1819 (1923).

(9) Values of δ in parts per million are taken as positive downfield from tetramethylsilane used as internal standard.

SCHEME I



(δ 7.80) is that expected[10] for an aromatic proton *ortho* to an acyl substituent; hence the singlets at δ 7.80 and 6.94 are clearly assignable to the protons at positions 5 and 10, respectively.

The ketone **2** was converted in the usual way to its phenylhydrazone **4**, which readily underwent a Fischer ring closure in boiling glacial acetic acid to yield 1,2,-3,4,7,12-hexahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyran (**5**). Abstraction of a hydride ion from position 7 of this intermediate (**5**) with trityl perchlorate in acetic acid solution then afforded the thiopyrylium perchlorate **6a**. However, since the indole **5** had been isolated in only 28% yield, and since thin layer chromatography of the crude cyclization reaction mixture suggested that **5** was formed in significantly better yield, it was found expedient to conduct the two-step sequence (**4** → **5** → **6a**) without isolation of **5**. In this way a 73% over-all conversion of **4** to **6a** was realized.

The indolothiopyran **7** was obtained simply by reaction of the perchlorate salt **6a** with gaseous ammonia in anhydrous benzene solution. This free base was a stable, orange crystalline solid, which reverted to the parent perchlorate salt **6a** on treatment with perchloric acid, and which was readily converted to the corresponding indolothiopyrylium chloride **6b** by the action of anhydrous hydrogen chloride in benzene solution.

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," The Macmillan Co., New York, N. Y., 1959, p. 63.

The reversible acid–base system (**6** ⇄ **7**) is of particular interest since, unlike cyclopenta[*c*]thiopyran (**8**),[7] protonation does not require localization of a pair of π electrons in the free base (**7**), and indeed **6** and **7** are iso-π-electronic. More detailed studies and some observations concerning π delocalization in several simpler relatives of the interesting pseudoazulene (**7**) will be reported in a subsequent communication.

Experimental Section[11]

6,7,8,9-Tetrahydrobenzo[*g*]thiochroman-4-one Phenylhydrazone (4).—To a solution of 5.69 g. (0.0261 mole) of 6,7,8,9-tetrahydrobenzo[*g*]thiochroman-4-one (**2**, m.p. 58–60°, lit.[8] m.p. 60–61°) in 150 ml. of methanol in a nitrogen atmosphere was added 5 drops of glacial acetic acid and 2.7 ml. (0.027 mole) of phenylhydrazine. The solution was refluxed for 5 min., then allowed to stand at room temperature until the phenylhydrazone had precipitated. The mixture was then chilled in a refrigerator, after which the precipitate was collected by filtration and washed with 150 ml. of cold methanol. The pale yellow product weighed 6.76 g. (84%), m.p. 189–192° (sealed tube). Several recrystallizations from methanol, under nitrogen, afforded an analytical sample, m.p. 190–193° (sealed tube).

Anal. Calcd. for $C_{19}H_{20}N_2S$: C, 73.98; H, 6.54; N, 9.08; S, 10.39. Found: C, 73.75; H, 6.52; N, 8.97; S, 10.27.

1,2,3,4,7,12-Hexahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyran (5).—When a stirred suspension of 3.00 g. (9.75 mmoles) of 6,7,8,9-tetrahydrobenzo[*g*]thiochroman-4-one phenylhydrazone (**4**) in 30 ml. of glacial acetic acid under nitrogen was gently refluxed, the phenylhydrazone slowly dissolved to give a pale yellow solution. After dissolution was complete (75 min.), reflux was continued for 2 hr. The cooled solution yielded 2.15 g. of light brown needles, m.p. 150–170°. Recrystallization from benzene–cyclohexane gave 1.58 g. of product, m.p. 175–180° with some material still unmelted at 200°. This product, when refluxed with cyclohexane, left 0.30 g. of cyclohexane-insoluble residue, m.p. 180–200°, and the cyclohexane extract, when cooled, yielded 0.80 g. (28%) of the desired indole (**5**) as yellow crystals, m.p. 176–182°. Repeated recrystallization from petroleum ether (b.p. 60–70°) gave pure **5** as pale yellow crystals, m.p. 183.0–184.5° (sealed tube).

Anal. Calcd. for $C_{19}H_{17}NS$: C, 78.31; H, 5.88; S, 11.00. Found: C, 78.11; H, 5.88; S, 11.03.

1,2,3,4-Tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyrylium Perchlorate (6a).—A suspension of 1.00 g. (3.24 mmoles) of the phenylhydrazone **4** in 50 ml. of acetic acid was gently refluxed in a nitrogen atmosphere. Within 20 min. the solid had completely dissolved, and, after 2.5 hr., 1.12 g. (3.26 mmoles) of trityl perchlorate[12] was added. The mixture was stirred for 30 min. without further heating and then allowed to stand overnight. The yellow solid product was collected by filtration and washed with anhydrous ether. The yield was 0.91 g. (73%) of **6a**, m.p. 290° dec. Several recrystallizations from nitromethane afforded pure product, m.p. 286–287° dec.

Anal. Calcd. for $C_{19}H_{16}ClNO_4S$: C, 58.53; H, 4.14; S, 8.22. Found: C, 58.69; H, 4.65; S, 7.99.

1,2,3,4-Tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyran (7).—Gaseous ammonia was bubbled slowly for 1 hr. through a slurry of 1.93 g. (4.95 mmoles) of **6a** in 75 ml. of benzene. The mixture was then filtered, and the precipitate was washed with fresh benzene. Evaporation of the combined filtrate and washing gave 1.24 g. of orange solid which melted at 98°, resolidified above 112°, and remelted at 189–192°. This solid was heated with 200 ml. of petroleum ether, and, after most of the solvent had evaporated, the precipitate was recollected by filtration. This precipitate weighed 1.08 g. (76% yield) and had m.p. 186–194°. Recrystallization from acetonitrile yielded pure **7**, m.p. 195–197°.

Anal. Calcd. for $C_{19}H_{15}NS$: C, 78.86; H, 5.23; S, 11.09. Found: C, 78.79; H, 5.31; S, 11.12.

1,2,3,4-Tetrahydronaphth[2,3-*b*]indolo[2,3-*d*]thiopyrylium Chloride (6b).—Ammonia was bubbled for 30 min. through a

(11) Melting points were determined in capillary tubes using a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) and are corrected. The n.m.r. spectrum was determined on a Varian A-60 spectrometer.

(12) Freshly prepared according to K. A. Hoffman and H. Kimmreuther, *Ber.*, **42**, 4865 (1909).

slurry of 2.77 g. (7.11 mmoles) of the perchlorate **6a** in benzene. The mixture was then filtered and the precipitate was washed with fresh benzene. The combined benzene solutions were evaporated on a steam bath to assure complete removal of ammonia, and the residue was again dissolved in benzene. Gaseous hydrogen chloride was bubbled through the solution for 15 min.; then the resulting precipitate was collected by filtration, washed with benzene, and air dried. The crude product (2.22 g., 96% yield), when recrystallized from methanol and dried at 137° and 0.05 mm., yielded 1.78 g. (77%) of pure **6b** as brown-orange needles, which gradually darkened and decomposed above 280°.

Anal. Calcd. for $C_{19}H_{16}ClNS$: C, 70.03; H, 4.95; Cl, 10.88; S, 9.84. Found: C, 69.80; H, 4.65; Cl, 10.89; S, 9.74.

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A New Synthesis of *o*-Nitrophenylacetaldehyde

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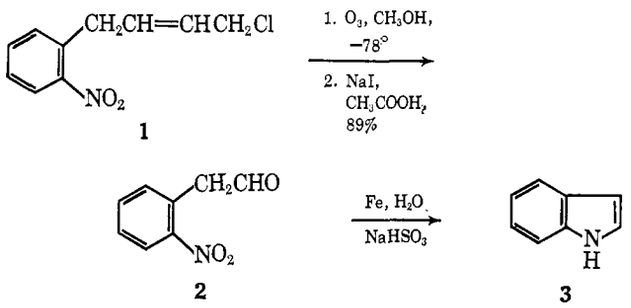
o-Nitrophenylacetaldehyde (**2**) is the key intermediate in the synthetic proof of structure of triindole,[2,3] indole–di-2-methylindole mixed trimer,[2-4] indole–di-1,2-dimethylindole mixed trimer,[2,3] indole–di-2,5-dimethylpyrrole mixed trimer,[2,3] and tri-1-methylindole.[3] It has also been used in a synthesis of indole (**3**), by reduction with iron powder and aqueous sodium bisulfite.[5] The previously reported route[5,6] to **2** gives only a 21% yield[3] from *o*-nitrocinnamamide. Nitration of phenylacetaldehyde at −10 to −15° did not give **2**.[5,7]

The present procedure for the synthesis of **2** involves ozonolysis of 1-chloro-4-(*o*-nitrophenyl)-2-butene[8-11] (**1**), the product of the Meerwein reaction of diazotized *o*-nitroaniline and 1,3-butadiene. The procedure is simpler, shorter, and proceeds in much higher yield (72%) from the more readily available *o*-nitroaniline than does the older method[5] starting from *o*-nitrocinnamic acid.



Application of the Meerwein reaction to diazotized readily available *o*-nitroaniline derivatives and appropriate 1,3-dienes, followed by ozonolysis of the products according to the procedure illustrated here and subsequent reductive cyclization, should greatly increase the usefulness of the Baeyer–Jackson synthesis[12] of indoles.

Experimental Section

1-Chloro-4-(*o*-nitrophenyl)-2-butene (1).—The procedure is essentially that of Braude and Fawcett[8] and Goldberg and Scott.[9] A solution was prepared by adding solutions of sodium acetate trihydrate (80 g., 0.59 mole) in water (100 ml.) and cupric chloride dihydrate (38 g., 0.22 mole) in water (42 ml.) to acetone (1 l.) in a 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and a Dry Ice–acetone condenser set up for reflux. The resulting solution was cooled in an ice–salt bath. 1,3-Butadiene (125 ml., 1.44–1.50 moles) was condensed in a precalibrated 250-ml. erlenmeyer flask cooled in a Dry Ice–acetone bath. The butadiene was then poured into the cooled acetone solution. An aqueous suspension of diazotized *o*-nitroaniline [from *o*-nitroaniline (140 g., 1.01 moles), concentrated hydrochloric acid (240 ml.) in water (200 ml.), and sodium nitrite (70 g., 1.01 moles) in water (120 ml.)] kept at −2 to 0°[13] was then siphoned slowly over about 1 hr. into the mechanically stirred, cooled butadiene solution. The liquid mixture was stirred for 6 hr. (or overnight), during which the ice in the bath melted and the solution warmed to room temperature.

The resulting dark brown supernatant oil was separated. The light green, aqueous lower layer was diluted with water (1 l.), and the resulting solution (about 2.7 l.) was extracted with ether (two 500-ml. portions). The ether extracts were combined with the oil, shaken gently (to avoid an emulsion, which separates only slowly) with water (two 500-ml. portions) and saturated salt solution (two 250-ml. portions), and dried over anhydrous sodium sulfate. The ether was then evaporated at aspirator pressure with a rotary evaporator, leaving a brown oil (201 g., 94%), $n^{24}D$ 1.5657, lit.[8] 75%. Vacuum distillation, without significant forerun,[13] gave a brown oil (173 g., 81%): b.p. 108–118° (0.35 mm.), $n^{25}D$ 1.5662; lit. 66%,[10,11] b.p. 126° (0.005 mm.),[8] 155–156° (3 mm.),[10,11] $n^{20}D$ 1.5653,[8] 1.5692[10,11]; ν 1660 (w), 1610 (m), 1580 (mw) (C=C), 1530 (vs), 1350 (s) (NO_2) cm.$^{-1}$ on the oil. The n.m.r. spectrum of a 60% (w./v.) solution in deuteriochloroform contains (with areas relative to 10 protons given in parentheses; δ scale, 1 p.p.m. = 60.00 c.p.s.) an extensively split doublet (1.1) centered at about 7.97 (J = 7 c.p.s., proton *ortho* to the nitro group), a complex multiplet (3.4) from 7.75 to 7.25 with a strong peak at 7.50 (remaining three aromatic protons), a complex multiplet (1.9) centered at 5.87 (two vinyl protons), a doublet (1.8) centered at 4.05 (J = 5.4 c.p.s., methylene group attached to chlorine), and another doublet (1.8) centered at 3.71 (J = 5.4 c.p.s., methylene group attached to the phenyl ring).

***o*-Nitrophenylacetaldehyde (2).**—A solution of 1-chloro-4-(*o*-nitrophenyl)-2-butene (25 g., 0.118 mole) in technical grade methanol[14] (180 ml.) in a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a gas inlet tube extending below the surface of the solution, and a gas exit tube, was cooled in a Dry Ice–isopropyl alcohol bath until extensive precipitation of the starting material occurred as a yellow precipitate.

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(12) (a) A. Baeyer and O. R. Jackson, *Chem. Ber.*, **13**, 187 (1880); (b) A. Baeyer, *ibid.*, **13**, 2254 (1880); (c) O. R. Jackson, *ibid.*, **14**, 879 (1881); (d) for a comprehensive list of reactions and references, see P. L. Julian, E. W. Meyer, and H. C. Printy, in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 38, 39.

(13) On one occasion, during distillation of the product, a significant amount (~5 g.) of forerun, b.p. 105° (0.4 mm.), was encountered, which solidified in the condenser and receiver. This by-product may have resulted from allowing the temperature of the diazotized *o*-nitroaniline solution to rise as high as 5–7°.

(14) When absolute methanol was used, the yellow precipitate did not form on cooling, and the resulting product did not seem to be so pure as when ordinary hydrous methanol was used.