Experimental Section

All ultraviolet spectra were measured with a Beckman Model DC instrument in 95% alcohol. Infrared spectra were measured in a Perkin-Elmer Infracord either in chloroform or Nujol mulls.

Isolation of Irisolidone (I, R = H).—Air-dried powdered rhizomes (50 kg.) of *Iris nepalensis* were extracted four times with hot petroleum ether (b.p. 60–80°) and then with chloroform. The chloroform extract yielded irisolone[1] and irigenin,[2] whereas the petroleum ether extract, on concentration to about 2 l. and standing in refrigerator for a few days, deposited a solid. This was dissolved in methanol and the solution on concentration yielded a yellow compound which on further crystallization gave irisolidone (5 g.), m.p. 195–196°, lit.[8] m.p. 191–192°. Irisolidone gave a blue color with ferric chloride, positive tests with boric acid,[10] boric acid in acetic anhydride (Dimroth reagent), and Gibb reagent,[11] and negative tests with chloropentaminocobaltic chloride[12] and sodium amalgam.[13] Infrared bands (in chloroform) occurred, *inter alia*, at 2.85, 6.05, 6.15, 6.25, 6.35, 6.65, 6.90, 9.40, 9.65, 10.10, and 11.98 μ. The ultraviolet spectrum in 95% ethanol showed a single maximum at 270 mμ (log ϵ 4.65). On the addition of 3 drops of 10% aqueous aluminum chloride the maximum shifted to 280 mμ (log ϵ 4.72). Addition of saturated alcoholic fused sodium acetate solution also shifted the maximum to 275 mμ (log ϵ 4.65).

Anal. Calcd. for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49; 2-OMe, 19.17. Found: C, 64.76; H, 4.56; OMe, 19.14.

Irisolidone Diacetate (I, R = Ac).—The acetate was prepared from irisolidone (0.1 g.), acetic anhydride (1 ml.), and pyridine (2 drops) by allowing to stand at room temperature for 24 hr.; it crystallized from methanol in colorless needles, m.p. 162–163°.

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55. Found: C, 63.45; H, 4.60.

Irisolidone Methyl Ether (I, R = CH_3).—A mixture of irisolidone (1.5 g.), freshly distilled dimethyl sulfate (6.4 ml.), anhydrous potassium carbonate (8.4 g.), and dry acetone (120 ml.) was refluxed for 36 hr. On working up in the usual manner, colorless plates of irisolidone methyl ether (1.35 g.), m.p. 181°, were obtained, identical with tri-O-methyltectorigenin (mixture melting point and infrared spectrum).

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.52; H, 5.26.

Irisolidone Ethyl Ether (I, R = C_2H_5).—Irisolidone (2 g.), potassium carbonate (4 g.), ethyl iodide (20 ml.), and acetone (200 ml.) were refluxed together for 40 hr. Work-up in the usual manner gave irisolidone ethyl ether, m.p. 113–114°; infrared bands (in chloroform) occurred, *inter alia*, at 6.05, 6.25, 6.35, 6.75, 6.90, 9.30, 9.45, 9.70, 10.00, and 12.00 μ.

Anal. Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.00; H, 6.30.

4′-Methoxybenzyl 2-Hydroxy-4,6-diethoxy-5-methoxyphenyl Ketone (II).—Irisolidone ethyl ether (450 mg.) was suspended in water (30 ml.) and a slow current of nitrogen free from oxygen was passed through the suspension. After 5 min. aqueous sodium hydroxide (15 ml., 10%) was added, and the mixture was refluxed for 2 hr., cooled to room temperature, and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated, and the residue was crystallized from methanol: m.p. 102–103°. It gave a brown color with alcoholic ferric chloride.

Anal. Calcd. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.42, H, 6.82.

Oxidation of Irisolidone Ethyl Ether.—The ethyl ether (0.5 g.) in acetone (50 ml.) was heated on a water bath and treated with powdered potassium permanganate in small lots until the pink color persisted. The solution was filtered and the solid was washed with acetone and then extracted with hot water. Acidification of the acqueous solution gave a solid, m.p. 186–187° (from hot water), lit.[14] m.p. 184°. It gave no depression with an authentic sample of anisic acid.

Alkali Fusion of Irisolidone Ethyl Ether.—Irisolidone ethyl ether (1 g.), sodium hydroxide (2.5 g.), and water (2 ml.) were heated in a copper tube at 220° for 45 min. Work-up in the usual manner yielded 3,5-diethoxy-4-methoxyphenol, m.p. 72°, lit.[15] m.p. 74°, and anisic acid. No depression in mixture melting points was obtained with authentic samples.

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(10) C. W. Wilson, *J. Am. Chem. Soc.*, **61**, 2303 (1939).
(11) F. E. King, T. J. King, and E. Sellars, *J. Chem. Soc.*, 563 (1957).
(12) Y. Asahina, J. Asano, and U. Ueno, *Bull. Chem. Soc. Japan*, **17**, 104 (1942).
(13) G. Bargellini, *Gazz. chim. ital.*, **49**, 47 (1919).
(14) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. I, Eyre Spottiswoode, London, 1953, p. 178.
(15) M. Krishnamurti and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **39A**, 144 (1954).

Abnormal Products during Isolation of Isonicotinic Acid Hydrazide

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In the course of isolation of isonicotinic acid hydrazide (I) from the reaction mixture of ethyl isonicotinate and hydrazine hydrate (free from ammonia) three basic by-products, namely, symmetrical diisonicotinyl hydrazine (II), hydrazodicarbonamide (III), and 3,5-bis(4-pyridyl)-1,2,4-triazole-1-carboxhydrazide (IV), have been isolated in small quantities as artifacts arising from the large-scale operation. Their separation is to be specially considered when isonicotinic acid hydrazide is required in high purity. The solubility of II and III in dilute alkali and the solubility of II in ethanol have rendered separation possible, and the products could be finally purified by crystallization from water.

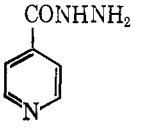
The product IV affords benzylidene and cinnamylidene derivatives. Oxidation under diverse conditions such as moderately dilute nitric acid, acid potassium permanganate, or sodium hypobromite IV gives rise to the formation of 3:5-bis(4-pyridyl)-1,2,4-triazole (V), carbon dioxide, and nitrogen. The identity of V has been confirmed by synthesis from I and isonicotinamide.[1]

Compound IV in solution of 10% sulfuric acid or in glacial acetic acid, when treated with bromine, gives a perbromide which by the action of alkali changes to V.

A solution of I in hydrazine hydrate saturated with carbon dioxide or a mixture of I, isonicotinamide, and carbohydrazide in aqueous medium when heated to reflux for some time leads to the formation of IV. Similarly, a solution of hydrazine hydrate saturated with carbon dioxide admixed with ammonia affords III.

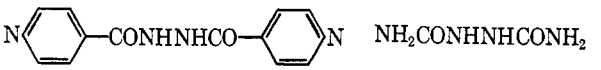
In the formation of the by-products III and IV, the mechanism of reaction involves the participation of atmospheric carbon dioxide, hydrazine, and ammonia (decomposition product of hydrazine[2]). Hydrazine and carbon dioxide form carbazic acid[3] which with ammonia and hydrazine lead to the formation of semi-

(1) O. Silberrad, *J. Chem. Soc.*, **77**, 1185 (1900).
(2) M. Berthelot and C. Matignon, *Compt. rend.*, **126**, 1042 (1896).
(3) R. Stolle and K. A. Hofmann, *Ber.*, **37**, 4523 (1904).



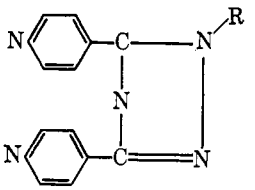
I

carbazide and carbohydrazide, respectively, through the corresponding ammonium and hydrazinium salts of carbazic acid. Additional ammonia reacts with I to form isonicotinamide[4] which again reacts with I to give diisonicotinylamide.[5] Semicarbazide[6] affords III, whereas diisonicotinylamide and carbohydrazide react to furnish IV.[7]



II

III



IV, R = $CONHNH_2$

V, R = H

Experimental Section[8]

Isolation of Symmetrical Diisonicotinylhydrazine (II), Hydrazodicarbonamide (III), and 3,5-Bis(4-pyridyl)-1,2,4-triazole-1-carboxhydrazide (IV).—The separation of first crop of I (m.p. 171–173°, purity 99.5%) from the reaction mixture of ethyl isonicotinate (b.p. 218°, sp. gr. 1.1003 at 25°, 25 kg., 165 moles) and hydrazine hydrate (free from ammonia, 35% w./v., 175 l.) afforded a mother liquor which on concentration, cooling, and filtration gave a solid cake consisting of the mixture of I, II, III, and IV. This cake, after trituration with cold water (18 l.) and filtration, afforded insoluble material (0.55 kg., a mixture of II, III, and IV), and the filtrate gave isonicotinic acid hydrazide on concentration. Caustic soda solution (10%, 200 ml.) dissolved II and III leaving behind IV as an insoluble material, which on crystallization from water, ethanol, or pyridine gave IV (9.8 g.) in fine white needles, showing m.p. 338–340° dec.

Anal. Calcd. for $C_{13}H_{11}N_7O$: C, 55.5; H, 3.9; N, 34.8. Found: C, 55.42; H, 3.76; N, 34.6.

The **picrate** crystallized from ethanol in yellow needles and showed m.p. 238–240° dec.

Anal. Calcd. for $C_{13}H_{11}N_7O \cdot 2C_6H_3N_3O_7$: N, 24.56. Found: N, 23.8.

The **hydrochloride** crystallized from water in beautiful yellow shining needles showing m.p. 308–310° dec.

Anal. Calcd. for $C_{13}H_{11}N_7O \cdot 2HCl$: HCl 20.6; N, 27.7. Found: HCl, 20.4; N, 27.5.

The alkaline solution on adjustment of pH to 6–7 gave a mixture of II and III from which III was obtained as an insoluble material by stirring with ethanol at room temperature. III was crystallized from water in beautiful shining needles (9.1 g.) showing m.p. 244–246° dec.[6] and no depression when admixed with an authentic sample of III. Removal of ethanol gave II which crystallized from water in white needles (500 g.) showing m.p. 262–264° (lit.[9] m.p. 262–264° and no depression when admixed with an authentic sample of II.

1-Benzylidenecarboxhydrazino-3,5-bis-(4-pyridyl)-1,2,4-triazole.—A clear solution of benzaldehyde (10 g., 0.94 mole), IV (10 g., 0.034 mole), and acetic acid (50 ml.) was heated to reflux for 4 hr., cooled, and diluted with ice-cold water (200 ml.). The aqueous part, after extraction of unreacted benzaldehyde with ether, was basified with 10% caustic soda solution in the cold and the crystalline solid that separated was crystallized from ethanol in brilliant cream-colored needles to afford the benzilidene derivative, 6.8 g., m.p. 196–198°.

Anal. Calcd. for $C_{20}H_{15}N_7O$: N, 26.55. Found: N, 26.7.

The hydrochloride crystallized from ethanol in light brown needles, m.p. 316–318°.

Anal. Calcd. for $C_{20}H_{15}N_7O \cdot 2HCl$: HCl, 16.5. Found: HCl, 16.3.

In a similar way the cinnamyledene derivative of IV was obtained in brown needles, m.p. 206–208°.

Anal. Calcd. for $C_{22}H_{17}N_7O$: N, 24.8. Found: N, 24.28.

Oxidation of 3,5-Bis(4-pyridyl)-1,2,4-triazole-1-carboxhydrazide (IV) to 3,5-Bis(4-pyridyl)-1,2,4-triazole (V).—The triazole IV (15 g., 0.051 mole) dissolved in 10% sulfuric acid (200 ml.) was treated with potassium permanganate (30 g., 0.19 mole) added gradually in small installments at room temperature. When the color of one addition was discharged, another addition followed. The gas evolved during oxidation was introduced to freshly prepared calcium hydroxide solution (100 ml., 5%) protected from atmospheric carbon dioxide. As the oxidation progressed, the calcium hydroxide solution turned milky indicating the formation of carbon dioxide. After oxidation, the reaction mixture was treated with 48% (w./w.) caustic soda solution to make the solution alkaline. The manganese dioxide which separated was filtered off and washed with water (100 ml.). The combined filtrate and washing were brought to pH 6–7 with hydrochloric acid and the product that separated was purified by crystallization from a water–ethanol mixture (1:1) to afford V in white flaky crystals, 8.2 g., m.p. 280–282°. It is amphoteric in nature being soluble both in acid and alkali, including ammonia and hydrazine.

Anal. Calcd. for $C_{12}H_9N_5$: C, 64.5; H, 4.0; N, 31.3. Found: C, 64.3; H, 4.1; N, 31.1.

The **picrate** crystallized from ethanol in yellow needles, m.p. 258–260° dec.

Anal. Calcd. for $C_{12}H_9N_5 \cdot 2C_6H_3N_3O_7$: N, 22.5. Found: N, 22.3.

The **hydrochloride** crystallized from water–ethanol mixture (1:1) in white needles, m.p. 338–340° dec.

Anal. Calcd. for $C_{12}H_9N_5 \cdot 2HCl$: N, 23.61; HCl, 24.6. Found: N, 23.8; HCl, 24.2.

On oxidation of IV with moderately dilute nitric acid the triazole V was isolated as its nitrate, which on crystallization from water in white needles showed m.p. 244–246° dec.

Anal. Calcd. for $C_{12}H_9N_5 \cdot 2HNO_3$: N, 28.1. Found: N, 28.6.

From the above nitrate V was isolated at pH 6–7.

Formation of V from IV by Bromine and 10% Caustic Soda.—To the triazole IV (20 g., 0.068 mole), suspended in 10% caustic soda solution (250 ml.), bromine (10 ml.) was slowly added with stirring and ice cooling; IV underwent decomposition with evolution of gas (nitrogen) and gradually goes into solution. The straw-colored solution (pH 10–11) obtained after complete addition of the bromine was brought to pH 6–7 with hydrochloric acid with evolution of carbon dioxide and separation of the triazole V, 12 g., after crystallization. It showed no depression in melting point when mixed with a sample of V obtained from the previous experiment.

Perbromide from IV.—To the triazole IV (25 g., 0.085 mole) dissolved in 10% sulfuric acid (250 ml.), bromine (10 ml.) was added slowly under external ice cooling. The semisolid mass that separated solidifies to crystalline material (orange-yellow needles) on stirring. The material was filtered, washed with water thoroughly until sulfate free, and finally washed with alcohol and ether to afford the perbromide, 48 g. It did not melt even at 340°.

Anal. Calcd. for $C_{13}H_{11}Br_4N_7O$: Br, 53.2. Found: Br, 52.7.

The perbromide, on refluxing with acetone, afforded monobromoacetone, b.p. 64° (50 mm.), and the hydrobromide of IV which crystallized from ethanol in light yellow needles showing m.p. 262–264° dec.

Anal. Calcd. for $C_{13}H_{11}N_7O \cdot 2HBr$: N, 22.10; HBr, 36.65. Found: N, 21.85; HBr 36.4.

The perbromide underwent instantaneous decomposition in contact with 10% caustic soda solution at room temperature with

(4) T. Curtius and C. Sturve, *J. prakt. Chem.*, [ii] **50**, 295 (1895).
(5) G. Pellizzari, *Gazz. chim. ital.*, [ii] **24**, 222 (1894).
(6) R. Stolle, *Ber.*, **46**, 260 (1913).
(7) K. Brunner, *Monatsh.*, **36**, 509 (1915).
(8) Melting points were determined in capillary tubes using an electrical air bath or a silicone oil bath and are uncorrected. Microanalyses were performed in the microanalytical laboratory of Bengal Immunity Research Institute, Calcutta 16, India.
(9) H. H. Fox and J. T. Gibas, *J. Org. Chem.*, **17**, 1653 (1952).

evolution of nitrogen and went into solution, which at pH 6–7 with evolution of carbon dioxide afforded the triazole V showing no depression in melting point when admixed with a sample of V obtained from the previous experiment.

Synthesis of 3,5-Bis(4-pyridyl)-1,2,4-triazole (V).—An intimate mixture of isonicotinic acid hydrazide (13.7 g., 0.1 mole) and isonicotinamide (0.1 mole) was heated in an oil bath for 16 hr. at 170–220° but mainly in the vicinity of 200° for last 4 hr. Water formed in the reaction escaped as there was no condenser attached to the flask in which the experiment was being done. The reaction mixture on being cooled, solidified and dissolved on treatment with water (150 ml.) and ammonia (10 ml.). This solution, being adjusted to pH 6–7 with hydrochloric acid, afforded V, 10.5 g.; the mixture melting point with a sample of V obtained by oxidation of IV was not depressed.

Synthesis of 3,5-Bis(4-pyridyl)-1,2,4-triazole-1-carboxhydrazide (IV) from Isonicotinic Acid Hydrazide, Carbon Dioxide, and Hydrazine Hydrate.—Isonicotinic acid hydrazide (25 g., 0.18 mole) suspended in hydrazine hydrate [150 ml., 50% (w./v.), free from ammonia] was saturated with carbon dioxide under external ice cooling and then heated to reflux with a small flame. The reaction mixture became clear on heating and after 8–10 hr. of refluxing, separation of white crystalline material began. The heating to reflux was continued for 18 hr. The reaction mixture was cooled and the white crystalline material that separated was filtered, washed with water, and crystallized from water, in which it is very sparingly soluble, in white needles to afford IV, 4.2 g., m.p. 338–340° dec., no depression when admixed with a sample of IV isolated as by-product.

Synthesis of IV from Isonicotinic Acid Hydrazide, Isonicotinamide, and Carbohydrazide.—A mixture of isonicotinic acid hydrazide (13.7 g., 0.1 mole), isonicotinamide (12.2 g., 0.1 mole), and carbohydrazide (9 g., 0.1 mole) in water (100 ml.) was heated to reflux. During heating the solution became clear and after 4–5 hr. white crystalline material began to separate. After refluxing for 12 hr. the reaction mixture was cooled; the white crystalline solid that separated was isolated and finally crystallized from water to afford IV, 6 g. The mixture melting point with a sample of IV from the previous experiment showed no depression.

Lactols Derived from Steroidal 17a-Oxa-D-homo Lactones

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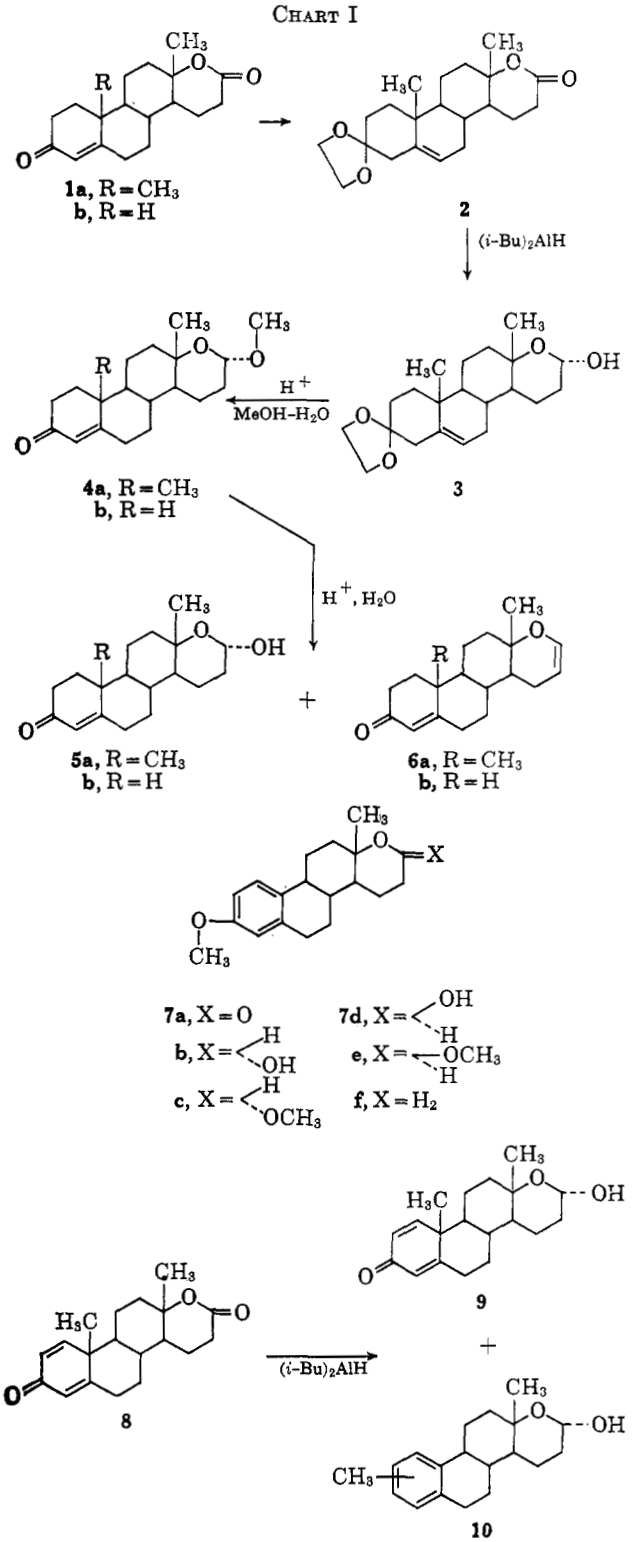
17a-Oxa-D-homoandrosta-1,4-diene-3,17-dione (1-dehydrotestololactone,[1] (**8**) has been found clinically useful in causing objective regression in breast cancer of some patients.[2] Such evidence led to the consideration that the lactols derived from testololactone (**1a**), 19-nortestololactone (**1b**), and 1-dehydrotestololactone (**8**) might have antitumor activity. The synthesis of these lactols by the reduction of the appropriate lactones with diisobutylaluminum hydride in toluene at about −70°, a mode of reduction by which esters are reduced to aldehydes,[3] was accomplished.[4]

Thus, the 3-ethylene ketal **2**, derived from **1a**, was reduced with diisobutylaluminum hydride to the lactol **3** which on methanolysis in aqueous acid to **4a** followed by hydrolysis yielded **5a** and **6a** (see Chart I). In similar fashion, the reduction of 3-methoxy-17a-oxa-D-homoestra-1,3,5(10)-trien-17-one (estrololactone 3-methyl ether, **7a**) with diisobutylaluminum hydride proceeded to the lactol **7b** which, when dissolved in methanol containing some *p*-toluenesulfonic acid, gave the dimethyl ether **7c**. This substance was then reduced with sodium, *t*-butyl alcohol, and ammonia to a 1,4-dihydro derivative which was selectively hydrolyzed to **4b**. The latter compound on hydrolysis yielded a mixture of **5b** and **6b**. An attempt to reduce 1-dehy-

CHART I



(1) J. Fried and R. W. Thoma, U. S. Patent, 2,744,120 (May 1, 1956).

(2) (a) *Cancer Chemother. Rept.*, **11**, 127 (1961); (b) *ibid.*, **41**, Supplement No. 1, 1 (1964); (c) A. Segaloff, J. B. Weeth, K. K. Meyer, E. L. Rongone, and M. E. G. Cuningham, *Cancer*, **15**, 633 (1962).

(3) L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Letters*, 619 (1962).

(4) This Note further illustrates the utility of diisobutylaluminum hydride as a reducing agent capable of yielding lactols from lactones in high yields. The reduction of a lactone to a lactol with diisobutylaluminum hydride was also noted independently by J. Schmidtlin and A. Wettstein, *Angew. Chem. Intern. Ed. Engl.*, **3**, 240 (1964).