did not depress the m.p. of authentic 2-butanone p-nitrophenylhydrazone. p-Nitrophenylhydrazones were not obtained from fractions B or C. Semicarbazones were not obtained from any of the fractions.

Acknowledgment.—The authors wish to express their appreciation to the American Gilsonite Co., Salt Lake City, Utah, for a research grant that made this investigation possible.

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17β-Methyl-Δ^5-androstene-3β-ol

BY RICHARD T. RAPALA AND EUGENE FARKAS

A report by Ghosh[1] on the isolation of a $C_{20}H_{32}O$ compound, called serposterol from a Rauwolfia serpentina plant, suggested the tentative structure as methylandrostenol. We have prepared the postulated compound, 17β-methyl-Δ^5-androstene-3β-ol, previously unknown, and found that it is not identical with the natural material.[2]

The mixture of 17-methylene-3β-acetoxy-$\Delta^{5,6;17,20}$-androstadiene and 17-methyl-3β-acetoxy-$\Delta^{5,6;16,17}$-androstadiene, resulting from dehydration of 3β-acetoxy-17α-methyl-$\Delta^{5,6}$-androstene-17β-ol, was selectively reduced with palladium-on-charcoal catalyst to give a single compound. Hydrolysis gave the compound proposed as serposterol. Comparison of the X-ray pattern and a mixed melting point determination showed that the two compounds were different. Comparison of the infrared spectra however showed great similarities but the curves were not superimposable.

That the hydrogenation gave the 17β-methyl compound was shown by the work of Heusser[3] in the hydrogenation of the same 17-methylene-3β-acetoxy-$\Delta^{5,6;17,20}$-androstadiene with platinum catalyst to give, after mild hydrolysis, the known 17β-methylandrostane-3-ol. Furthermore, Hershberg[4] obtained a 17β-ethyl compound by the reduction of $\Delta^{5,16}$-pregnadien-20-yne-3β-ol with palladium-on-charcoal as in the present series.

Experimental

3β-Acetoxy-17α-methyl-Δ^5-androstene-17β-ol.—The acetate was prepared from 2.0 g. of 17α-methyl-Δ^5-androstene-3β-17β-diol in 12 cc. of anhydrous pyridine and 6 cc. of acetic anhydride. After 6 hours the mixture was poured into ice, and the product filtered. Recrystallization from ethyl acetate yielded 1.15 g. of colorless needles, m.p. 164–165° (first crop), and 0.750 g., m.p. 162–164° (second crop); lit.[5] reports m.p. 160–161°.

A Mixture of 3β-Acetoxy-17-methyl-$\Delta^{5,6;16,17}$-androstadiene and 3β-Acetoxy-17-methylene-$\Delta^{5,6;17,20}$-androstadiene.—The acetate was dehydrated by the procedure of Julia and Heusser[3] using phosphorus oxychloride–pyridine. From 1.9 g. of acetate there was obtained 0.8 g. of product, m.p. 116–118°. This was found to be a mixture of dienes which could be used directly in the hydrogenation without separation.

3β-Acetoxy-17β-methyl-Δ^5-androstene.—The reduction of the mixture of dienes (800 mg.) in absolute ethanol was

(1) G. B. Ghosh and R. K. Basu, *Naturwiss.*, **42**, 130 (1955).

(2) We are indebted to Dr. B. P. Ghosh for an authentic sample of serposterol.

(3) S. A. Julia and H. Heusser, *Helv. Chim. Acta*, **35**, 2080 (1952).

(4) E. B. Hershberg, E. P. Oliveto, C. Gerold and L. Johnson, THIS JOURNAL, **73**, 5073 (1951).

(5) K. Miescher and W. Klarer, *Helv. Chim. Acta*, **22**, 962 (1939).

carried out using 400 mg. of prereduced 5% palladium-on-charcoal catalyst in an atmosphere of hydrogen. One mole of hydrogen was absorbed in 20 minutes. Recrystallization of the product from methanol, after removal of catalyst and solvent, gave 250 mg. of fine needles, m.p. 129–131°, $[\alpha]^{26}$D −64°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.71; H, 10.21.

17β-Methyl-Δ^5-androstene-3β-ol.—To a solution of 500 mg. of potassium carbonate in 10 cc. of water, 10 cc. of dioxane and 100 cc. of methanol was added 250 mg. of the acetoxyandrostene. The solution was refluxed for one hour, then evaporated to dryness and water added. The solid was collected and recrystallized from methanol to give 0.190 g. of colorless rods, m.p. 163–165°. The analytical sample was recrystallized two additional times from methanol, m.p. 164–165°, $[\alpha]^{26}$D −65.7°; $\lambda_{max}^{CHCl_3}$ 2.84, 3.40, 6.85, 7.27, 9.56.

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.09; H, 11.30.

Upon admixture with authentic serposterol (m.p. 151–153°) there was a depression in melting point to 124–131°. In addition, X-ray pattern and infrared spectra were not identical.

LILLY RESEARCH LABORATORIES
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Derivatives of Piperazine. XXVIII. Synthesis of 1-Aryl-4-thioaryloylpiperazines and 1-Aryl-4-thioalkanoylpiperazines by the Kindler Modification of the Willgerodt Reaction

BY C. B. POLLARD AND JOHN C. BRAUN

The Kindler modification of the Willgerodt reaction has been found to be applicable to both ketones[1,2] and aldehydes of the aromatic series[3,4] and the aliphatic series.[5,6]

Heterocyclic amines such as morpholine[7] and piperazine[8] were found to be especially suitable, since their use permitted reactions to be run in vessels which were open to the atmosphere.

The authors have found that N-phenylpiperazine and N-phenylpiperazines which have substituents on the benzene ring also undergo the reaction when refluxed with an aldehyde or ketone and sulfur in pyridine solution.

Purification of the products was rather difficult, and considerable differences in procedure were required, depending on whether the aldehyde or ketone was aliphatic or aromatic. Thioamides derived from the latter are moderately to slightly soluble in ethanol, while those derived from the former are generally very soluble.

Experimental

The N-phenylpiperazines were prepared by the methods of Pollard and Wicker[9] and Pollard and MacDowell.[10] The

(1) K. Kindler, *Arch. Pharm.*, **265**, 389 (1927).

(2) K. Kindler and T. Li, *Ber.*, **74**, 321 (1941).

(3) K. Kindler, German Patent 385,376 (Nov. 23, 1923).

(4) K. Kindler, *Ann. Chem., Justus Liebigs*, **431**, 193, 222 (1923).

(5) L. Cavalieri, D. B. Pattison and M. Carmack, THIS JOURNAL, **67**, 1783 (1945).

(6) E. Cerwonka, R. C. Anderson and E. V. Brown, *ibid.*, **75**, 28 (1953).

(7) E. Schwenk and E. Bloch, *ibid.*, **64**, 3051 (1942).

(8) P. Chabrier and S. T. Renard, *Compt. rend.*, **228**, 850 (1949).

(9) C. B. Pollard and T. H. Wicker, Jr., THIS JOURNAL, **76**, 1853 (1954).

(10) C. B. Pollard and L. G. MacDowell, *ibid.*, **57**, 2363 (1935).

TABLE I

PHYSICAL AND ANALYTICAL DATA OF THIOAMIDES FROM PIPERAZINES

Piperazine	Mol. formula	M.p., °C. (cor.)	Yield, %	Carbon Calcd.	Found	Hydrogen Calcd.	Found	Others, % Calcd.	Found
1-Phenyl-4-(thiobutanoyl)-	C₁₄H₂₀N₂S	66.8– 67.8	29	...	...	..	..	N, 11.28	11.35
1-Phenyl-4-(thioisobutanoyl)-	C₁₄H₂₀N₂S	62.7– 63.7	50	...	...	..	..	N, 11.28	11.12
1-Phenyl-4-(thiopentanoyl)-	C₁₅H₂₂N₂S	47.5– 48.5	13	68.65	68.82	8.45	8.52		
1-Phenyl-4-(thiohexanoyl)-	C₁₆H₂₄N₂S	62.7– 63.7	14	69.51	69.75	8.75	8.77		
1-Phenyl-4-(2-ethylthiobutanoyl)-	C₁₆H₂₄N₂S	94.0– 95.0	30	69.51	69.70	8.75	8.70		
1-Phenyl-4-(4-methylthiopentanoyl)-	C₁₆H₂₄N₂S	77.8– 78.8	5	69.51	68.84	8.75	8.65		
1-Phenyl-4-(thioheptanoyl)-	C₁₇H₂₆N₂S	62.7– 63.7	14	70.29	70.57	9.02	8.82		
1-Phenyl-4-(thioöctanoyl)-	C₁₈H₂₈N₂S	48.5– 49.5	25	71.00	70.98	9.27	9.30		
1-Phenyl-4-(thiononanoyl)-	C₁₉H₃₀N₂S	52.6– 53.6	28	71.64	71.41	9.49	9.21		
1-Phenyl-4-(thiodecanoyl)-	C₂₀H₃₂N₂S	51.6– 52.6	36	72.23	71.90	9.70	9.85		
1-Phenyl-4-(thiobenzoyl)-	C₁₇H₁₈N₂S	93.5– 94.5	83	...	...	..	..	N, 9.92; S, 11.35	9.73; 11.75
1-Phenyl-4-(thio-2-thenoyl)-	C₁₅H₁₆N₂S₂	106.1–107.1	35	62.46	62.75	5.59	5.71	N, 9.71	9.45
1-Phenyl-4-(phenylthioacetyl)-	C₁₈H₂₀N₂S	125.2–126.2	62	...	...	..	..	N, 9.45	9.42
1-Phenyl-4-(thio-p-anisoyl)-	C₁₈H₂₀ON₂S	160.2–161.7	61	69.19	69.75	6.45	6.64		
1-Phenyl-4-(thiopiperonyloyl)-	C₁₈H₁₈O₂N₂S	130.3–131.3	65	...	...	..	..	N, 8.58	8.76
1-Phenyl-4-(thioveratroyl)-	C₁₉H₂₂O₂N₂S	160.7–162.7	70	66.63	67.01	6.48	6.66		
1-Phenyl-4-(1-naphthylthioacetyl)-	C₂₂H₂₂N₂S	134.7–136.2	14	...	...	..	..	N, 8.09	8.29
1-(o-Tolyl)-4-(thiobutanoyl)-	C₁₅H₂₂N₂S	71.8– 72.8	38	68.65	67.84	8.45	8.35		
1-(o-Tolyl)-4-(thiobenzoyl)-	C₁₈H₂₀N₂S	116.2–117.2	56	72.93	73.09	6.80	6.48		
1-(o-Tolyl)-4-(thio-2-thenoyl)-	C₁₆H₁₈N₂S₂	129.3–130.3	66	63.54	64.51	6.00	6.17		
1-(o-Tolyl)-4-(phenylthioacetyl)-	C₁₉H₂₂N₂S	107.6–108.6	61	73.50	74.12	7.14	6.70		
1-(o-Tolyl)-4-(thio-p-anisoyl)-	C₁₉H₂₂ON₂S	118.2–119.2	71	69.90	69.74	6.79	6.71		
1-(o-Tolyl)-4-(thiopiperonyloyl)-	C₁₉H₂₀O₂N₂S	143.5–144.5	79	67.03	67.30	5.92	5.83		
1-(o-Tolyl)-4-(2-naphthylthioacetyl)-	C₂₃H₂₄N₂S	148.6–149.6	38	76.62	77.11	6.71	6.80		
1-(m-Tolyl)-4-(thiobenzoyl)-	C₁₈H₂₀N₂S	82.9– 83.9	77	72.93	73.26	6.80	6.49		
1-(m-Tolyl)-4-(phenylthioacetyl)-	C₁₉H₂₂N₂S	85.1– 86.1	52	73.50	72.96	7.14	6.99		
1-(m-Tolyl)-4-(thioveratroyl)-	C₂₀H₂₄O₂N₂S	157.2–158.2	77	67.38	67.41	6.79	6.89		
1-(m-Tolyl)-4-(1-naphthylthioacetyl)-	C₂₃H₂₄N₂S	159.7–160.7	33	76.62	76.49	6.71	6.52		
1-(p-Tolyl)-4-(thiobenzoyl)-	C₁₈H₂₀N₂S	137.4–138.4	84	...	...	..	..	N, 9.45; S, 10.82	9.35; 10.75
1-(p-Tolyl)-4-(thio-2-thenoyl)-	C₁₆H₁₈N₂S₂	122.2–123.2	55	63.54	64.05	6.00	5.98		
1-(p-Tolyl)-4-(phenylthioacetyl)-	C₁₉H₂₂N₂S	106.1–107.1	32	73.50	73.64	7.14	6.53		
1-(p-Tolyl)-4-(thiopiperonyloyl)-	C₁₉H₂₀O₂N₂S	134.3–135.3	65	67.03	67.20	5.92	6.04		
1-(p-Tolyl)-4-(thioveratroyl)-	C₂₀H₂₄O₂N₂S	153.7–154.7	94	67.38	67.60	6.79	7.40		
1-(o-Chlorophenyl)-4-(thiobenzoyl)-	C₁₇H₁₇N₂SCl	120.7–121.7	86	...	...	..	..	N, 8.84; Cl, 11.19	8.63; 11.60
1-(o-Chlorophenyl)-4-(thio-2-thenoyl)-	C₁₅H₁₅N₂S₂Cl	123.2–124.2	54	55.80	56.62	4.68	4.98		
1-(o-Chlorophenyl)-4-(phenylthioacetyl)-	C₁₈H₁₉N₂SCl	103.1–104.1	33	65.34	66.04	5.79	6.14		
1-(o-Chlorophenyl)-4-(thiopiperonyloyl)-	C₁₈H₁₇O₂N₂SCl	123.8–124.8	71	59.91	60.18	4.75	5.03		
1-(o-Chlorophenyl)-4-(1-naphthylthioacetyl)-	C₂₂H₂₁N₂SCl	139.5–141.5	4	69.36	68.28	5.56	5.64		
1-(m-Chlorophenyl)-4-(thiobenzoyl)-	C₁₇H₁₇N₂SCl	100.0–101.0	49	64.44	64.61	5.41	4.90		
1-(m-Chlorophenyl)-4-(thio-2-thenoyl)-	C₁₅H₁₅N₂S₂Cl	95.0 –96.0	51	55.80	55.62	4.68	4.70		
1-(m-Chlorophenyl)-4-(thiopiperonyloyl)-	C₁₈H₁₇O₂N₂SCl	114.1–115.1	80	59.91	59.93	4.75	4.76		
1-(m-Chlorophenyl)-4-(thioveratroyl)-	C₁₉H₂₁O₂N₂SCl	157.2–158.7	96	60.54	60.50	5.62	5.69		
1-(m-Chlorophenyl)-4-(1-naphthylthioacetyl)-	C₂₂H₂₁N₂SCl	122.2–123.2	13	69.36	68.38	5.56	5.78		
1-(p-Chlorophenyl)-4-(thiobenzoyl)-	C₁₇H₁₇N₂SCl	115.1–116.1	49	64.44	64.44	5.41	5.16		
1-(p-Chlorophenyl)-4-(thio-2-thenoyl)-	C₁₅H₁₅N₂S₂Cl	155.7–157.2	48	55.80	56.14	4.68	4.74		
1-(p-Chlorophenyl)-4-(thiopiperonyloyl)-	C₁₈H₁₇O₂N₂SCl	130.3–131.3	62	59.91	60.48	4.75	4.42		
1-(p-Chlorophenyl)-4-(1-naphthylthioacetyl)-	C₂₂H₂₁N₂SCl	146.5–147.5	3	69.36	68.48	5.56	5.62		

ketones and aldehydes were obtained from commercial sources and were used without purification. Reagent or C.P. grades were used when available. U.S.P. flowers of sulfur and Karl Fischer reagent grade pyridine were used.

Preparation of 1-Phenyl-4-thiobenzoylpiperazine.—Sulfur (3.2 g.) was placed in a 200-ml. flask and pyridine was added until the flask was about one-third full. The flask was swirled gently as 10.6 g. (10.1 ml.) of benzaldehyde and 16.2 g. (16.0 ml.) of N-phenylpiperazine were added. The flask was filled to three-fourths of its capacity with pyridine, attached immediately to a condenser, and held at reflux temperature for 2 hours; yield 83%, m.p. 93.5–94.5°.

Purification of Thioaroyl Derivatives.—The hot reaction mixture was diluted with 400–500 ml. of 95% ethanol and allowed to cool. The product was collected and washed with ethanol. Repeated recrystallizations from ethanol, with decolorizing charcoal, gave analytically pure samples.

Those compounds having very limited solubilities in ethanol were dissolved in an acetone–ethanol mixture.

Purification of Thioalkanoyl Derivatives.—After the pyridine was removed by steam distillation, the non-aqueous layer was extracted with boiling hexane and decolorized with charcoal. The solution was cooled in a Dry Ice-bath, and the crystals were filtered off. They were further purified by recrystallizations from ethanol or ethanol–water mixtures.

Description of the Compounds.—These compounds range in color from a deep orange through all shades of yellow to a very pale ivory; the aromatic derivatives are generally much more strongly colored than the aliphatic derivatives. Some of the compounds are very lustrous.

Physical and analytical data on the compounds prepared during this research are given in Table I. Yields probably reflect difficulty of purification rather than degree of reaction. Analytical work was done by Geller Microanalytical Laboratories, Hackensack, N. J.

Alkaloid Studies. IX.[1] Rauwolfia Alkaloids. IV.[2] Isolation of Reserpine and Other Alkaloids from Rauwolfia sellowii Muell. Argov.[3]

BY S. C. PAKRASHI,[4a] CARL DJERASSI,[4a] RICHARD WASICKY[4b]
AND N. NEUSS[4c]

RECEIVED AUGUST 17, 1955

The recent interest in different *Rauwolfia* species[5] as possible sources for reserpine and other new alkaloids of this type led us to a chemical investigation of the brazilian tree, *Rauwolfia sellowii* Muell. Argov. This species has been characterized histochemically[6] and an alkaloidal fraction derived from

(1) For paper VIII in the Wayne series "Alkaloid Studies" see C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, THIS JOURNAL, **77**, 4801 (1955).

(2) For paper III in the Lilly series "Rauwolfia Alkaloids" see N. Neuss, *et al., ibid.*, **77**, 4087 (1955).

(3) An investigation of the alkaloids of *R. sellowii* was started independently in the Lilly Research Laboratories and as part of a coöperative Wayne University–Universidade de São Paulo research project. Upon learning of each other's results, it was decided to publish the work as a joint contribution from the three laboratories. Reprint requests should be addressed to N. Neuss, Eli Lilly and Co., Indianapolis, Ind.

(4) (a) Wayne University; (b) Universidade de São Paulo; (c) Eli Lilly and Co.

(5) *Cf.* (a) A. Chatterjee and S. Talapatra, *Naturwiss.*, **42**, 182 (1955); (b) C. Djerassi and J. Fishman, *Chemistry and Industry*, 627 (1955), and references cited therein.

(6) Th. A. Neubern de Toledo and Robert Wasicky, *Scientia Pharm.*, **22**, 217 (1954).

it has been shown to possess hypotensive activity with an indication of an action in the hypothalamic region.[7] More recently,[8] the isolation of ajmaline, ajmalinine, serpentine and two unidentified crystalline alkaloids has been reported. However, these alkaloids were neither fully characterized nor compared with authentic specimens while the most active fraction remained in an amorphous form.

By a procedure, based in part upon that employed by Hochstein, *et al.*,[9] in their investigation of *R. heterophylla*, and outlined in the Experimental portion, we have been able to isolate seven alkaloids. While all but one are known, the relative proportions and, in particular, the co-occurrence of several of them in the same plant is of some significance.

Quantitatively, the principal alkaloids of the root bark of *R. sellowii* proved to be ajmaline[10] (1.2%) and aricine[11] (1.5%), thus making this plant by far the most abundant source for the former. Of considerable biogenetic interest is the fact that both alkaloids are accompanied in trace amounts by closely related bases. In addition to aricin, there has been encountered 0.0009% of ajmalicine,[12] which from a structural standpoint may be considered to be the parent compound of this class, and 0.0056% of its stereoisomer, py-tetrahydroalstonine.[13] This represents the first isolation of py-tetrahydroalstonine from a *Rauwolfia* species.

Two dihydroindoles of unknown constitution appear to belong to the ajmaline group. The first, tetraphyllicine, has been isolated recently[5b] from *R. tetraphylla* and is the first oxygen-free ($C_{20}H_{26}N_2$) *Rauwolfia* alkaloid. The remarkable similarity of its physical constants with those of ajmaline have been mentioned already[5b] and it was suggested at that time that tetraphyllicine may conceivably be the oxygen-free parent substance of the ajmaline group. This suggestion is now somewhat strengthened by the observed coexistence of the two alkaloids in *R. sellowii*; ajmaline had not been found in *R. tetraphylla*.[5b] The other alkaloid, m.p. 241–242°, now named ajmalidine, appears to be new and is formulated tentatively as $C_{20}H_{24}N_2O_2$. Lack of material prevented degradative experiments but its physical properties strongly suggest a close relationship to ajmaline ($C_{20}H_{26}N_2O_2$). The color reaction with nitric acid and the ultraviolet absorption spectrum are practically identical with those of ajmaline. The infrared spectrum of ajmalidine resembles that of ajmaline except for the presence of a pronounced band at 5.77 μ (CHCl$_3$), which on the basis of its position and molar intensity can be assigned to a five-membered ring ketone.

(7) R. A. Seba, J. S. Campos and J. G. Kuhlmann, *Rev. quim. farm.*, **19**, 11 (1954).

(8) R. A. Seba, J. S. Campos and J. G. Kuhlmann, *Bol. inst. vital Brazil*, **5**, 175 (1954).

(9) F. A. Hochstein, K. Murai and W. H. Boegemann, THIS JOURNAL, **77**, 3551 (1955).

(10) F. C. Finch, J. D. Hobson, R. Robinson and E. Schlittler, *Chemistry and Industry*, 653 (1955), and references cited therein.

(11) (a) R. Goutarel, M. M. Janot, A. Le Hir, H. Corrodi and V. Prelog, *Helv. Chim. Acta*, **37**, 1805 (1954); (b) A. Stoll, A. Hofmann and R. Brunner, *ibid.*, **38**, 270 (1955).

(12) *Cf.* M. W. Klohs, M. D. Draper, F. Keller, W. Malesh and F. J. Petracek, THIS JOURNAL, **76**, 1332 (1954).

(13) For leading references, *cf.* N. Neuss, H. E. Boaz and J. W. Forbes, *ibid.*, **76**, 3234 (1954).