duced to crystallize. After acetylation with pyridine and acetic anhydride the product was crystallized from ether containing a few drops of methanol. This material had the following properties: m.p. 212–214°, $\alpha^{26}D$ −10.2° (chloroform), M_D −47°. The ultraviolet absorption spectrum showed no maximum below 275 mμ. The infrared spectrum showed a peak at 9.54 μ, which is in the range associated with the carbon–oxygen stretching of an aliphatic ether. The peak at 2.6–2.8 μ characteristic of a hydroxyl group was completely absent.

Anal. Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.69; H, 8.01.

Ethanolic Potassium Hydroxide Hydrolysis.—The remaining one-fourth portion of the oxidized pseudokammogenin triacetate was dissolved in 40 cc. of absolute ethanol containing 1.0 g. of potassium hydroxide and the solution was allowed to stand at 60–65° for 15 min. After cooling and neutralizing with acetic acid, the solution was evaporated *in vacuo* and the oily steroid was extracted with ether. After processing in the manner described above, the acetylated product was crystallized from methanol–ether; m.p. 202–203°, mixed m.p. with product from methanol hydrolysis 186–187°, $\alpha^{26}D$ −12.3° (chloroform), M_D −58°; no ultraviolet absorption below 270 mμ. It is of interest to note that the molecular rotation difference between the ethoxy and methoxy derivatives, (M_D-OEt − M_D-OMe), −11°, corresponds quite closely to the same value (ΔM_D −13°) for the ethoxy and methoxy derivatives reported by Fukushima and Gallagher.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.18; H, 8.39.

Acknowledgment.—We are indebted to Dr. H. M. Crooks, Jr., for his helpful advice. We thank Dr. T. F. Gallagher for communicating his findings prior to publication. We thank Miss G. Saladonis and Mr. C. E. Childs for the microanalyses and Drs. J. M. Vandenbelt and R. B. Scott and the Misses D. Lundquest and P. Welch for ultraviolet and infrared absorption spectra.

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Some Thermochromic Spirans

BY C. F. KOELSCH AND W. R. WORKMAN[1]

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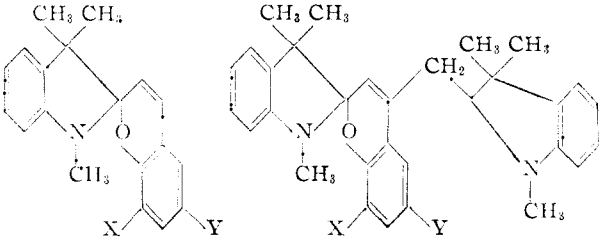
A theory was advanced almost simultaneously by Knott[2] and by one of us[3] to account for the thermochromism of certain spirans. The report of Knott included supporting evidence based on a study of spirans bearing polar substituents, and therefore our projected investigation into this aspect of the problem is no longer necessary. The present paper describes some results we had already obtained, differing in small details from those of previous investigators. These differences in no way affect the conclusions drawn by Knott and concurred in by us.

Condensation of salicylaldehyde with 1,3,3-trimethyl-2-methyleneindoline has been reported[4] to form a compound, m.p. 208°, assigned structure I. It has been found that the reaction actually yields two products: I, m.p. 93–94°, and II, m.p. 206–207°. Analytical figures for carbon and hydrogen, relied on in the older work, are not sufficient to identify I or II, nitrogen content, however, is characteristic. A separate synthesis of II, demethylation of *o*-methoxybenzalbis-(1,3,3-trimethyl-2-methyleneindoline), further supports the structure now suggested.



I, X = Y = H
III, X = OCH_3, Y = H
V, X = H, Y = Br
VII, X = H, Y = NO_2
VIII, X = Y = NO_2

II, X = Y = H
IV, X = OCH_3, Y = H
VI, X = H, Y = Br

o-Vanillin and 1,3,3-trimethyl-2-methyleneindoline yield not only III, m.p. 123–124° as previously reported,[4] but also IV, m.p. 223–224°. 5-Bromosalicylaldehyde yields two analogous products, V, m.p. 86–87°, and VI, m.p. 199–200°. But 5-nitrosalicylaldehyde gives only one product, VIII, m.p. 179.5–180°.[5] Similarly, 3,5-dinitrosalicylaldehyde gives only one product, VIII, m.p. 270° dec.

Experimental

Condensation of 1,3,3-Trimethyl-2-methyleneindoline with Salicylaldehyde.—A solution of 6.5 g. of the freshly distilled indoline and 4.1 g. of salicylaldehyde in 20 ml. of alcohol was boiled for two hours. The hot mixture was then filtered, and the solid was washed with hot alcohol. Recrystallization from acetone gave 2.5 g. of 1,3,3-trimethyl-4′-(1,3,3-trimethyl-2-indolinylmethyl)-indoline-2-spiro-2′-benzopyran (II), colorless crystals that melted at 209–210° to a pink liquid. The compound gave a violet solution in hot diphenyl ether.

Anal. Calcd. for $C_{31}H_{34}N_2O$: C, 82.6; H, 7.6; N, 6.4. Found[6]: C, 82.55; H, 7.6; N, 6.2.

The reaction mother liquors and the alcohol wash were distilled to a small volume, and the resulting solid was recrystallized from dilute alcohol, giving 5.4 g. of 1,3,3-trimethylindoline-2-spiro-2′-benzopyran (I), colorless crystals that melted to a colorless liquid at 92–94°. The compound gave a colorless solution in boiling xylene, a violet one in boiling diphenyl ether.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.3; H, 6.9; N, 5.0. Found: C, 82.7; H, 6.9; N, 5.1.

***o*-Methoxybenzalbis-(1,3,3-trimethyl-2-methyleneindoline).**—A solution of 5.9 g. of 1,3,3-trimethyl-2-methyleneindoline and 2.4 g. of *o*-methoxybenzaldehyde in 20 ml. of alcohol was boiled for four hours.[7] The product was removed by filtration and crystallized from acetone, giving 5 g. of colorless needles, m.p. 159–161°.

Anal. Calcd. for $C_{32}H_{36}N_2O$: N, 6.04. Found: N, 6.06.

A mixture of 1.0 g. of the methoxy compound, 8.7 g. of aluminum chloride and 20 ml. of benzene was boiled for 2.5 hours. The benzene was then decanted, and the residual thick oil was treated with aqueous potassium hydroxide. The pink solid remaining was crystallized from acetone, giving colorless crystals, m.p. 209–210°, alone or mixed with the compound obtained directly from salicylaldehyde.

Condensation with *o*-Vanillin.—A solution of 1.7 g. of 1,3,3-trimethyl-2-methyleneindoline and 1.5 g. of *o*-vanillin in 40 ml. of alcohol was boiled for 2.5 hours. The solid which separated directly was washed with alcohol and

(1) From the Ph.D. Thesis of W. R. Workman.
(2) E. B. Knott, *J. Chem. Soc.*, 3038 (1951).
(3) C. F. Koelsch, *J. Org. Chem.*, **16**, 1352 (1951).
(4) R. Wizinger and H. Wenning, *Helv. Chim. Acta*, **23**, 247 (1940).
(5) This is the m.p. reported by Knott for the isomer obtained from 3-nitrosalicylaldehyde, whereas the condensation product from 5-nitrosalicylaldehyde was stated to melt at 147°. In the present work only 5-nitrosalicylaldehyde m.p. 125–126° was used.
(6) The figures for C and H are taken from ref. 4.
(7) *Cf.* A. Ferratine, *Gazz. chim. ital.*, **24II**, 194 (1894); G. Plancher, *ibid.*, **28II**, 37 (1898); *Ber.*, **31**, 1494 (1898).

acetone, giving a small amount of 8′-methoxy-1,3,3-trimethyl-4′-(1,3,3-trimethyl-2-indolinylmethyl)-indoline-2-spiro-2′-benzopyran (IV), colorless crystals that melted to a pink liquid at 223–224°.

Anal. Calcd. for $C_{32}H_{36}N_2O_2$: C, 80.0; H, 7.6. Found: C, 80.0; H, 7.9.

From the mother and wash liquors there was obtained 1.3 g. of 8′-methoxy-1,3,3-trimethyl-2-spiro-2′-benzopyran (III), colorless crystals that gave a violet melt at 123–124°, and a purple solution in boiling diphenyl ether.

Condensation with 5-Bromosalicylaldehyde (a).—A solution of 6.7 g. of 5-bromosalicylaldehyde and 5.7 g. of 1,3,3-trimethyl-2-methyleneindoline in 90 ml. of alcohol was boiled for two hours and then cooled. The solid (0.35 g., VI) was removed, and the main product was precipitated with water. Recrystallization from alcohol gave 3.7 g. of 6′-bromo-1,3,3-trimethylindoline-2-spiro-2′-benzopyran (V), colorless crystals m.p. 86–87° to a colorless liquid. A solution of the compound in boiling xylene was colorless, in boiling diphenyl ether blue.

Anal. Calcd. for $C_{19}H_{18}BrNO$: C, 64.1; H, 5.1. Found: C, 64.4; H, 5.3.

(b).—A solution of 3.4 g. of 5-bromosalicylaldehyde and 5.7 g. of 1,3,3-trimethyl-2-methyleneindoline in 75 ml. of alcohol was boiled for two hours. The solid was removed, washed with acetone, and crystallized from benzene. There was obtained 7.1 g. of 6′-bromo-1,3,3-trimethyl-4′-(1,3,3-trimethyl-2-indolinylmethyl)-indoline-2-spiro-2′-benzopyran (VI), colorless crystals, m.p. 199–200° to a pink liquid. A solution in boiling diphenyl ether was violet.

Anal. Calcd. for $C_{31}H_{33}BrN_2O$: C, 70.4; H, 6.3. Found: C, 70.6; H, 6.4.

Condensation with 5-Nitrosalicylaldehyde.—A solution of 1.8 g. of 5-nitrosalicylaldehyde and 1.7 g. of 1,3,3-trimethyl-2-methyleneindoline in 40 ml. of alcohol was kept at room temperature for eleven days. The green precipitate was then removed, dissolved in pyridine and treated with charcoal. Precipitation with water gave 1.9 g. of 1,3,3-trimethyl-6′-nitroindoline-2-spiro-2′-benzopyran (VII), pale orange crystals that melted at 179–180° to a blue liquid.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.8; H, 5.6. Found: C, 70.8; H, 5.7.

Condensation with 3,5-Dinitrosalicylaldehyde.—A solution of 2.4 g. of 3,5-dinitrosalicylaldehyde and 1.7 g. of 1,3,3-trimethyl-2-methyleneindoline was treated as the preceding preparation. There was obtained a good yield of 6′,8′-dinitro-1,3,3-trimethylindoline-2-spiro-2′-benzopyran (VIII), dark green crystals that charred at 270°. The compound evidently exists in a dipolar form, giving a violet solution in cold diphenyl ether that becomes blue when it is heated.

Anal. Calcd. for $C_{19}H_{17}N_3O_5$: C, 62.1; H, 4.6. Found: C, 62.3; H, 5.0.

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A Synthesis of Isonicotinic Acid by Halogen–Metal Exchange and Its Application to the Preparation of Isonicotinic-C^{14} Acid Hydrazide[1]

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The recent discovery of the tuberculostatic activity of isonicotinic acid hydrazide made it desirable to prepare the C^{14}-labeled drug for metabolic studies. Labeling isonicotinic acid in the ring, by any of the many known preparative routes, would require a long costly synthesis involving many steps with radioactive material. The halogen–metal interconversion reaction which has wide application[2] and which was used to prepare nicotinic-C^{14} acid,[3] provided a synthesis of the desired compound in good yield with carboxyl labeling in the final step.

The very unstable intermediate, 4-bromopyridine, was first adequately described by Wibaut, *et al.*[4] Because of poor yields, these workers abandoned the preparation by halogenation of 4-hydroxypyridine in favor of the Sandmeyer reaction with 4-nitroaminopyridine. However, yields were reported to be small and no figures were given. Two runs, in this Laboratory, by the latter procedure gave less than 10% yield. The Craig[5] modification of the Sandmeyer procedure for α-substituted pyridines does not appear to have been applied to 4-aminopyridine. By adapting this procedure and Wibaut's method of isolation, 4-bromopyridine was prepared in yields of 85–95%. The dry compound in ether solution, at concentrations of 0.3–0.4 millimole per ml., is satisfactorily stable for use, but storage in an ice-box is recommended. The hydrochloride was prepared and found to be quite stable, and 4-bromopyridine is readily regenerated quantitatively as needed.

Experimental[6]

4-Aminopyridine.—The compound was prepared by two methods.[7] (a) The Hofmann reaction with isonicotinamide gave crude product (m.p. 155–159°) in 55–62% yield, isolated by continuous benzene extraction. (b) The method of Koenigs and Greiner[8,4] gave crude product (m.p. 155–158°) in yields of 70–78% from 4-pyridylpyridinium dichloride. A steel bomb, tested to 2000 p.s.i., was used in the ammonolysis. Recrystallization from water, alcohol, benzene or chloroform gave pure material melting at 159–160°.

4-Bromopyridine.—To 24 ml. of redistilled 48% hydrobromic acid, in a 100-ml. flask cooled in ice, was added 4.00 g. (0.0425 mole) of 4-aminopyridine. To this cold, stirred solution, 20.4 g. (0.128 mole) of bromine was added dropwise over a period of 10 minutes. The resulting slurry of perbromide was then diazotized at −10° by adding 7.57 g. (0.107 mole) of sodium nitrite in 11 ml. of water over a period of 30 minutes. After an additional 10-minute period of stirring, the bath was removed and the vigorously stirred reaction mixture was allowed to warm slowly to room temperature while a vigorous evolution of brown fumes ensued. The flask and contents were again chilled in the ice-bath and the stirred mixture was decolorized by adding saturated sodium sulfite solution. The mixture was then transferred to a 500-ml. flask with an equal volume of water and the resulting solution was heated under reflux for 7–10 minutes to expel sulfur dioxide. After making the cooled solution strongly basic, the product was submitted to steam distillation, without delay, and collected in a small separatory funnel. The colorless oil (4.5 ml., 6.539 g., 97.3%) was quickly separated and diluted with 100 ml. of absolute ether.[9] The solution was dried for at least 24 hours by stirring with powdered "Drierite" and then separated by gravity filtration through a large sintered glass funnel protected by "Drierite" guard tubes.

The solution was assayed for 4-bromopyridine by pipetting a 2-ml. aliquot into 20 ml. of dry ether saturated with mercuric chloride. The precipitate ($C_5H_4NBr \cdot HgCl_2$, m.p. 273° dec.) was washed with 2–3 ml. of ether and weighed,

(1) Work done under the auspices of the A.E.C.

(2) R. G. Jones and Henry Gilman, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 339.

(3) A. Murray, III, W. W. Foreman and W. Langham, THIS JOURNAL, **70**, 1037 (1948).

(4) J. P. Wibaut, J. Overhoff and H. Geldof, *Rec. trav. chim.*, **54**, 807 (1935).

(5) L. C. Craig, THIS JOURNAL, **56**, 232 (1934).

(6) All melting points are uncorrected.

(7) R. Camps, *Arch. Pharm.*, **240**, 345 (1902) [*Chem. Zentr.*, **73**, II, 647 (1902)]; D. G. Leis and B. C. Curran, THIS JOURNAL, **67**, 79 (1945).

(8) E. Koenigs and H. Greiner, *Ber.*, **64**, 1055 (1931).

(9) Unless the product is dispersed in solvent as soon as possible, it quickly decomposes to a yellow, ether-insoluble, water-soluble compound.