Fractionation of the Saccharinic Anilides on a Cellulose Column.—A concentrated ethanol solution containing the saccharinic anilides formed from 1 g. of sugar was applied to the top of a 2 by 22 inch cellulose column (Whatman Cellulose powder) and washed with about 2 liters of 9:1:2 acetone–water–benzene during a period of 20 hours. The first 500 cc. of effluent were discarded, and then 12-cc. fractions taken every 7.5 minutes. The anilides were eluted very rapidly, the slowest fraction, of R_f 0.60, being found in fractions 48 to 56. The **C_6-saccharinic anilide**, isolated from a mixture prepared from D-glucose, was obtained in 150 mg. crude and 60 mg. purified yield, m.p. 120–121° cor. (crystallized from ethyl acetate and ligroin), $[\alpha]^{23}D$ −23.9° (95% EtOH, *c* 3.3). Calcd. for $C_{12}H_{17}O_6N$: C, 56.50; H, 6.70; N, 5.48. Found: C, 56.41; H, 6.74; N, 5.38. The **C_5-saccharinic anilide**, isolated from a mixture prepared from L-arabinose, was obtained in 10 mg. yield, m.p. 108–110° cor. (crystallized from ethyl acetate–benzene, and then benzene–ligroin). It is quite soluble in ether. No rotation was taken. Calcd. for $C_{11}H_{15}O_4N$: C, 58.70; H, 6.70; N, 6.22. Found: C, 59.30; H, 7.33; N, 5.68.

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Glucoluteolin Isolated from the Leaves of *Sophora angustifolia*

BY SHIZUO HATTORI AND HIROAKI MATSUDA

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Sophora angustifolia Siebold et Zuccarini is a perennial herbaceous plant of the family *Leguminosae* which is very common in Japan. Its root contains the alkaloid matrin.[1]

From the concentrated aqueous extract of the leaves of this plant, ethyl acetate extracted a pale yellow glycoside, which was purified by recrystallization from pyridine–water and melted at 254°. On hydrolysis, it yielded the luteolin (5,7,3′,4′-tetrahydroxyflavone) and the sugar glucose. By direct comparison, this glycoside proved to be identical with glucoluteolin which we had isolated from the leaves of *Humulus japonicus* Siebold et Zuccarini[2] and has the structure luteolin-7-glucoside.

Experimental

Twelve kg. of fresh leaves, collected in June, was extracted with 10 l. of boiling water; the decoction was concentrated to 1 l. and after extraction with ether repeatedly extracted with ethyl acetate. On concentration of the combined yellow ethyl acetate solution by distillation a yellow residue was obtained.

Pale yellow needles, m.p. 233–234°, yield 0.02%, resulted on recrystallization several times from ethanol. The crystals were further purified by recrystallization from water on addition of pyridine and obtained as somewhat lustrous, pale yellow needles of m.p. 254°. An ethanolic solution of this substance gave a greenish-brown coloration, was easily oxidized by means of pentamminecobaltic chloride, showed strongly positive Molisch reaction, and, when reduced with magnesium powder and concd. hydrochloric acid, gave an orange-yellow color. The R_f is 0.47 in *n*-butyl alcohol–acetic acid–water (4:1:1). All of these properties were the same as those exhibited by authentic glucoluteolin ($C_{21}H_{20}O_{11}$) and no lowering occurred in a mixed melting test with the authentic sample.

The crystals are very difficultly soluble in hot water and dilute ethanol, and contain 6% (1.5 moles) of water of crystallization.

It is very difficult to hydrolyze glucoluteolin completely. The hydrolysis was achieved by heating it with 30% sulfuric acid for 6 hours. After cooling, the precipitated aglycone was filtered (yield, about 55% of the glycoside used) and when recrystallized from ethanol, yellow needles gradually separated. These crystals of the aglycone did not melt under 300°, showed a dark greenish-brown coloration and, when reduced with magnesium powder and concd. hydrochloric acid, gave an orange color.

Part of the aglycone was acetylated by the usual method and the purified acetate consisted of white long needles of m.p. 222°. This melting point did not alter when the acetylated product was mixed with authentic tetraacetylluteolin. Further, the methylated aglycone, which was obtained by methylating with dimethyl sulfate and potassium carbonate in acetone, consisted of colorless needles and melted at 144°. When mixed with authentic tetramethylluteolin, the methylated product did not lower the melting point.

By means of osazone formation, glucose was identified as the only sugar in the hydrolysate.

The methylated glucoside, which was obtained by methylating the glucoluteolin with dimethyl sulfate and potassium carbonate in acetone, gave, on hydrolysis with boiling 30% sulfuric acid, colorless needles of m.p. 284°. These were identical with authentic 5,3′,4′-trimethylluteolin by mixed melting test.

Not only the leaves, but also the pale yellow flowers of this plant contain glucoluteolin. In this latter case, however, 50% ethanol was found to be more convenient than hot water for its extraction. The yield was a little higher, that is, 0.06% of the fresh material.

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(1) N. Nagai and H. Kondo, *J. Pharmac. Soc. Japan*, **23**, 993 (1903).

(2) S. Hattori and H. Matsuda, *Acta Phytochimica (Japan)*, **15**, 233 (1949).

Derivatives of Reserpine. Communication on the Rauwolfia Alkaloids. XIII

BY CHARLES F. HUEBNER

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We wish to report some new derivatives of reserpine[1] prepared with the object of determining the effect of chemical change on pharmacological activity. Chemical modifications of reserpine (I) resulted in compounds obtained from alkylation of the indole nitrogen (II and III) and by conversion of the carbomethoxy group to the corresponding amide IV.

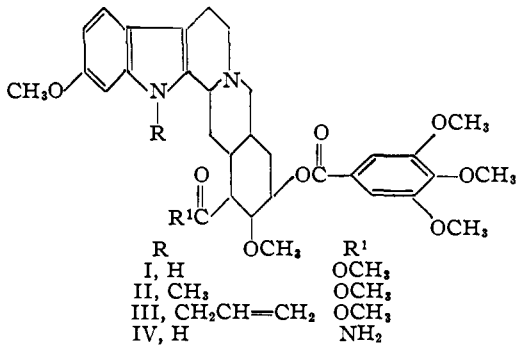
Methyl reserpate, in the form of its N-potassium derivative, readily undergoes alkylation in liquid ammonia with methyl iodide and with allyl bromide according to an adaptation of the method recently described for the preparation of N-methylharman.[2] The N-alkyl methyl reserpates are then esterified with 3,4,5-trimethoxybenzoyl chloride (II and III). Reserpine itself, can be directly N-alkylated; however, this is the less convenient of the two alternative methods because of the relative insolubility of reserpine and its N-potassium derivative in liquid ammonia. The amide of reserpic acid results from the action of a large excess of sodium amide on reserpine in liquid ammonia, ammonolysis occurring at both its ester linkages. Reesterification of reserpamide with 3,4,5-trimethoxybenzoyl chloride gives the amide corresponding to reserpine (IV).

Pharmacological investigation of these reserpine derivatives by Dr. Plummer and his associates showed that they are devoid of the tranquillizing and hypotensive properties characteristic of the

(1) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. André, *Helv. Chim. Acta*, **37**, 59 (1954).

(2) F. A. L. Anet, D. Chakravarti, R. Robinson and E. Schlittler, *J. Chem. Soc.*, 1242 (1954); see also H. Plieninger, *Ber.*, **87**, 127 (1954).

parent alkaloid. In fact, N-methylreserpine acts as a reserpine antagonist. Details of these pharmacological experiments will be published elsewhere.



	R	R^1
I	H	OCH_3
II	CH_3	OCH_3
III	$CH_2CH{=}CH_2$	OCH_3
IV	H	NH_2

Experimental[3]

N-Methyl Methyl Reserpate.—Methyl reserpate (2.95 g.) is added with stirring to a solution of potassium amide (prepared from 0.35 g. of potassium) in 50 ml. of liquid ammonia. Solution of methyl reserpate as the N-potassium salt occurs almost immediately. After ten minutes, a solution of 0.6 ml. of methyl iodide in 10 ml. of anhydrous ether is then added. After one-half hour of stirring, the ammonia is allowed to evaporate and the crystalline solid separating on the addition of ice-water collected. It is dissolved in hot methanol, filtered through Super-cel to remove the iron oxide used originally to catalyze the formation of potassium amide and precipitated by the addition of water. The N-methyl methyl reserpate (2.50 g.) thus obtained melts at 210–215° with a transition point at 130° probably due to loss of water of solvation. Recrystallization from ethanol gives a product melting sharply at 210–211° with no transition point.

Anal. Calcd. for $C_{24}H_{32}N_2O_6$: C, 67.27; H, 7.53; N, 6.54. Found: C, 67.18; H, 7.65; N, 6.71.

N-Methylreserpine (II).—(A) A solution of 0.4 g. of N-methyl methyl reserpate and 1.2 g. of 3,4,5-trimethoxybenzoyl chloride in 12 ml. of pyridine is allowed to stand for 4 days at room temperature and then is treated with 30 g. of ice. A precipitate of 3,4,5-trimethoxybenzoic anhydride is removed and the filtrate concentrated to dryness. The residue is dissolved in chloroform and washed successively with 2% hydrochloric acid, 2% sodium hydroxide and with water. The residue remaining after removal of the chloroform crystallizes on rubbing with methanol. This material (0.15 g.) is recrystallized by dissolving in a minimum of hot chloroform and adding methanol until needles begin to appear. N-Methylreserpine (II) melts at 265–266° and a mixture with reserpine (I) surprisingly shows no depression in melting point. Infrared absorption of N-methylreserpine in a Nujol mull shows complete absence of a band in the NH region (reserpine has a band at 3417 cm.$^{-1}$).

Anal. Calcd. for $C_{34}H_{42}N_2O_9$: C, 65.58; H, 6.80; N, 4.50. Found: C, 65.88; H, 6.77; N, 4.47.

(B) Finely powdered reserpine (5 g.) is added to a stirred solution of 0.35 g. of potassium in 100 ml. of anhydrous liquid ammonia. Conversion of reserpine to its potassium salt occurs relatively slowly because of the insolubility of both substances. The powdered reserpine becomes replaced by a voluminous precipitate of the potassium salt after 45 minutes of vigorous stirring. A solution of 0.5 ml. of methyl iodide in 20 ml. of anhydrous ether is added and stirring continued for 30 minutes. The ammonia is allowed to evaporate, and ice-water added with stirring gives a white powder (3.5 g.) which is collected by filtration. It is recrystallized from a large volume of acetone–water and from chloroform–methanol to give 1.8 g. of N-methylreserpine (II) indistinguishable from a sample prepared by method A.

N-Allylreserpine (III).—Reaction of the potassium derivative formed from 1.6 g. of methyl reserpate and the potassium amide equivalent to 0.2 g. of potassium with 0.37 ml. of allyl bromide is carried out as described above. After removal of the ammonia and addition of ice-water, an oil separates. It is extracted with chloroform and the extract washed successively with water, 2% hydrochloric acid and 2% sodium hydroxide. Removal of the chloroform (after drying over anhydrous sodium sulfate) gives 1.5 g. of crude N-allyl methyl reserpate as a gum. The latter is esterified with 3,4,5-trimethoxybenzoyl chloride and worked up as described above. The residue remaining after evaporation of the chloroform is dissolved in benzene and chromatographed on 20 g. of alumina. Development with 45 ml. of benzene elutes 1.5 g. of a yellow resinous material from the column. On trituration with methanol it crystallizes. Filtration of the crude ester and recrystallization from chloroform–methanol gives 0.5 g. of N-allylreserpine (III), m.p. 226–230°. Infrared absorption in a Nujol mull shows no band in the NH region.

Anal. Calcd. for $C_{36}H_{44}N_2O_9$: C, 66.65; H, 6.84; N, 4.32. Found: C, 66.67; H, 7.04; N, 4.12.

Reserpamide.—Finely powdered reserpine (2.5 g.) is stirred for one hour in 100 ml. of liquid ammonia with the sodium amide prepared from 2 g. of sodium. The ammonia is allowed to evaporate and 50 g. of ice-water added to the residue. The crystalline material separating is filtered. It is resuspended in 25 ml. of water and filtered again. This material (0.7 g.) is 3,4,5-trimethoxybenzamide, m.p. 178–180°. The melting point of a mixture of it with an authentic sample shows no depression. The aqueous filtrate contains the desired reserpamide. Saturation of this solution with chloroform, followed by chilling, causes the separation of 1.2 g. of crude reserpamide. It is recrystallized by the addition of ethanol to a hot aqueous solution, m.p. 270–272°.

Anal. Calcd. for $C_{22}H_{29}N_3O_4$: C, 66.14; H, 7.32; N, 10.52; OCH_3, 15.54. Found: C, 65.90; H, 7.67; N, 10.54; OCH_3, 15.31.

O-3,4,5-Trimethoxybenzoylreserpamide (IV).—Reserpamide (0.5 g.) reacts with 1.5 g. of 3,4,5-trimethoxybenzoyl chloride in 15 ml. of pyridine for three days. After most of the pyridine is removed by distillation *in vacuo*, ice and benzene are added to the residue. The solid hydrochloride of the alkaloid ester separates at the liquid interface when the mixture is shaken vigorously with an excess of 5% hydrochloric acid. The hydrochloride suspended in ethyl acetate is triturated with 5% aqueous sodium hydroxide to convert it to the base. Evaporation of the ethyl acetate solution leaves a resin which crystallizes on trituration with methanol. Recrystallization from chloroform–methanol gives 0.2 g. of O-3,4,5-trimethoxybenzoylreserpamide (IV), m.p. 240–242°.

Anal. Calcd. for $C_{32}H_{39}N_3O_8$: C, 64.74; H, 6.62; N, 7.08. Found: C, 64.35; H, 6.37; N, 6.99.

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(3) Melting points are uncorrected.

Methyl 3-*O*-Methyl-α-D-glucopyranoside and Derivatives[1]

BY ROGER W. JEANLOZ AND MARCEL GUT

RECEIVED JULY 8, 1954

In the course of a study of the preparation of derivatives of 3-*O*-methyl-D-glucuronic acid, it was found necessary to prepare pure methyl 3-*O*-methyl-α-D-glucopyranoside and some of its derivatives. Reeves[2] was able to separate the mixture of α- and β-anomers obtained through glycosidification of 3-*O*-methyl-D-glucose by fractional crystallization of its 4,6-*O*-ethylidene derivative. However, the yield was very small, and the purity of the final product was uncertain. A separation of this type, using the 4,6-*O*-benzylidene derivative, was reported by Freudenberg, *et al.*,[3] but was shown by

(1) This is publication No. 167 of the Robert W. Lovett Memorial Foundation for the Study of Crippling Diseases, Harvard Medical School, Boston, Mass.

(2) R. E. Reeves, THIS JOURNAL, **66**, 845 (1944).

(3) K. Freudenberg, H. Toeppfer and C. C. Andersen, *Ber.*, **61**, 1750 (1928).