3-Acetamido-2,3-dihydro-4H-pyrido[1,2-a]pyrimidine-2,4-dione. 2-Aminopyridine (1 g., 0.01 mole) and ethyl acetaminomalonate (2.2 g., 0.01 mole) were heated in an oil bath at 70° for 3 hr. The temperature was then raised to 200° and maintained for 2 hr. Purification of the reaction product from alcohol benzene–petroleum ether followed by crystallization from 90% ethanol gave bright yellow platelets, m.p. 270° dec.; yield 14%.

Anal. Calcd. for $C_{10}H_9O_3N_3 \cdot H_2O$: C, 50.6; H, 4.6; N, 17.7. Found: C, 50.3; H, 4.8; N, 17.6.

The 8-methyl derivative similarly prepared separated from benzene–petroleum ether in pale yellow prisms, m.p. 274° dec.; yield 10%.

Anal. Calcd. for $C_{11}H_{11}O_3N_3$: C, 56.6; H, 4.7; N, 18.0. Found: C, 56.5; H, 4.6; N, 17.9.

AGOUZA, CAIRO, EGYPT

[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]

Steroids with Functional Sulfur Groups. I. 9α-Thiocyanocortisone and -cortisol[1]

TOSHIO KAWASAKI[2] AND ERICH MOSETTIG

Received October 16, 1961

The synthesis 9α-thiocyanocortisone and -cortisol and their acetates from the appropriate 9β,11β-epoxides is described. By an analogous route 9α,11α-epoxy-5β-pregnane-17α,21-diol-3,20-dione acetate was converted to the expected 3α,9α-epoxy-11β-thiocyano derivatives.

This paper and following ones of this series describe our efforts toward the partial synthesis of various steroid hormone analogs in which the oxygen of functional groups is replaced by sulfur.

A considerable number of sulfur analogs of steroids have been described in the recent literature. The majority of them are steroids with the sulfur-containing group in the 3-position,[3] and specifically corticoids and androgens with sulfur functions attached to C-21[4] or to C-17.[5] A few other types worthy of mentioning are the pregnane-20-thiones,[6] 6β-isothiocyano-3α,5-cyclo-5α-cholestane,[7] and the 1α- and 7α-acylthio(or thiol)- and the 1α,7α-diacylthio(or thiol)-Δ⁴-3-keto steroids.[8,9]

The present study was undertaken primarily with the aim of synthesizing corticoids or androgens with a sulfur-containing substituent at C-11. A few of the negative attempts toward this end may be mentioned cursorily. The direct conversion of an epoxide to an episulfide with potassium thiocyanate[10] could not be realized when attempted with 11β,12β-epoxy-23a-bromotigogenin acetate and 9β,11β-epoxy-Δ⁴-pregnene-17α,21-diol-3,20-dione acetate.[11] Attempts at adding thiolacetic acid or trichlorothiolacetic acid to the 9,11-double bond (of Δ⁹⁽¹¹⁾-tigogenin acetate or of Δ⁴,⁹⁽¹¹⁾-pregnadiene-17α,21-diol-3,20-dione acetate) were unsuccessful in spite of a wide variation of experimental conditions including irradiation with incandescent light (G.E. Photospot lamp). Only starting material was recovered. Equally unsuccessful were the attempts of replacing the 11α-bromine (in 11α,23a-dibromo-12-ketotigogenin acetate and 11α,23a-dibromo-12β-

(1) A preliminary account of this paper was published by T. Kawasaki and E. Mosettig, *J. Org. Chem.*, 24, 2071 (1959).

(2) Visiting Scientist (1957–1959), National Institutes of Health, under the sponsorship of the Cancer Chemotherapy National Service Center, National Cancer Institute.

(3) (a) T. Wagner-Jauregg and T. Lennartz, *Ber.*, 74, 27 (1941); L. C. King, R. M. Dodson and L. A. Subluskey, *J. Am. Chem. Soc.*, 70, 1176 (1948); J. Strating and H. J. Backer, *Rec. trav. chim.*, 69, 638 (1950). (b) S. Bernstein and K. Sax, *J. Org. Chem.*, 16, 679 (1951); J. A. K. Butsman and P. Westerhof, *Rec. trav. chim.*, 71, 925 (1952). (c) R. Bourdon, *Bull. soc. chim. France*, 722 (1958). (d) R. Bourdon, *Bull. soc. chim. France*, 1117 (1958).

(4)(a) L. H. Sarett, *J. Am. Chem. Soc.*, 71, 1175 (1949). (b) C. Djerassi and A. L. Nussbaum, *J. Am. Chem. Soc.*, 75, 3700 (1953).

(5)(a) R. M. Dodson and P. B. Sollman (to G. D. Searle & Co.) U. S. Patent 2,763,669 (1956); *Chem. Abstr.*, 51, 5134a (1957). (b) R. M. Dodson and P. B. Sollman (to G. D. Searle & Co.) U. S. Patent 2,837,538 (1958); *Chem. Abstr.*, 53, 4357c (1959).

(6) R. M. Dodson and P. B. Sollman (to G. D. Searle & Co.) U. S. Patent 2,837,539 (1958); *Chem. Abstr.*, 53, 3282 (1959).

(7) R. Charonnat and R. Bourdon, *Bull. soc. chim. France*, 719 (1958).

(8)(a) R. C. Tweit and R. M. Dodson, *J. Org. Chem.*, 24, 277 (1959). (b) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, 81, 1224 (1959).

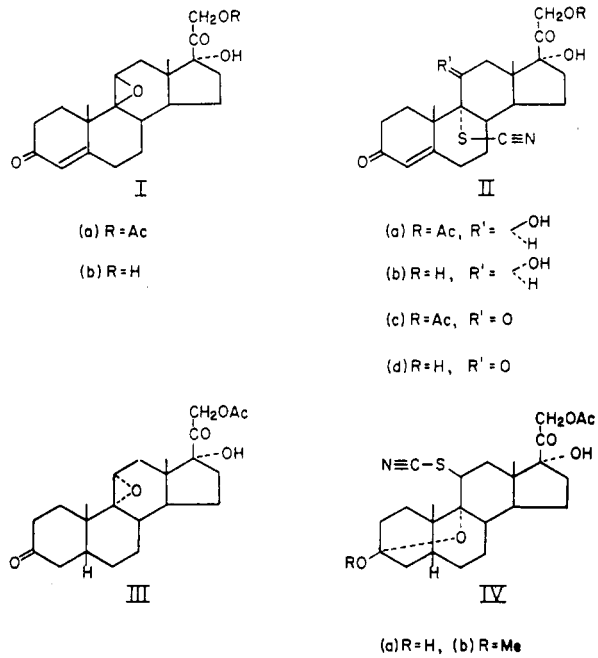
(9) While this part of our work has been prepared for the regular full-length publication there appeared a series of papers dealing with thio analogs of a variety of steroids by members of the Research Laboratory, Shionogi & Co., Ltd., Imafuku, Amagasaki, Hyogo-ken: (a) K. Takeda and T. Komeno, *Chem. Pharm. Bull.* (Japan), 8, 468 (1960); (b) K. Takeda, T. Kubota, and J. Kawanami, *ibid.* p. 615; (c) K. Takeda, T. Komeno, and J. Kawanami, *ibid.* p. 621; (d) T. Komeno, *ibid.* p. 668; (e) T. Komeno, *ibid.* p. 672; (f) T. Komeno, *ibid.* p. 680. The compounds described therein are 19-C, 21-C, 24-C, and 27-C steroids substituted in positions 5, 6, 11, 12, and 16, with thiocyano and thiol groups.

(10) (a) E. E. van Tamelen, *J. Am. Chem. Soc.*, 73, 3444 (1951). (b) E. E. van Tamelen, *Org. Syntheses*, 32, 39 (1952).

(11) A successful preparation of an 11,12β-episulfide from methyl 3α-acetoxy-11β-thiocyano-12α-chlorocholanate has been reported by Takeda *et al.*, see ref. 9c.

hydroxytigogenin acetate) by a thiol group with potassium hydrogen sulfide. In the former instance the corresponding $\Delta^{9(11)}$-derivative was formed, and in the latter the corresponding epoxide. 9α,11α-Epoxytigogenin acetate reacted at room temperature neither with trichlorothiolacetic acid nor with thiocyanic acid. 9α,11α-Epoxy-Δ^4-pregnene-17α,-21-diol-3,20-dione acetate[12] could not be induced to react with thiocyanic acid. On the other hand, 9α,-11α-epoxy-5β-pregnane-17α,21-diol-3,20-dione acetate (III) gave with thiocyanic acid readily and in good yields, depending on the conditions, 3α,9α-epoxy-3β-hydroxy(or methoxy)-11β-thiocyano-5β-pregnane-17α,21-diol-20-one acetate, IVa or IVb. The opening of the 9β,11β-epoxide ring in Δ^4-3-ones with thiocyanic acid proceeded quite well, and 9α-thiocyano-Δ^4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (9α-thiocyanohydrocortisone acetate, IIa) was obtained from 9,11β-epoxy-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (Ia) in a yield of *ca.* 55%. Although the thiocyanate ion may exist in either as S—C≡N⁻ or N=C=S⁻, the former was thought to predominate under the conditions employed, and for reasons of analogy we formulate the new derivatives (II)—*i.e.* as 9α-thiacyano derivatives. A strong and very sharp absorption band near 4.62 μ supports the assumption of a thiocyano group rather than of an isothiocyano group.[9b,13] Oxidation of IIa with chromic acid gave 9α-thiocyano-Δ^4-pregnene-17α,21-diol-3,11,20-trione acetate (9α-thiocyanocorticone acetate IIc) in a yield of about 64%.

The hydrolysis of the acetates (IIa, IIc) offered considerable difficulties. Hydrolysis with 0.27 *N* methanolic perchloric acid as recommended by Fried and Sabo[14] for the analogous 9α-halogeno compounds converted IIa, in poor yields, into nitrogen-free sulfur-containing derivatives which were not further investigated, while the corresponding 11-keto compound IIc remained largely unchanged under these conditions. Compound IIc, however, could be hydrolyzed with hydrogen chloride in methanol-chloroform[14,15] to give 9α-thiocyano-Δ^4-pregnene-17α-21-diol-3,11,20-trione (IId) in a yield of *ca.* 58%. The attempted hydrolysis of IIc in aqueous methanolic potassium carbonate solution gave a compound containing sulfur and nitrogen and was thought to be a 9α-thiocarboxamidocortisone. Analytical and infrared spectral data of this and analogous derivatives in the 19-C series, however, revealed an entirely different structure, as will be shown in a subsequent paper. 9α-Thiocyanocortisol (IIb) could be obtained only, and in moderate yields (*ca.* 28%) by opening the epoxide ring in Ib with thiocyanic acid. It is hoped that compounds of type IV (particularly of the 19-C series) will lend themselves for the synthesis of 11β-thiol analogs of corticoids and androgens.



The 9α-thiocyano derivatives of cortisone and cortisol and their 21-acetates were submitted for testing to the Endocrine Evaluation Branch of the Cancer Chemothrapy National Service Center. Compounds IIa, IIb, IIc, and IId showed in the thymus, liver glycogen, and granuloma tests no appreciable corticoid activity.[16] Tests with these compounds for antitumor activity are under way.

EXPERIMENTAL[17]

9α-Thiocyano-Δ^4-pregnene-11β,17α,21-triol-3,20-dione acetate (IIa). A solution of 1.176 g. of Ia[14] in a mixture of 17.6 ml. of glacial acetic acid and 17.6 ml. of *ca.* 1 *N* thiocyanic acid solution in 70% acetic acid[18] was allowed to stand for

(12) It should be noted that Takeda and Komeno (see ref. 9a) succeeded in opening the 11,12α-epoxide ring with hydrogen thiocyanide in 11,12α-epoxytigogenin acetate, in methyl 11,12α-epoxy-3α-acetoxycholenate and the corresponding 3-keto compound.

(13) Invariably minor amounts of by-products were obtained having an absorption band at *ca.* 4.8 μ (—N=C=S).

(14) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(15) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951); *cf.* V. R. Mattox, *J. Am. Chem. Soc.*, **74**, 4340 (1952).

(16) Compound IIb was also subjected to the granuloma tests in the Research Laboratories of Merck Sharp & Dohme, and found considerably less active than hydrocortisone (private communication by Dr. Max Tishler).

(17) All melting points were determined on a Kofler block and recorded as read. Optical rotations were measured in chloroform at 20° unless mentioned otherwise. The ultraviolet absorption spectra were measured in ethanol solution with a Cary self-recording spectrophotometer Model 11, infrared spectra in Nujol with a Perkin-Elmer double beam spectrophotometer, Model 21. Analytical samples were dried over phosphorus pentoxide at 80° and a pressure of 0.02–0.1 mm. for 3 hr.

(18) To an ice-cold solution of 97.2 g. of potassium thiocyanate in 250 ml. of 4 *N* sulfuric acid was added a mixture of 700 ml. of glacial acetic acid and 50 ml. of water. The resulting supernatant solution was used (approx. equal to 1 l. of 1 *N* HSCN in 70% aqueous acetic acid).

26.5 hr. at room temperature. The lemon yellow clear solution was diluted with a large amount of water and extracted three times with chloroform. The combined chloroform extracts were washed with water to neutrality and until free of thiocyanate ion (tested with ferric chloride), dried over sodium sulfate, and evaporated *in vacuo* to dryness. The semicrystalline residue was crystallized from methanol, and yielded 550 mg. of lemon yellow crystals melting at 147–150°, dec. From the mother liquor two further crops (76 mg. and 97 mg. melting at 146–149°, dec.) were obtained,[19] total yield 53.6%. The analytical sample was obtained by recrystallization from methanol; m.p. 149–153°, dec.; $[\alpha]_D$ +224.9° (*c* 0.37, dioxane); λ_{max} 243 mμ (14,000); 2.86 μ (OH); 4.66 μ (SCN); 5.80, 5.99 μ (CO). Lit.[9a] m.p. 154–156° (dec.) $[\alpha]_D$ +188.6 ± 4° ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{31}O_6NS$: C, 62.45; H, 6.77; N, 3.04; S, 6.95. Found: C, 62.43; H, 6.84; N, 3.25; S, 6.72.

In another experiment (with 16.55 g. of Ia) the resulting clear solution was poured into 3 l. of ice water and after 2 hr. the lemon yellow precipitate was collected and thoroughly washed with water. The filtrate was nearly neutralized with sodium bicarbonate and allowed to stand in the coldroom overnight whereby an additional amount of precipitate could be obtained. The total yield of crystalline material of m.p. 149–151°, dec., was 55.3%.

9α-Thiocyano-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione (IIb). A solution of 4.08 g. of Ib[14] in a mixture of 62.5 ml. of glacial acetic acid and 62.5 ml. of thiocyanic acid solution[18] was allowed to stand at room temperature for 17 hr. and poured into 1.5 l. of ice water. After 1 hr. a lemon yellow precipitate was filtered and thoroughly washed with water. It weighed after drying 0.33 g., had an ill defined m.p., and the infrared spectrum revealed the presence of both the thiocyano group (4.66 μ) and the isothiocyano group (4.8 μ). The lemon yellow filtrate was saturated with sodium chloride and extracted three times with chloroform. The latter extract was washed with water to neutrality, dried and evaporated *in vacuo* to dryness leaving 3.13 g. of a slightly discolored crystalline residue. Treatment of this material with ether removed about 0.7 g. of light yellow glass-like material. The ether insoluble portion was recrystallized from acetone-ether and gave 1.33 g. (28%) of IIb as very slightly discolored crystals of m.p. 173–174°, dec. Further crystallization from the same solvents did not materially change the m.p. (174–175°, dec.); $[\alpha]_D$ +283.3° (*c* 0.37, dioxane); λ_{max} 243 mμ (13,430); 2.93, 3.02 μ (OH); 4.64 μ (SCN); 5.82, 6.01 μ (CO).

Anal. Calcd. for $C_{22}H_{29}O_5NS$: C, 62.98; H, 6.97; N, 3.34; S, 7.64. Found: C, 63.21; H, 7.16; N, 3.41; S, 7.65.

By acetylation of IIb (21 mg.) with acetic anhydride and pyridine at room temperature the acetate IIa (16 mg.) was obtained as colorless needles of m.p. 148–155°, dec., identical, by direct comparison, with the authentic sample.

9α-Thiocyano-Δ⁴-pregnene-17α,21-diol-3,11,20-trione acetate (IIc). To a stirred solution of 2.10 g. of IIa in 180 ml. of glacial acetic acid a solution of 2.5 g. of chromic acid in 46 ml. of water was added within 10 min. at room temperature. Stirring was continued for 1.5 hr., the mixture poured in 1300 ml. of ice-water, and allowed to stand in the coldroom overnight. The long needles which had deposited were collected, washed with water, and recrystallized from a large volume of methanol. The compound (IIc) consisted of colorless silky needles (1.32 g.) containing 1 mole of methanol and melted at 218–223° (dec.). The mother liquor gave a second crop (0.11 g.) of IIc, total yield 63.7%. The analytical sample was recrystallized from methanol; m.p. 218–219°, dec.; $[\alpha]_D$ +333.7° (*c* 0.99, dioxane); λ_{max} 238 mμ (16,310); 3.00 μ (OH); 4.64 μ (SCN); 5.75 μ (OAc); 5.83, 5.98 μ (CO). Lit.[9a] m.p. 217–219°; $[\alpha]_D$ +339.2 ± 2° ($CHCl_3$), given without methanol of crystallization.

Anal. Calcd. for $C_{24}H_{29}O_6NS \cdot CH_3OH$: C, 61.08; H, 6.77; N, 2.85; S, 6.52, OCH_3, 6.31. Found: C, 61.22; H, 6.84; N, 2.87; S, 6.55; OCH_3, 6.12.

9α-Thiocyano-Δ⁴-pregnene-17α,21-diol-3,11,20-trione (IId).[15] A mixture of 1.69 g. of IIc, 16.5 ml. of chloroform, 58.0 ml. of methanol, 5.6 ml. of water, and 3.5 ml. of concd. hydrochloric acid was allowed to stand at room temperature. After 48 hr. 20 ml. of water was added and the reaction mixture placed in the cold room (0–1°) for another 24 hr. After dilution with water the hydrolysate was exhaustively extracted with ethyl acetate and the extract washed with water, dried, and evaporated *in vacuo* leaving IId as a glass-like material. Crystallization from acetone-ether gave colorless lustrous plates (0.656 g.) of m.p. 238–242°, dec. From the mother liquor another crop of crystalline IId (0.182 g., m.p. 238–240°, dec.) was obtained. Yield 58%. The analytical sample was recrystallized from the same solvents and dried at 0.007 mm. at 130° for 3 hr.; m.p. 245–246°, dec.; $[\alpha]_D$ +337.2 (*c* 0.43, dioxane); λ_{max} 238 mμ (16,200); 3.02 μ (OH); 4.63 μ (SCN); 5.83, 6.02 μ (CO).

Anal. Calcd. for $C_{22}H_{27}O_5NS$: C, 63.29; H, 6.52; N, 3.36; S, 7.68. Found: C, 63.37; H, 6.53; N, 3.38; S, 7.62.

By treatment of IId (20 mg.) with acetic anhydride in pyridine IIc (15 mg.), m.p. 220–222°, dec., was obtained as colorless silky needles, identical in every respect with the compound IIc, described above.

9α,11α-Epoxy-5β-pregnane-17α,21-diol-3,20-dione acetate (III).[20] A mixture of 600 mg. of 9,11α-epoxy-Δ⁴-pregnene-17α,21-diol-3,20-dione acetate[14] and 300 mg. of 10% palladium-charcoal in 60 ml. of ethyl acetate was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure. After the calculated amount of hydrogen had been absorbed, the catalyst was removed by filtration and washed with ethyl acetate. The residue left by evaporation *in vacuo* of the filtrate was recrystallized from methanol yielding 483 mg. of colorless wooly crystals melting at 230–232°. The mother liquor gave another crop of crystals melting from 210–233°, total yield approx. 90%. The analytical sample was obtained by one recrystallization from the same solvent. After drying for 3 hr. at 0.02 mm. and at 110°, it melted at 231–234°; $[\alpha]_D$ +30.0° (*c* 0.2).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 68.29; H, 7.97. Found: C, 68.56; H, 8.13.

3α,9α-Epoxy-3β-methoxy-11β-thiocyano-5β-pregnane-17α,-21-diol-20-one acetate (IVb). A solution of 7.79 g. of III in 150 ml. of glacial acetic acid and 150 ml. of the thiocyanic acid solution[18] was allowed to stand at room temperature for 24 hr., water was added, and the mixture extracted with chloroform. The extracts after thorough washing with water and drying left by evaporation *in vacuo* an oily residue which was dissolved in 100 ml. of methanol with the addition of two drops of concd. hydrochloric acid. The solution was stirred for 3 hr., water was added, and the mixture again extracted with chloroform. The oily residue from these dried chloroform extracts was triturated with methanol, and the crystalline material thus obtained recrystallized from methanol yielding 2.85 g. of IVb, melting at 179–181° (31%). The analytical sample crystallized from methanol in colorless prisms and melted at 182–183°, $[\alpha]_D$ +121.1 ±0.5° (*c* 1.4), λ_{max} 2.87 μ (OH); 4.63 μ(SCN); 5.71 μ (OAc); 5.78 μ(CO).

Anal. Calcd. for $C_{25}H_{35}O_6NS$: C, 62.87; H, 7.39; N, 2.93; S, 6.71; OCH_3, 6.50. Found: C, 62.85; H, 7.54; N, 3.11; S, 6.58; OCH_3, 6.79.

3α,9α-Epoxy-11β-thiocyano-5β-pregnane-3β,17α,21-triol-20-one acetate (IVa). A solution of 203 mg. of III in a mixture of 3.5 ml. of glacial acetic acid and 3.5 ml. of the thiocyanic

(19) A fourth crop of crude crystalline material showed a very strong absorption at *ca.* 4.8 μ (—N=C=S). In some experiments colorless crystalline material separated from the chloroform extract. After washing with chloroform and drying, they melted at 143–144° and constituted about half of the total crop. The remainder of the reaction product (IIa) was recovered from the mother liquor.

(20) *Cf.* A. J. Lemin and C. Djerassi, *J. Am. Chem. Soc.*, 76, 5672 (1954), ftn. 14.

acid solution[18] was allowed to stand for 24 hr. at room temperature. The mixture was then diluted with ice water, saturated with sodium chloride, and extracted with ethyl acetate. The extracts, after thorough washing with water and drying, yielded 240 mg. of a nearly colorless glass-like substance. Crystallization from acetone-hexane gave slightly discolored crystalline material which upon a second recrystallization from the same solvent mixture gave IVa, depending on the conditions (concentration), as colorless long thin needles or plates. The yield in two experiments was 54% and 65%, respectively; m.p. 154–156°, dec. (some change in appearance at 80–90°); further crystallization did not change the melting point, $[\alpha]_D$ +144.4° (*c* 0.31); λ_{max} 2.94 μ (OH); 4.62 μ (SCN); 5.66 μ (OAc); 5.75 μ (CO).

Anal. Calcd. for $C_{24}H_{33}O_6NS$: C, 62.18; H, 7.18; N, 3.02; S, 6.92. Found: C, 62.07; H, 7.19; N, 3.03; S, 6.96.

Ackdowledgment. The authors wish to express their great indebtedness for the supply of valuable starting materials to the Cancer Chemotherapy National Service Center, The Squibb Institute for Medical Research, and The Upjohn Company.

BETHESDA, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

The Condensation of Phthalaldehydic Acids with Tryptophan and Tryptamine

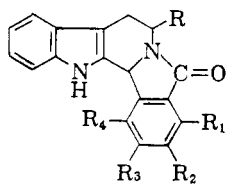
S. WAWZONEK AND G. E. NELSON[1]

Received April 25, 1961

Tryptophan and tryptamine have been condensed with phthalaldehydic, opianic, *m*-opianic, and 3,4,5-trimethoxyphthalaldehydic acids. Tryptophan gives 1-(2-carboxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acids which upon treatment with methanol and hydrogen chloride are cyclized to 5,7,8,13b-tetrahydro-5-oxo-13*H*-indolo[2,3-*c*]isoindolo[2,1-*a*]pyridines. Tryptamine in the same condensation gives these compounds directly. Cyclization occurs on the tetrahydropyridine nitrogen rather than the indole nitrogen, as alkylation of the sodium derivative with methyl iodide gives 13-methyl-5,7,8,13b-tetrahydro-5-oxo-indolo[2,3-*c*]isoindolo[2,1-*a*]pyridine. This product was also synthesized by the condensation of 1-methyl-3-(2-aminoethyl)indole with phthalaldehydic acid. Reduction of the lactam carbonyl group with lithium aluminum hydride was successful only for the condensation products from tryptamine and phthalaldehydic and opianic acids. The preparation of a similar derivative by the irradiation of 1-*o*-tolyl-2-bromo-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole in carbon tetrachloride failed.

The synthesis of compounds containing the β-carboline nucleus has been of interest because this ring system occurs in a number of physiologically active compounds.

In the present work the syntheses of the pentacyclic compounds I and II, which resemble reserpine in certain respects, for testing as hypotensive agents are described.



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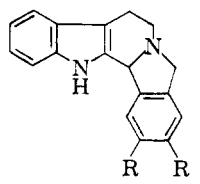
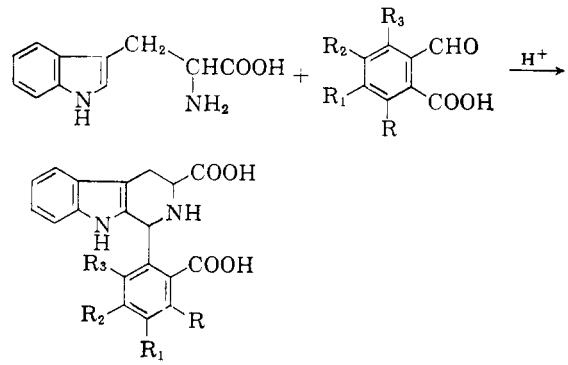


IIa. R = H
b. R = OCH_3

The preparation of 1-substituted β-carbolines was accomplished by means of the Pictet-Spengler reaction[2] using *dl*-tryptophan and tryptamine with various phthalaldehydic acids.

The reactions were carried out using approximately equimolar quantities of the aldehyde and amine in water with sufficient ethanol to give a homogeneous reaction mixture. The sulfuric acid concentration used in the condensation varied for the various examples and was in the range of 0.1 *N* to 0.33 *N*.

The condensation of tryptophan with phthalaldehydic acids gave the corresponding 1-(2-carboxyphenyl) - 1,2,3,4 - tetrahydro - 9*H* - pyrido-[3,4,-*b*]indole-3-carboxylic acids (III). These compounds were difficult to purify, retained solvents tenaciously and became highly colored when treated with polar solvents or acids. Pure samples (IIIa, IIId) were obtained only in the condensation with phthalaldehydic and 3,4,5-trimethoxyphthalaldehydic acids. The use of *dl*-tryptophan should



IIIa. R = R_1 = R_2 = R_3 = H
b. R = R_1 = OCH_3; R_2 = R_3 = H
c. R_1 = R_2 = OCH_3; R = R_3 = H
d. R_1 = R_2 = R_3 = OCH_3; R = H

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(1) Abstracted in part from the Ph.D. thesis, June 1959, of G. E. Nelson.

(2) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1951).