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.

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17β-Methyl-Δ⁵-androstene-3β-ol

BY RICHARD T. RAPALA AND EUGENE FARKAS

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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-Δ⁵-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-Δ⁵-androstene-17β-ol.—The acetate was prepared from 2.0 g. of 17α-methyl-Δ⁵-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-Δ⁵-androstene.—The reduction of the mixture of dienes (800 mg.) in absolute ethanol was 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-Δ⁵-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.

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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

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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

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TABLE I

PHYSICAL AND ANALYTICAL DATA OF THIOAMIDES FROM PIPERAZINES

Piperazine	Mol. formula	M.p., °C. (cor.)	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Others, % Calcd.	Others, % Found
1-Phenyl-4-(thiobutanoyl)-	$C_{14}H_{20}N_2S$	66.8–67.8	29	...	...	..	..	N, 11.28	11.35
1-Phenyl-4-(thioisobutanoyl)-	$C_{14}H_{20}N_2S$	62.7–63.7	50	...	...	..	..	N, 11.28	11.12
1-Phenyl-4-(thiopentanoyl)-	$C_{15}H_{22}N_2S$	47.5–48.5	13	68.65	68.82	8.45	8.52		
1-Phenyl-4-(thiohexanoyl)-	$C_{16}H_{24}N_2S$	62.7–63.7	14	69.51	69.75	8.75	8.77		
1-Phenyl-4-(2-ethylthiobutanoyl)-	$C_{16}H_{24}N_2S$	94.0–95.0	30	69.51	69.70	8.75	8.70		
1-Phenyl-4-(4-methylthiopentanoyl)-	$C_{16}H_{24}N_2S$	77.8–78.8	5	69.51	68.84	8.75	8.65		
1-Phenyl-4-(thioheptanoyl)-	$C_{17}H_{26}N_2S$	62.7–63.7	14	70.29	70.57	9.02	8.82		
1-Phenyl-4-(thioöctanoyl)-	$C_{18}H_{28}N_2S$	48.5–49.5	25	71.00	70.98	9.27	9.30		
1-Phenyl-4-(thiononanoyl)-	$C_{19}H_{30}N_2S$	52.6–53.6	28	71.64	71.41	9.49	9.21		
1-Phenyl-4-(thiodecanoyl)-	$C_{20}H_{32}N_2S$	51.6–52.6	36	72.23	71.90	9.70	9.85		
1-Phenyl-4-(thiobenzoyl)-	$C_{17}H_{16}N_2S$	93.5–94.5	83	...	...	..	..	N, 9.92 S, 11.35	9.73 11.75
1-Phenyl-4-(thio-2-thenoyl)-	$C_{15}H_{16}N_2S_2$	106.1–107.1	35	62.46	62.75	5.59	5.71	N, 9.71	9.45
1-Phenyl-4-(phenylthioacetyl)-	$C_{18}H_{20}N_2S$	125.2–126.2	62	...	...	..	..	N, 9.45	9.42
1-Phenyl-4-(thio-*p*-anisoyl)-	$C_{18}H_{20}ON_2S$	160.2–161.7	61	69.19	69.75	6.45	6.64		
1-Phenyl-4-(thiopiperonyloyl)-	$C_{18}H_{18}O_2N_2S$	130.3–131.3	65	...	...	..	..	N, 8.58	8.76
1-Phenyl-4-(thioveratroyl)-	$C_{19}H_{22}O_2N_2S$	160.7–162.7	70	66.63	67.01	6.48	6.66		
1-Phenyl-4-(1-naphthylthioacetyl)-	$C_{22}H_{22}N_2S$	134.7–136.2	14	...	...	..	..	N, 8.09	8.29
1-(*o*-Tolyl)-4-(thiobutanoyl)-	$C_{15}H_{22}N_2S$	71.8–72.8	38	68.65	67.84	8.45	8.35		
1-(*o*-Tolyl)-4-(thiobenzoyl)-	$C_{18}H_{20}N_2S$	116.2–117.2	56	72.93	73.09	6.80	6.48		
1-(*o*-Tolyl)-4-(thio-2-thenoyl)-	$C_{16}H_{18}N_2S_2$	129.3–130.3	66	63.54	64.51	6.00	6.17		
1-(*o*-Tolyl)-4-(phenylthioacetyl)-	$C_{19}H_{22}N_2S$	107.6–108.6	61	73.50	74.12	7.14	6.70		
1-(*o*-Tolyl)-4-(thio-*p*-anisoyl)-	$C_{19}H_{22}ON_2S$	118.2–119.2	71	69.90	69.74	6.79	6.71		
1-(*o*-Tolyl)-4-(thiopiperonyloyl)-	$C_{19}H_{20}O_2N_2S$	143.5–144.5	79	67.03	67.30	5.92	5.83		
1-(*o*-Tolyl)-4-(2-naphthylthioacetyl)-	$C_{23}H_{24}N_2S$	148.6–149.6	38	76.62	77.11	6.71	6.80		
1-(*m*-Tolyl)-4-(thiobenzoyl)-	$C_{18}H_{20}N_2S$	82.9–83.9	77	72.93	73.26	6.80	6.49		
1-(*m*-Tolyl)-4-(phenylthioacetyl)-	$C_{19}H_{22}N_2S$	85.1–86.1	52	73.50	72.96	7.14	6.99		
1-(*m*-Tolyl)-4-(thioveratroyl)-	$C_{20}H_{24}O_2N_2S$	157.2–158.2	77	67.38	67.41	6.79	6.89		
1-(*m*-Tolyl)-4-(1-naphthylthioacetyl)-	$C_{23}H_{24}N_2S$	159.7–160.7	33	76.62	76.49	6.71	6.52		
1-(*p*-Tolyl)-4-(thiobenzoyl)-	$C_{18}H_{20}N_2S$	137.4–138.4	84	...	...	..	..	N, 9.45 S, 10.82	9.35 10.75
1-(*p*-Tolyl)-4-(thio-2-thenoyl)-	$C_{16}H_{18}N_2S_2$	122.2–123.2	55	63.54	64.05	6.00	5.98		
1-(*p*-Tolyl)-4-(phenylthioacetyl)-	$C_{19}H_{22}N_2S$	106.1–107.1	32	73.50	73.64	7.14	6.53		
1-(*p*-Tolyl)-4-(thiopiperonyloyl)-	$C_{19}H_{20}O_2N_2S$	134.3–135.3	65	67.03	67.20	5.92	6.04		
1-(*p*-Tolyl)-4-(thioveratroyl)-	$C_{20}H_{24}O_2N_2S$	153.7–154.7	94	67.38	67.60	6.79	7.40		
1-(*o*-Chlorophenyl)-4-(thiobenzoyl)-	$C_{17}H_{17}N_2SCl$	120.7–121.7	86	...	...	..	..	N, 8.84 Cl, 11.19	8.63 11.60
1-(*o*-Chlorophenyl)-4-(thio-2-thenoyl)-	$C_{15}H_{15}N_2S_2Cl$	123.2–124.2	54	55.80	56.62	4.68	4.98		
1-(*o*-Chlorophenyl)-4-(phenylthioacetyl)-	$C_{18}H_{19}N_2SCl$	103.1–104.1	33	65.34	66.04	5.79	6.14		
1-(*o*-Chlorophenyl)-4-(thiopiperonyloyl)-	$C_{18}H_{17}O_2N_2SCl$	123.8–124.8	71	59.91	60.18	4.75	5.03		
1-(*o*-Chlorophenyl)-4-(1-naphthylthioacetyl)-	$C_{22}H_{21}N_2SCl$	139.5–141.5	4	69.36	68.28	5.56	5.64		
1-(*m*-Chlorophenyl)-4-(thiobenzoyl)-	$C_{17}H_{17}N_2SCl$	100.0–101.0	49	64.44	64.61	5.41	4.90		
1-(*m*-Chlorophenyl)-4-(thio-2-thenoyl)-	$C_{15}H_{15}N_2S_2Cl$	95.0–96.0	51	55.80	55.62	4.68	4.70		
1-(*m*-Chlorophenyl)-4-(thiopiperonyloyl)-	$C_{18}H_{17}O_2N_2SCl$	114.1–115.1	80	59.91	59.93	4.75	4.76		
1-(*m*-Chlorophenyl)-4-(thioveratroyl)-	$C_{19}H_{21}O_2N_2SCl$	157.2–158.7	96	60.54	60.50	5.62	5.69		
1-(*m*-Chlorophenyl)-4-(1-naphthylthioacetyl)-	$C_{22}H_{21}N_2SCl$	122.2–123.2	13	69.36	68.38	5.56	5.78		
1-(*p*-Chlorophenyl)-4-(thiobenzoyl)-	$C_{17}H_{17}N_2SCl$	115.1–116.1	49	64.44	64.44	5.41	5.16		
1-(*p*-Chlorophenyl)-4-(thio-2-thenoyl)-	$C_{15}H_{15}N_2S_2Cl$	155.7–157.2	48	55.80	56.14	4.68	4.74		
1-(*p*-Chlorophenyl)-4-(thiopiperonyloyl)-	$C_{18}H_{17}O_2N_2SCl$	130.3–131.3	62	59.91	60.48	4.75	4.42		
1-(*p*-Chlorophenyl)-4-(1-naphthylthioacetyl)-	$C_{22}H_{21}N_2SCl$	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.

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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]

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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 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.

(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.

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