pressed when mixed with synthetic 3-ethylacridine.[3] Moreover, the infrared spectra were identical.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.8; H, 6.32. Found: C, 85.8; H, 6.43.

3-Acetylacridine (VI). A hot suspension of 0.33 g. of III in 22 ml. of water (containing 20 drops of acetone) and 2.5 ml. of 2*N* sulfuric acid was oxidized with 0.18 g. of potassium dichromate in 4 ml. of water. The filtered solution was treated with 0.4 g. of potassium dichromate in 4 ml. of water and the precipitated salt converted to the free base (concd. ammonium hydroxide–ether). Concentration of the dried solution gave 0.24 g. of a light-yellow solid which was sublimed at 125–130°/0.1 mm., lemon yellow prisms, m.p. 135–136.5°. The compound possessed a strong carbonyl band at 5.95 μ.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.01. Found: C, 81.2; H, 5.04.

A Wolff-Kishner reduction of 60 mg. of VI in 4 ml. of diethylene glycol with 60 mg. of potassium hydroxide and 0.1 ml. of 85% hydrazine hydrate gave, after the usual work-up, 40 mg. of a tacky yellow solid which was chromatographed on 3 g. of aluminum oxide (benzene). The resulting base was converted to the *perchlorate*, m.p. 176–178° (undepressed when mixed with 3-ethylacridine perchlorate). Regeneration of the base gave a pale yellow oil which crystallized rapidly (scratching), m.p. 75–77°; not depressed when mixed with synthetic 3-ethylacridine. The infrared spectra of the regenerated base and 3-ethylacridine were the same.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Some Reactions of Solasodine*[1]

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The degradation of the steroidal alkaloid solasodine has led to 5,16-pregnadien-3β-ol-20-one. Solasodine has also been converted into a new isomeric solanidanone and into the diacetate and monoacetate of a "pseudosolasodine." Some reactions of the latter are discussed.

Solasodine (I),[2,3] the aglycone of solasonine[4] obtained from certain solanum species, can be converted to a pregnane derivative by treatment with acetic anhydride and oxidation of the resulting amorphous mass. Thus solasodine (I) yielded the acetate of 5,16-pregnadien-3β-ol-20-one (IV) and 16α-methoxy-5-pregnen-3β-ol-20-one. The latter presumably arose from the addition to the 15,16-double bond of the methanol used in the alkaline hydrolysis[5] of the side chain moiety.

The crude oil obtained from the acetic anhydride treatment of solasodine failed to crystallize, but yielded upon chromatography on alumina a crystalline compound. The analytical values of the latter indicated the structure of the unsaturated *O,N*-diacetyl derivative III. Its principal infrared absorption bands ($\lambda_{max}^{chlf.}$ 2.91 and 3.00 μ, NH; 5.98, 6.61 μ,  $\mathrm{HN{-}\underset{\underset{O}{\|}}{C}{-}CH_3}$) agreed well with those of the unsaturated *O,N*-diacetyl tomatidine[6] obtained by a similar chromatography on alumina of the so-called unsaturated triacetyltomatidine.[7]

The principal bands of III were also in agreement with those of *N*-acetyldihydrotomatidine and *N*-acetyltetrahydrosolasodine whose structures have been established.[8] The course of the oxidation of compound II, and the analogy of the latter with the unsaturated triacetyl derivative[7,9] of tomatidine obtained in the acetic anhydride treatment indicate strongly structures II and III, tentatively designated as derivatives of pseudosolasodine A. The amorphous material obtained from the acetic anhydride treatment of solasodine, unlike that from tomatidine,[7] was a mixture (indicated by infrared spectra and the isolation of another component as yet unidentified) and the yield of the pregnadienolone acetate (IV) was low (10–20%), while tomatidine had yielded about 60% of 16-allopregnenolone.[7] When 5,6-dihydrosolasodine was employed in this degradation the yield of 16-allopregnenolone again was quite poor showing that it is not the 5,6-double bond that is responsible for the difference in yields.

The exhaustive reduction of solasodine leads to the formation of tetrahydrosolasodine,[10] VIIa, with the uptake of 2 moles of hydrogen. When VIIa was

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) A preliminary account of portions of this work was published in the *J. Am. Chem. Soc.*, **73**, 5009 (1951), and in *Chemistry & Industry*, 444 (1955).

(2) L. H. Briggs, W E. Harvey, R. H. Locker, W. A. McGillirray, and R. N. Seelye, *J. Chem. Soc.*, 3013 (1950).

(3) F. C. Uhle, *J. Am. Chem. Soc.*, **75**, 2280 (1953); *J. Am. Chem. Soc.*, **76**, 4245 (1954).

(4) G. Oddo, *Ber.*, **62**, 267 (1929).

(5) D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).

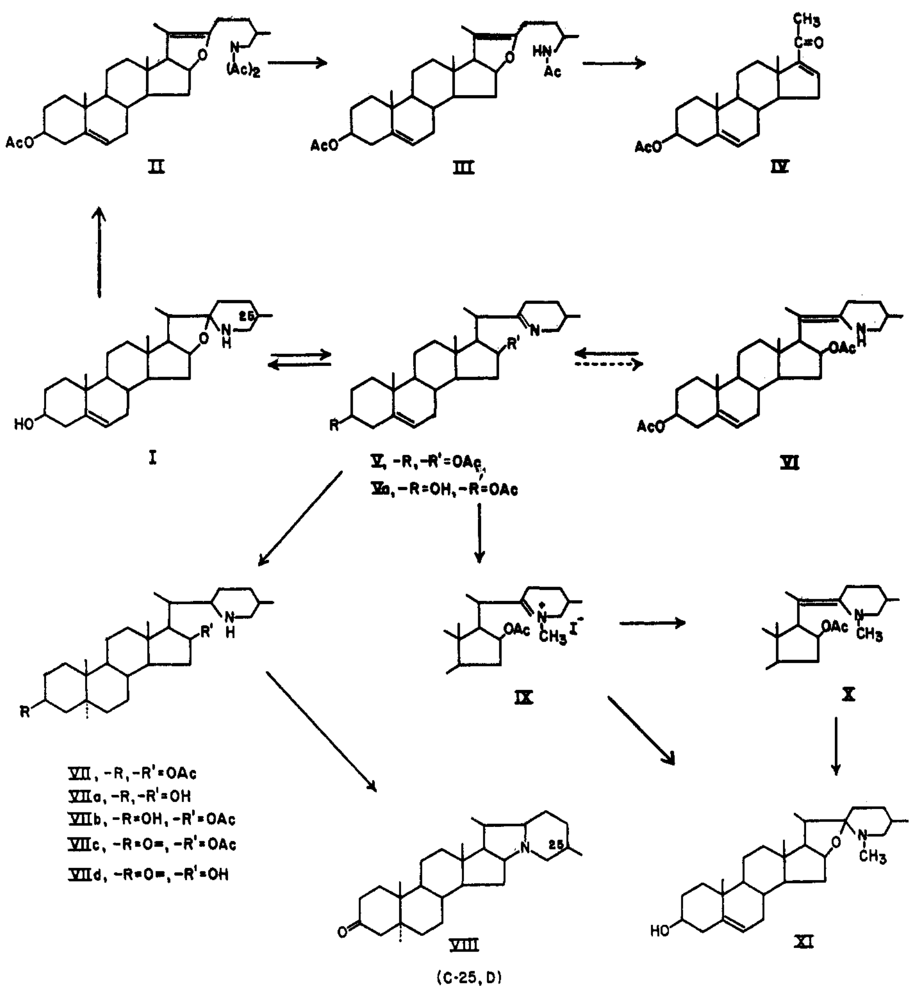
(6) To be published soon.

(7) Y. Sato, A. Katz, and E. Mosettig, *J. Am. Chem. Soc.*, **74**, 538 (1952).

(8) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3150 (1956).

(9) R. Kuhn and I. Löw, *Chem. Ber.*, **85**, 416 (1952).

(10) H. Rochelmeyer, *Arch. Pharm.*, **277**, 329 (1939).



oxidized with Kiliani's reagent[11] in acetone, and the product subsequently reduced on palladium-charcoal, a new isomeric solanidan-3-one (VIII) was obtained.

The structure of compound VIII is based upon the fact that it was formed in a manner entirely analogous to that in which the two C-22 isomeric solanidan-3-ones (C-25, L) were obtained from the C-22 isomeric dihydrotomatidines (ring E opened).[12] Compound VIII being derived from solasodine must have the C-25, D configuration.[13] It remains open to question to which of the two C-22 isomeric solanidanones having the C-25, L configuration[12,14,15] ketone VIII corresponds. During the course of these studies an analogous sequence of reactions was applied to 3-deoxytetrahydrosolasodine[16] which led to a new solanidane with the C-25, D configuration.

When solasodine was treated with a solution of zinc chloride in acetic anhydride and acetic acid, the diacetate (V) of a new unsaturated derivative isomeric with the parent compound was obtained. This compound which we name, for the time being, pseudosolasodine B, probably exists to a large extent in the form of V, and equilibrates only under constraint to its tautomeric form VI. The following spectroscopic data led us to consider the above formulation: Infrared spectra[17] revealed a band of medium intensity at 6.0 μ, (indicative of a >C=N- band) besides a strong acetate band (5.79 μ). In the ultraviolet region of the spectrum there is a modest absorption (ε 243) at 242 mμ. The hydrochloride[18] possesses a broad ammonium band at 4.03 μ and an immonium band of medium intensity at 4.93 μ, accompanied by a shift of the 6.0 μ band to 5.88 μ. The appearance of these bands with its concomitant

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[11] H. Kiliani, *Ber.*, **46**, 676 (1913). A solution of 53 g. of chromium trioxide and 80 g. of concentrated sulfuric acid in 400 g. of water.

[12] Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3146 (1956).

[13] F. C. Uhle and J. A. Moore, *J. Am. Chem. Soc.*, **76**, 6412 (1954).

[14] F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945).

[15] V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **27**, 390 (1944).

[16] L. H. Briggs, R. P. Newbold, and N. E. Stace, *J. Chem. Soc.*, 3 (1942).

[17] In normal concentrations (15 mg./ml., 0.5 mm. cell) no >NH stretching band is observed. An extremely weak band (3.03 μ) is observed in a saturated carbon disulfide solution.

[18] The perchlorate of V does not show an ammonium or immonium band but is accompanied by a shift of the 6.0 μ band at 5.91 μ. Some other perchlorates behave similarly.

shifts are in accord with the findings of Witkop[19] for a $>C=N-$ and a possible $>C=\underset{|}{C}-N<$ system as shown by Leonard and Gash.[20]

Also a number of chemical transformations support the structure of this unsaturated isomerization product. Mild hydrolysis of V with 2% methanolic potassium hydroxide or potassium bicarbonate selectively removed most likely the 3-acetyl group and gave the 16-acetate of pseudosolasodine B (Va) which was converted to the original solasodine (I) by further hydrolysis with 5% methanolic alkali. Vigorous hydrolysis of the 3,16-diacetylpseudosolasodine B (V) with 5% methanolic alkali yielded solasodine directly. Hydrogenation of V proceeded rapidly with the uptake of 2 moles of hydrogen to afford the oily tetrahydrodiacetyl derivative VII, which readily yielded the known tetrahydrosolasodine (VIIa) by alkaline hydrolysis. The lithium aluminum hydride reduction of V followed by catalytic hydrogenation of the 5,6-double bond led also to the same product (VIIa). Hydrogenation of the 16-acetylpseudosolasodine B (Va) afforded the 16-acetate of tetrahydrosolasodine (VIIb) which was oxidized to the 3-oxo derivative VIIc. Hydrolysis of VIIc in methanolic alkali to the keto-alcohol VIId, followed by oxidation and subsequent reduction led to the isomeric solanidan-3-one (VIII) which was prepared above directly from tetrahydrosolasodine (VIIa). Treatment of V with methyl iodide in acetone gave the methiodide of the diacetate (IX), $\lambda_{max}^{chlf.}$ 6.00 μ which when treated with sodium carbonate gave readily the tertiary amine (X) $\lambda_{max}^{chlf.}$ 6.06 μ, $\lambda_{max}^{alc.}$ 230 mμ (ε, 4650). The spectrophotometric measurements of X and its salts were in excellent agreement with the findings of Leonard *et al.*[20,21] for an α,β-unsaturated tertiary amine. Finally, the vigorous hydrolysis of IX or X with methanolic alkali produced XI which is very likely *N*-methylsolasodine. Although the elementary analytical values were acceptable, the compound could not be purified sufficiently to give a satisfactory melting range. Several attempts at a direct synthesis of XI from I failed.[22]

EXPERIMENTAL[23]

3β-Acetoxy-5,16-pregnadiene-20-one (IV). A mixture of 1.87 g. of solasodine and 30 ml. of acetic anhydride was refluxed for 1.5 hr. The acetic anhydride was removed *in vacuo* and the crude residue dissolved in 65 ml. of acetic acid. It was oxidized by gradual addition of 1.87 g. of chromium trioxide in 25 ml. of 90% acetic acid. The reaction mixture was allowed to stand for 1.8 hr. and poured into ice water. Methanol was added to destroy excess oxidant and the greenish solution was extracted with ether repeatedly. Some (450 mg.) acidic material soluble in 3% sodium carbonate solution was removed at this stage. The residue obtained by removal of the ether was dissolved in 30 ml. of 2% methanolic potassium hydroxide and refluxed for 20 min. The alkaline mixture was concentrated slightly and water added to it. Extraction with ether yielded 420 mg. of amorphous material. This was chromatographed on alumina, and the crystalline fractions eluted with benzene and ether (160 mg.) were acetylated in the usual manner with pyridine and acetic anhydride. Chromatography on alumina and elution with benzene–Skellysolve B (1:19) yielded the pregnadienolone acetate (IV) m.p. 174–176°, $[\alpha]_D^{20}$ −24.5° ± 4° (ethanol), identical in all respects with an authentic specimen.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.38: H, 9.39.

Fractions subsequently eluted with benzene–Skellysolve B were rechromatographed over alumina and the fractions eluted with benzene–Skellysolve B (1:19) were crystallized from petroleum ether to yield needles of m.p. 158–160°, which were identified by direct comparison (m.p., mixture m.p. and infrared spectra) with an authentic specimen of 3β-acetoxy-16α-methoxy-5-pregnen-20-one. The combined yields of the pregnenolone derivatives in general were about 10%.

Unsaturated O,N-diacetylsolasodine (III). Solasodine (300 mg.) was refluxed with 5 ml. of acetic anhydride for 3 hr. After removal of the acetic anhydride *in vacuo*, the residue was triturated with water. The amorphous mass ($\lambda_{max}^{chlf.}$ 5.79, 6.00, and 6.08 μ) was collected, dried, and adsorbed on a neutral alumina column and allowed to stand for 2 hr. before elution. Elution with ether-methanol (99:1) then yielded 104 mg. of plates, $\lambda_{max}^{chlf.}$ 2.90, 2.98 μ (N—H); 5.78 μ (acetoxy); 5.98, 6.60 μ (NH-acetyl), m.p. 134–138° from acetone-hexane. [The first portion of the ether-methanol (99:1) eluates gave an amorphous substance whose structure is still unknown.]

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52. Found: C, 74.55; H, 9.51.

Degradation of 5,6-dihydrosolasodine to 16-allopregnen-3β-ol-20-one acetate. Dihydrosolasodine[16] (0.68 g.) was refluxed with 13 ml. of acetic anhydride for 4.5 hr. The crude oil obtained by removal of the acetic anhydride was oxidized with chromic oxide (0.6 g.) and processed as in the preparation of IV. The material recovered after alkaline hydrolysis was chromatographed over alumina. Fractions eluted with benzene–Skellysolve B and benzene were combined and crystallized from aqueous methanol to yield 70 mg. (11.8%) of crystalline allopregnenolone acetate. A sample recrystallized from the same solvent gave hexagonal plates of m.p. 165–166°, identical with an authentic specimen.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.30; H, 9.43.

Isomeric solanidan-3-one (VIII) (5α, 25D). To 0.133 g. of tetrahydrosolasodine (VIIa) dissolved in 1 ml. of acetic acid and 25 ml. of acetone was slowly added 0.44 ml. of Kiliani's reagent[11] and the mixture allowed to stand for 15 min. in an ice bath. Several drops of water added to the reaction mixture rendered the turbid mixture clear and simultaneously a greenish oil was deposited. After decanting from

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(19) B. Witkop, *Experientia*, **10**, 420 (1954); *J. Am. Chem. Soc.*, **76**, 5597 (1954); *J. Am. Chem. Soc.*, **78**, 2873 (1956).

(20) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(21) N. J. Leonard and D. M. Locke, *J. Am. Chem. Soc.*, **77**, 437 (1955).

(22) Attempted methylation of solasodine by use of methyl iodide failed; *cf.* reference 16. The use of Eschweiler-Clarke modification of the Leuckart reaction seems to lead to an anomalous product. [*Org. Reactions*, **5**, 301 (1949)].

(23) All melting points were taken on the Kofler block and are uncorrected. Infrared spectra were taken on a Perkin-Elmer double beam spectrophotometer by Mr. H. K. Miller of this laboratory. Microanalyses were performed by the Analytical Service Laboratory under the direction of Dr. William C. Alford.

the oil the solution was made alkaline with dilute sodium hydroxide solution and saturated with sodium chloride. When the ethereal extract of the above solution was concentrated *in vacuo* the residue yielded a semi-crystalline mass. Crystallization from methanol yielded plates which melted at 126–129°. The compound is rather unstable and attempts at purification (chromatography) failed. The crude material was dissolved in ethyl acetate and reduced over 10% palladium-charcoal. After the uptake of 1 mol. of hydrogen, the product was chromatographed over alumina. The benzene-hexane, benzene, and benzene-ether eluates yielded plates from aqueous methanol which melted at 146–147°, $[\alpha]^{20}_{D}$ +49° (chlf.).

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.79; H, 11.02.

Fractions eluted subsequently with 1% methanol in ether yielded small amounts of an alcohol of m.p. 160–167°, crystallizing from aqueous acetone as plates.

Anal. Calcd. for $C_{27}H_{45}ON$: C, 81.14; H, 11.35. Found: C, 81.27; H, 11.46.

Isomeric solanidane. (5α, 25D). 3-Desoxytetrahydrosolasodine[16] was treated in the same manner as described for the preparation of VIII, except that the reduction was carried out with platinum oxide in glacial acetic acid. The product crystallized from aqueous methanol as plates, m.p. 111–113°.

Anal. Calcd. for $C_{27}H_{45}N$: C, 84.52; H, 11.82. Found: C, 84.48; H, 11.56.

3,16-Diacetate of pseudosolasodine B (V). To 2 g. of solasodine was added 70 ml. of a zinc chloride solution (prepared by dissolving 8 g. of zinc chloride in a mixture of 70 ml. of acetic anhydride and 30 ml. of glacial acetic acid), and the solution was allowed to stand at room temperature overnight. The reaction mixture was then poured into ice water. After standing for 0.5 hr. with occasional stirring, concentrated ammonium hydroxide was added until the solution was alkaline and a copious precipitate was obtained. Upon crystallization from aqueous methanol 2.07 g. of plates was obtained. After two crystallizations from aqueous methanol, the compound melted at 188.5–192.5°, $[\alpha]^{20}_{D}$ +46.6° (chlf) $\lambda^{chlf.}_{max}$ 5.78 μ (acetoxy), 6.00 μ (>C=N—).

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52; CH_3—CO, 17.30. Found: C, 74.44; H, 9.47; CH_3—CO, 17.5.

Perchlorate of the 3,16-diacetate of pseudosolasodine B (V). Addition of 65% perchloric acid to an ethanol solution of V gave the salt which crystallized as prisms from aqueous ethanol. The substance melted at 150–155°.

Anal. Calcd. for $C_{31}H_{48}O_8NCl$: C, 62.24; H, 8.09. Found: C, 62.39; H, 8.12.

16-Acetate of pseudosolasodine B (Va). Mild hydrolysis of V with saturated methanolic potassium bicarbonate or 2% methanolic potassium hydroxide yielded the 16-acetyl derivative Va, m.p. 110–113°, $\lambda^{chlf.}_{max}$ 2.75 μ (hydroxyl); 5.75 μ (acetate); 5.97 μ (>C=N—). The elemental analysis was unsatisfactory.

Anal. Calcd. for $C_{29}H_{45}O_3N$: CH_3—CO, 9.45. Found: CH_3—CO, 9.9.

A more vigorous hydrolysis of Va with 5% methanolic potassium hydroxide for several hours yielded solasodine. This can also be obtained directly from the 3,16-diacetate of pseudosolasodine B (V) by hydrolysis with 5% methanolic potassium hydroxide.

The crude solasodine thus obtained was purified by chromatography over alumina and elution with 1% methanol in ether. It melted at 204–206.5° and was identical in every respect with an authentic specimen of solasodine.

Anal. Calcd. for $C_{27}H_{43}O_2N$: C, 78.39; H, 10.49. Found: C, 78.51; H, 10.75.

Conversion of V to tetrahydrosolasodine (VIIa). (*a*) A mixture of 72.5 mg. of V and 35 mg. of PtO_2 absorbed under atmospheric pressure and at room temperature 2 molar equivalents of hydrogen. The reducion product failed to crystallize but the acetyl band of its infrared spectrum indicated the diacetyl tetrahydrosolasodine VII. It was hydrolyzed without further purification with 5% methanolic potassium hydroxide yielding a product melting at 288–290° after crystallization from aqueous methanol, and identical in every respect with an authentic sample of tetrahydrosolasodine.

Anal. Calcd. for $C_{27}H_{47}O_2N$: C, 77.64; H, 11.34. Found: C, 77.36; H, 11.29.

(*b*) To a solution of 226 mg. of V in 50 ml. of dry ether was added gradually 75 ml. of a 1.62*M* ethereal solution of lithium aluminum hydride. After refluxing the mixture for 1.75 hr. the excess reductant was decomposed with ice water. The ethereal phase was washed thoroughly with water, and left after drying and evaporation a product which crystallized from aqueous methanol as heavy granules melting at 258–262°, apparently identical with Briggs' dihydrosolasodenol of m.p. 260–264°.[24] A mixture of the above product (19 mg.) and PtO_2 (18 mg.) in 5 ml. of acetic acid absorbed one molar equivalent of hydrogen. The reduction product after crystallization from aqueous methanol (heavy compact granules), melted at 286–290° and was identical in every respect with an authentic sample of tetrahydrosolasodine.

16-Acetyltetrahydrosolasodine (VIIb). The 16-acetate of pseudosolasodine B (2.3 g., Va) was reduced with 0.25 g. of platinum oxide catalyst in 30 ml. of glacial acetic acid. Two molar equivalents of hydrogen were absorbed. After removal of the catalyst, the filtrate was made alkaline with dilute ammonium hydroxide solution. The precipitate (2.3 g.) was chromatographed over neutral alumina and elution with 0.5% methanol in ether yielded 1.66 g. of 16-acetyltetrahydrosolasodine of m.p. 227–231°, $[\alpha]^{20}_{D}$ +29.5 ± 0.50 (chlf.).

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.44. Found: C, 75.80; H, 10.44.

3-Oxo-16-acetyltetrahydrosolasodine (VIIc). 16-Acetyltetrahydrosolasodine (VIIb) (1.66 g.) was oxidized in three portions, each portion being dissolved in 100 ml. of acetone and treated with 1.6 ml. of Kiliani's reagent, at room temperature.[11] The reaction mixture was allowed to stand for 10 min. and a few drops of water was added to bring about solution, and almost simultaneously an oily mass of chromate salts was precipitated. The decantate was made alkaline with 6*N* sodium hydroxide solution with cooling, and after addition of an equal volume of water the resulting cloudy liquid was evaporated *in vacuo* until an amorphous precipitate flocculated. More water was added and the product collected and dried. After it was taken up in hexane-acetone (10:1) some insoluble matter was filtered off, and the solvent removed *in vacuo*. Two recrystallizations from hexane yielded needles (1.4 g.), m.p. 185–190°, $[\alpha]^{20}_{D}$ +57° (chlf.).

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35. Found: C, 76.06; H, 10.26.

3-Oxo-16-hydroxytetrahydrosolasodine (VIId). To 1.40 g. of VIIc was added 100 cc. of 5% potassium hydroxide in methanol, and the mixture refluxed for 1.5 hr. The resulting solution was concentrated and water added to precipitate a white solid which was collected and washed well with water. The yield was 1.18 grams, and the m.p. 197–208°. By chromatography over neutral alumina, and elution with 0.5% methanol in ether 0.677 g. of material was obtained, which gave after recrystallization from acetone-hexane colorless needles of m.p. 224.5–227°, $[\alpha]^{20}$ +4.5° (chlf.).

Anal. Calcd. for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91. Found: C, 77.86; H, 10.77.

Isomeric solanidan-3-one (VIII). (5β, 25D). VIId (180 mg.) was dissolved in 25 ml. acetone and oxidized with 0.32 ml. of Kiliani's reagent.[11] There was obtained 100 mg. of crude oil which crystallized as plates upon triturating with ether and methanol; m.p. 124–127°. A portion (79 mg.) of this crude crystalline mass was dissolved in 7 ml. of ethyl acetate and reduced over 44 mg. of palladium-charcoal

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(24) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3020 (1950).

(10%). One molar equivalent of hydrogen was absorbed. The product crystallized from aqueous ethanol as plates. A thrice crystallized sample melted at 145–147°. It was identical with the substance obtained from the direct oxidation of tetrahydrosolasodine (VIIa), and subsequent catalytic reduction.

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.67; H, 11.01.

Methiodide of 3,16-diacetate of pseudosolasodine B (IX). Compound V (133 mg.) was dissolved in 5 ml. of benzene and 10 ml. of acetone and refluxed with 1 ml. of methyl iodide for 75 min. Excess methyl iodide and solvent were removed *in vacuo* and the residue redissolved in acetone. Upon the addition of *n*-hexane, plates of m.p. 268–270° (dec.), $\lambda_{max}^{chlf.}$ 5.77, 6.00 μ, were obtained in a quantitative yield.

Anal. Calcd. for $C_{32}H_{50}O_4NI$: C, 60.08; H, 7.88; I, 19.85. Found: 60.07; H, 8.02; I, 19.78.

N-Methyl-3,16-diacetate of pseudosolasodine B (X). When IX was treated with a dilute aqueous sodium carbonate solution a compound was obtained which crystallized from aqueous methanol in rods of m.p. 194–197°, $\lambda_{max}^{chlf.}$ 5.77, 6.06 μ.

Anal. Calcd. for $C_{32}H_{49}O_4N$: C, 75.10; H, 9.65; —NCH_3, 2.9. Found: C, 74.91; H, 9.51; —NCH_3, 2.77.

The hydrochloride, $\lambda_{max}^{chlf.}$ 5.77, 5.98 μ, melted at 210–212° (dec.).

N-Methylsolasodine (XI). The methiodide of IX (110 mg.) was dissolved in 20 ml. of 5% methanolic potassium hydroxide and refluxed for 90 min. Although the resulting product was chromatographed over alumina, it appeared to be inhomogeneous, melting partly at 159–162° and partly at 176–180°. Infrared data of the eluates indicated the possible presence of another substance.

Anal. Calcd. for $C_{28}H_{45}O_2N$: C, 78.65; H, 10.60. Found: C, 78.59; H, 10.57.

BETHESDA, MD.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Practical Synthesis of Thieno[3,2-*b*]pyrrole[*][†]

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Pyrrole is converted to 3-thiocyanopyrrole (I) in 50% yield by thiocyanation with methanolic thiocyanogen at −70° or with cupric thiocyanate at 0°. Addition of excess dilute potassium hydroxide to a cold methanolic solution of bromoacetic acid and 3-thiocyanopyrrole leads to (3-pyrrolylthio)acetic acid (II), isolated as the ammonium salt in 90% yield. Under similar conditions, methyl iodide and 3-thiocyanopyrrole yield 3-(methylthio)pyrrole (Vc). Ring closure of the acid II with polyphosphoric acid furnishes 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (III) in 36% yield. The structure of III is proved by desulfurization with Raney nickel catalyst, which yields 2-acetylpyrrole. Reduction of III with sodium borohydride leads to thieno[3,2-*b*]pyrrole (IV) in 62% yield.

Thieno[3,2-*b*]pyrrole (IV) is an isostere of indole, having the fused thiophene ring in place of the benzene nucleus of the latter substance. The development of the chemistry of this simple, unsubstituted heterocycle may be expected to add to the fundamental knowledge of the thiophene and pyrrole systems and of interactions between them. Further, the possibility of preparing isosteres of physiologically active indole compounds from thieno[3,2-*b*]pyrrole makes the problem of devising a useful synthesis of the substance an intriguing one.

Although a synthesis of thieno[3,2-*b*]pyrrole (IV) from thiophene has been completed,[2] a great many steps were required and the final product was not obtained in a state of high purity. These difficulties prompted us to investigate the synthesis of thienopyrroles from pyrrole. Notwithstanding the well known sensitivity of pyrrole and such monosubstitution products as chloropyrrole and alkylpyrroles to air, light, and acids,[3] the readiness with which it undergoes electrophilic substitution reactions[3,4] made pyrrole an attractive raw material for the contemplated syntheses.

Thiocyanation appeared to be the most promising method for affixing a suitably substituted sulfur atom to the pyrrole ring. Numerous examples of thiocyanation of active aromatic systems under mild conditions are known.[5] Thiocyanation of carbethoxydimethylpyrroles has been reported.[6] Thiocyanation of pyrrole itself with ammonium thiocyanate and bromine has been reported to yield a dithiocyano derivative of undetermined structure.[6]

The fact that most reagents attack pyrroles at an unsubstituted α-position in preference to an unsubstituted β-position has been accounted for on the basis of the resonance theory.[4] However, recent molecular orbital calculations[7] indicate that the π-electron density in pyrrole is higher at the β-positions than at the α-positions. If, in the transition state, the pyrrole ring and an electrophilic reagent

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[*] This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

[†] For a preliminary communication on this subject, see D. S. Matteson and H. R. Snyder, *J. Am. Chem. Soc.*, **79**, 3610 (1957).

(1) National Science Foundation Predoctoral Fellow, 1954–1957.

(2) H. R. Snyder, L. A. Carpino, J. F. Zack, Jr., and J. F. Mills, *J. Am. Chem. Soc.*, **79**, 2556 (1957).

(3) H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, Vol. I, pp. 23–24, 37–38, 79.

(4) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1950, Vol. I, pp. 300–301.

(5) J. L. Wood, *Org. Reactions*, **3**, 240–266 (1946).

(6) P. Pratesi, *Atti reale accad. Lincei*, **16** (6) **9**, 443 (1933); *Chem. Zentralblatt* I, 2815 (1933).

(7) R. D. Brown, *Australian J. Chem.*, **8**, 100 (1955).