202–205°C, $[\alpha]_D^{22} = +7.6°$). In gleicher Weise entsteht in ähnlicher Ausbeute aus der N-Chlor-Verbindung VIII Soladulcidin (X; Smp. und Misch-Smp. 207–208°C, $[\alpha]_D^{23} = -50°$). Die IR-Spektren der so gewonnenen Spiroaminoketal-Alkaloide sind mit denen von authentischem Tomatidin bzw. Soladulcidin identisch.

Als nicht fassbare Zwischenprodukte dieser Umsetzungen nehmen wir die $\Delta^{22:N}$-ungesättigten Verbindungen V und IX an, die unter den gegebenen Reaktionsbedingungen sofort stereospezifisch zu den Spiroaminoketalen VI bzw. X cyclisieren[6].

Aus Dihydro-tomatidin B ist die tertiäre Base Demissidin (5α-Solanidan-3β-ol) in einer zellmöglichen Reaktionsfolge bereits synthetisiert worden[3,7]. Die nunmehr beschriebene stereospezifische Umwandlung der gleichen Verbindung (II) in Tomatidin (VI) stützt die schon von KUHN[7] und auch SANDER[8] geäusserte Ansicht, dass diesem Ring-E-offenen sekundären Amin eine Schlüsselstellung bei den biogenetischen Umwandlungen der Solanum-Alkaloide zukommen könnte. In diesem Zusammenhang sei auf das gemeinsame Vorkommen von Demissidin- und Tomatidin-glykosiden in *Solanum demissum* Lindl. hingewiesen[9].

Summary. The ring-E opened dihydro derivatives of tomatidine and soladulcidine give the corresponding N-chloroamines with N-chlorosuccinimide. Treatment of these compounds with sodium methoxide yields the spiroaminoketal alkaloids, tomatidine and soladulcidine respectively, in high yields, probably via instable C=N-unsaturated intermediates which undergo spontaneous stereospecific cyclisation.

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Rauwolfia Alkaloids XXXV. Potent, Fast-Acting Sedatives Derived from Methyl Reserpate

Interest in reserpine (Ia), the primary sedative and hypotensive principle of the Rauwolfia genus, has stimulated efforts in this Laboratory to separate these two types of activity by suitable modification of the structure of the molecule. Isolation of the second type of activity was realized in the preparation of methyl reserpate 18-(3, 5-dimethoxy-4-ethoxyformyloxybenzoate) (Ib), a compound which has a hypotensive effect comparable to that of reserpine, but which has a greatly decreased sedative action[1]. This communication describes the preparation of methyl reserpate derivatives possessing pronounced sedative effect of rapid onset, but lacking significant hypotensive properties.

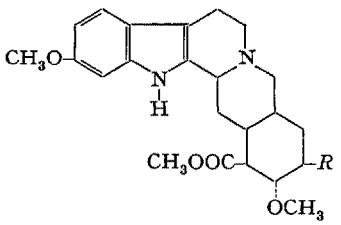
Treatment of methyl reserpate (Ic) in methylene chloride solution with diazomethane and fluoboric acid[2] results in methylation of the 18-hydroxy group to form methyl reserpate methyl ether (Id), m.p. 236–238° dec., $[\alpha]_D^{25} = -111$ ($CHCl_3$). Anal., Calculated for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; N, 6.54; OCH_3, 28.97. Found: C, 67.19; H, 7.61; N, 6.58; OCH_3, 29.34. The water-soluble hydrochloride salt has m. p. 237–242° dec. Anal., Calculated for $C_{24}H_{32}N_2O_5 \cdot HCl \cdot H_2O$: C, 59.68; H, 7.30; N, 5.80. Found: C, 60.06; H, 7.30; N, 5.95.

The unusual activity of these derivatives provoked an intensive effort to prepare Id by other methods. In the course of the investigation, an isomeric ether of comparable activity was eventually produced by methanolysis of methyl reserpate 18-*p*-bromobenzenesulfonate (Ie). The latter, m.p. 219–221° dec., was synthesized by reaction of methyl reserpate with *p*-bromobenzenesulfonyl chloride in pyridine. Anal., Calculated for $C_{29}H_{33}N_2O_7BrS$: C, 54.97; H, 5.25; N, 4.42. Found: C, 54.94; H, 5.54; N, 4.23.

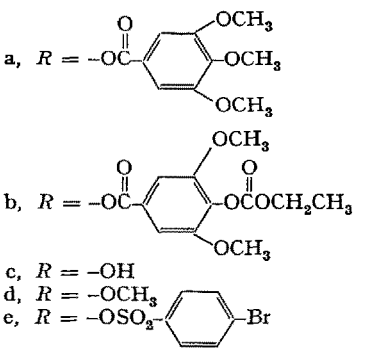
Reaction of the bromobenzenesulfonate with methanol was effected by heating at 100°C in a sealed vessel in the presence of triethylamine. Methanolysis of the ester proceeded in high yield to form methyl 18-epireserpate methyl ether (IIa), m.p. 239–241° dec., $[\alpha]_D^{26} = -37.5$ ($CHCl_3$). Anal., Calculated for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; OCH_3, 28.97. Found: C, 67.28; H, 7.57; OCH_3, 29.55. The water-soluble hydrochloride has m.p. 240–242° dec. Anal., Calculated for $C_{24}H_{32}N_2O_5 \cdot HCl \cdot {}^1/_2 H_2O$: C, 60,81; H, 7.23; N, 5.91. Found: C, 61.03; H, 7.15; N, 6.10.

Methyl 18-epireserpate ethyl ether (IIb) was prepared by a similar ethanolysis reaction. The product, m.p. 229 to 230° dec., had $[\alpha]_D^{26} = -27$ ($CHCl_3$). Anal., Calculated for $C_{25}H_{34}N_2O_5$: C, 67.85; H, 7.75; N, 6.33. Found: C, 67.99; H, 7.82; N, 6.14. The hydrochloride had m.p. 233 to 235° dec. Anal., Calculated for $C_{25}H_{34}N_2O_5 \cdot HCl$: C, 62.68; H, 7.37; N, 5.85. Found: C, 62.96; H, 7.82; N, 5.42.

By analogous processes displacements of the *p*-bromobenzenesulfonate moiety by other nucleophilic reagents have been carried out. Other substituted benzenesulfonates have also been employed. That the second methyl ether differs from the first only in the stereochemistry at position 18 has been demonstrated by relating the epi compound and methyl reserpate to common transformation products, in which the configurations at other points



I a, b, c, d, e



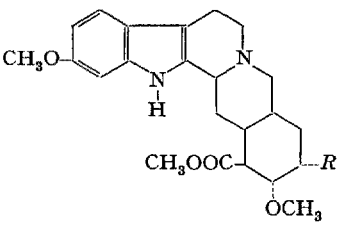
a, R = –OC(=O)–(3,4,5-trimethoxyphenyl)

b, R = –OC(=O)–(3,5-dimethoxy-4-ethoxyformyloxyphenyl)

c, R = –OH

d, R = –OCH_3

e, R = –OSO_2–(4-bromophenyl)



II a, b

a, R = –OCH_3

b, R = –OC_2H_5

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[2] M. NEEMAN, M. C. CASERIO, J. D. ROBERTS, and W. S. JOHNSON, Tetrahedron *6*, 36 (1959).

of asymmetry have been preserved. The details of these structure proofs, together with other transformations of the reserpine E ring, will be reported elsewhere.

Pharmacological evaluation of the ethers Id and II and their hydrochloride salts revealed a preponderance of sedative action in mice and dogs without any demonstrable hypotensive effect in dogs. The quieting action of the ethers differed from that caused by reserpine itself in several important respects: The onset of action was within minutes rather than hours. The duration of action was considerably shorter than that of reserpine. Cumulation was not evident upon repeated administration. Oral absorption was rapid and quite complete, since tranquilization of the same degree was achieved in 30 to 60 min following administration by either the oral or intravenous route. In contrast to the experience with reserpine, there was no evidence of drug action on the following day.

There were also distinct differences between the effects of reserpine and those of the ethers upon the gastrointestinal tract of the dog. The latter did not evoke increased motor activity in the small intestine of the dog as recorded from a Thiry-Vella intestinal loop. For this reason undoubtedly diarrhea, which was so common following reserpine in the dog, was not noted following sedative doses of the ethers. Their effect on gastric secretion was less than one-tenth that of reserpine.

A further interesting pharmacological property of the epiethers was the antagonism of the fibrillatory and cardiac depressant actions of aconitine upon the isolated cat heart. The epiethers were considerably more active than the normal ethers of methyl reserpate in this respect.

Zusammenfassung. Durch Umsetzung des Methyl-Reserpates (Ic) mit Diazomethan in Gegenwart von Fluoborsäure wird 18-O-Methylreserpsäure-methylester (Id) gewonnen. Reaktion des 18-O-*p*-Brombenzolsulfonylreserpsäure-methylesters (Ie) mit Methanol und Triäthylamin führt dagegen zum isomeren 18-epi-Methyläther (IIa). Diese Produkte, und besonders ihre wasserlöslichen Hydrochloride, besitzen ausgeprägte sedative Eigenschaften mit schnellem Wirkungseintritt; sie sind aber nicht hypotensiv wirksam.

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CIBA Pharmaceutical Products Inc., Summit (N. J.), November 9, 1960.

Uzarigenin and Desglucouzarin from *Asclepias syriaca* L.

ZECHNER[1] isolated from *Asclepias syriaca* L. of Croatian origin an amorphous glycoside with typical digitaloid effects[2], which was not chemically characterized in detail. PETRIČIĆ et al.[3] showed by paper chromatography the presence in *Asclepias syriaca* L. of five substances which gave a positive Baljet reaction. One of them was isolated in crystalline state; on hydrolysis it yielded rhamnose and glucose but the aglycone was not described.

We have examined *Asclepias syriaca* L. obtained from Western Slovakia. Paper chromatography showed the presence of nine substances, which gave positive reactions with *m*-dinitrobenzene[4] and with 3, 5-dinitrobenzoic acid[5].

Ether, chloroform, and chloroform-ethanol-(2:1) extracts were prepared in the usual manner from the ethanol extract of the drug, after removal of impurities with lead acetate. From these extracts six substances were obtained (two in crystalline form) by counter-current separation and chromatography on aluminium oxide.

The first crystalline substance isolated had the formula $C_{23}H_{34}O_4$, m.p. 243–250°C (from diluted ethanol), $[\alpha]_D^{21} = +14.9 \pm 2°$ (ethanol), λ_{max} 218 mμ in ethanol ($\log \varepsilon = 4.24$). The aforementioned UV-absorption is typical for an $\alpha\beta$-unsaturated-γ-lactone. The substance gave a monoacetyl derivative $C_{25}H_{36}O_5$, m.p. 248–256°C (from acetone-ether), $[\alpha]_D^{24} = +3.5 \pm 2°$ (chloroform). The substance was compared with uzarigenin, using as criteria mixed m.p., IR-spectrum, and paper chromatographic behaviour, and was identical.

The second crystalline substance isolated had the formula $C_{29}H_{44}O_9 \cdot H_2O$, m.p. 260–272° (from diluted ethanol), $[\alpha]_D^{28} = -44.1 \pm 2°$ (pyridine); on acetylation it gave a tetra-acetyl-derivative of the formula $C_{37}H_{52}O_{13}$, m.p. 174–176° (from acetone-ether); $[\alpha]_D^{22} = -8.85 \pm 3°$ (chloroform); λ_{max} at 217 mμ in ethanol ($\log \varepsilon = 4.24$). On hydrolysis with 1% hydrochloric acid in dioxane, it gave uzarigenin and D-glucose. This evidence shows that the isolated substance is a monoglucoside of uzarigenin, viz. desglucouzarin, which has not as yet been obtained from a natural source.

From *Asclepias curassavica* L., a botanically differentiated species[6] of *Asclepias*, TSCHESCHE et al.[7,8] were able to isolate uzarigenin besides six other digitaloid genins[9].

Zusammenfassung. In *Asclepias syriaca* L. wurden neun Cardenolide nachgewiesen. Zwei Substanzen konnten in kristallisiertem Zustand isoliert und eine davon mit Uzarigenin identifiziert werden. Das zweite kristallisierte Produkt war das β-D-Glucosid von Uzarigenin.

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Department of Chemistry of Natural Products, Slovak Academy of Science, Bratislava (CSR), September 19, 1960.

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Zum Mechanismus der Immuncytolyse durch heterologe Antikörper und Komplement

Die Glykolyse von Zellen des Ehrlich-Aszitestumors (EAT) wird durch heterologe Antikörper und Komplement vollständig gehemmt[1]. Dabei ist es unklar, ob die zu beobachtende Cytolyse die Ursache oder die Folge der Glykolysehemmung ist. Die Stoffwechseluntersuchungen und die Ergebnisse der Elektronenmikroskopie[2] gaben Hinweise, dass der Effekt auf die Glykolyse die Folge einer Störung im Stoffwechsel der Adenosintriphosphorsäure (ATP) ist.

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