able activity. Results of testing are listed in Table II. It may be of interest to note that a simple compound like N-butylpyrrolidine hydrochloride also possesses appreciable oral hypoglycemic activity. This substance is also highly toxic. It is too premature to arrive at the cause of activity among hexahydroindeno-[1,2-*c*]pyrroles as well as the mode of action of such compounds. The work is in progress and will be reported later. From experimental results it appears that among hexahydroindeno[1,2-*c*]pyrroles of the type I which have been tested, compound (I, X = Y = OMe; R = *n*-Bu) is the most active one in alloxan diabetic rabbits. Preliminary examination of this compound in the anesthetized cat reveals[4] that very little fall in blood pressure and slight slowing of heart rate occur on administration of the compound by the i.v. route at a dosage of 2 mg./kg. An *in vitro* test indicates that this compound does not possess any effect on smooth muscle. The LD_{50} of this compound in the mouse has been found to be 130 and 1800 mg./kg. by the intramuscular and oral routes, respectively (data on six mice). The results indicate that this compound might attract interest as an oral hypoglycemic agent.

Experimental[5]

N-Substituted Indan-1,2-dicarboximides (IV).—A mixture of an appropriate ethyl indan-1,2-dicarboxylate[6] (0.05 mole) and an appropriate primary amine (0.1 mole) was heated in a sealed tube in an oil bath at 150° for 8 hr. Excess of the amine was removed on a boiling water bath under reduced pressure. The residual mass was then heated on a sand bath until evolution of the amine was complete. The residual mass was extracted with ether and the amide was distilled under reduced pressure.

1,2,3,3a,8,8a-Hexahydro-2-alkylindeno[1,2-*c*]pyrroles (V).—The appropriate indan-1,2-dicarboximide (4 g.) was reduced with lithium aluminum hydride (1 g.) in absolute ether (150 ml.) under reflux for 12 hr. Excess of lithium aluminum hydride was then decomposed slowly with the required quantity of water, the ethereal solution was filtered, the ether was dried (Na_2SO_4), and the amine was distilled under reduced pressure. The hydrochloride was prepared by the addition of dry ethereal HCl to the ethereal solution of the amine. The hydrochloride crystallized from ethyl acetate.

1-Methylindan-2-carboxylic Acid.—A mixture of ethyl 2-benzylacetoacetate (10 g.) and concentrated sulfuric acid (98%, 30 ml.) was kept for 4 hr. at 30°. The mass was then poured onto crushed ice and the precipitated 1-methylindene-2-carboxylic acid was filtered, washed with water, and dried; m.p. 200°.

The indenecarboxylic acid was reduced with sodium amalgam in the usual manner. The reduced acid crystallized from dilute alcohol, m.p. 79°.[5] Its acid chloride was prepared with thionyl chloride in the usual manner. It boiled at 140–141° (10 mm.).

1-Methylindan-2-carboxamide (III).—The above acid chloride (1 mole) was added dropwise under stirring to a mixture of an amine (1.5 moles) and NaOH solution (10%, 1 mole) cooled in an ice bath. The amide was extracted with ether and distilled. Characteristics of the amides are listed in Table II.

1-Methyl-2-alkylaminomethylindan (II).—1-Methylindan-2-carboxamide was reduced with lithium aluminum hydride in the usual manner and the amine was isolated by distillation under reduced pressure. The secondary amine was methylated by heating a mixture of the amine, formic acid, and formaldehyde on a water bath in the usual method.[7]

(4) Dr. D. Chakravarty of Messrs Smith Stanistreet & Co. (Pvt.) Ltd., Calcutta, kindly informed the pharmacological data.

(5) Melting points are corrected and were determined with a Gallenkamp apparatus. Boiling points are uncorrected.

(6) W. Roser, *Ber.*, **20**, 1574 (1887).

(7) W. E. Bachmann, *Org. Syn.*, **25**, 89 (1945).

17α-Methylandrostane-3α,17β-diol

K. R. BHARUCHA AND F. M. MARTIN

Research Laboratories, Canada Packers Ltd., Toronto 9, Ontario, Canada

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Intramuscular injection of androsterone (3α-hydroxyandrostan-17-one), an end product of androgen metabolism in man, is accompanied by substantial reduction in serum cholesterol levels of hypercholesterolemic patients.[1] While the mode of administration and the inactivity of the steroid, when given orally,[2] detract from its therapeutic potential as a hypocholesterolemic agent, this important observation has nevertheless opened up the interesting possibility that other steroids might be discovered, which would be more efficacious, particularly by the oral route. Since the introduction of a methyl group in the steroid molecule often results in potentiation of activity (*cf.* 17α-methyltestosterone *vs.* testosterone), it seemed of interest to have 17α-methylandrostane-3α,17β-diol, a close relative of androsterone, tested as a possible anticholesterol steroid. The preparation of this diol is the subject of the present report.

17α-Methyl-Δ⁵-androstene-3β,17β-diol (I), a precursor of 17α-methyltestosterone, was chosen as the starting material because of its ready availability. The hydrogenation of 3β-substituted Δ⁵-steroids generally proceeds with difficulty as regards completion of reduction unless catalyzed by strong acids ($pK < 3$).[3] In view of this, it was gratifying to find a fairly rapid uptake of hydrogen when I was stirred with hydrogen under 3.51 kg./cm.² (50 p.s.i.) pressure in ethanol–acetic acid in the presence of platinum catalyst. The reduction was stereospecific and afforded in 90% yield the expected A/B *trans* compound, 17α-methylandrostane-3β,17β-diol (II) as a monohydrate, the structure of which was established by oxidation to the known 17α-methylandrostan-17β-ol-3-one, identified by comparison with an authentic sample. Tosylation of II with 2.5 *M* proportions of *p*-toluenesulfonyl chloride in pyridine at 0° furnished, in near quantitative yield, the desired 3-monotosylate. When the latter was heated in dimethylformamide (DMF) at 78° for 45 hr.,[4] a mixture of 17α-methylandrostane-3α,17β-diol (III) and the corresponding (Δ²) olefin was obtained, after saponification, and was resolved by chromatography on alumina. Without crystallization of the intermediates, the over-all yield of III, m.p. 182–184°, from I is *ca.* 35%. Improved results were obtained when the displacement of the 3β-tosylate was carried out with potassium acetate in aqueous DMF, utilizing conditions successfully employed with compounds of the hyodesoxycholic acid series.[5]

(1) L. Hellman, H. L. Bradlow, B. Zumoff, D. K. Fukushima, and T. F. Gallagher, *J. Clin. Endocrinol. Metab.*, **19**, 1936 (1959).

(2) W. D. Cohen, N. Higano, and R. W. Robinson, *Circulation*, **22**, 659 (1960).

(3) (a) E. B. Hershberg, O. M. Rubin, H. Staeudle, and L. Kuhlen, *J. Am. Chem. Soc.*, **73**, 1144 (1951); (b) J. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, 1365 (1955).

(4) F. C. Chang and R. T Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

(5) (a) P. Ziegler and K. R. Bharucha, *Chem. Ind.* (London), 1351 (1955); (b) K. R. Bharucha, G. C. Buckley, C. K. Cross, L. J. Rubin, and P. Ziegler, *Can. J. Chem.*, **34**, 982 (1956); (c) K. R. Bharucha, *Experientia*, **14**, 5 (1958).

As an alternative to platinum in the catalytic hydrogenation of methylandrostenediol (I), described above, the more readily available Raney nickel was considered. This catalyst is unique among others in that it can function with or without extraneous hydrogen.[6] In the latter case, it is the hydrogen contained in the catalyst in the form of substitutional replacement of nickel atoms in the lattice[7] that is responsible for the reduction, although there is some evidence to indicate that in hydroxylic solvents, the process may also involve hydrogen transfer from solvent donor to the substrate acceptor.[6d,8] When I was refluxed with Raney nickel in the aprotic solvent, benzene, with a view to obtaining the corresponding saturated compound II, the resultant product was found to be ketonic. By careful chromatography, there was isolated *ca.* 32% of 17α-methylandrostan-17β-ol-3-one. While dehydrogenations of primary and secondary alcohols with nickel are not unknown, these usually require elevated (~200°) temperatures[9] unless promoted by hydrogen acceptors.[8c,10] The present oxidation is thus remarkable for its ease and simplicity. In view of the mild nature of the oxidation,[11] the reaction has been explored further and some pertinent observations have been made, which are not entirely without interest. (1) In the conversion of the 3β-hydroxy-Δ⁵-compound to the corresponding saturated 3-ketone (of the allo series), the reduction of the double bond precedes oxidation at C-3. The noninvolvement of 3-keto-Δ⁵-compound and hence methyltestosterone as an intermediate in the oxidation was clearly demonstrated by the survival of the latter to the extent of *ca.* 40% (by ultraviolet absorption measurement) under experimental conditions under which the unsaturated diol I gave a product transparent in the ultraviolet region, indicating total absence of methyltestosterone. It may, however, be pointed out that the latter was present to the extent of 10% (based on ultraviolet absorption) in the crude oxidation product, when less (2 g./g. of steroid *vs.* 10 g./g. of steroid) Raney nickel was employed. (2) The efficacy of the nickel is in some way related to its pyrophoric nature. Thus, the catalyst, which had been rendered essentially hydrogen free[6b] by heating *in vacuo* at 200–210° (bath temp.) for 2.25 hr., was relatively ineffective and led to *ca.* 40% recovery of the starting material, together with 20% of 17α-methyltestosterone. Presumably, the heating process alters the active site at which the reaction occurs. (3) Benzene does not appear to be necessary for the oxidation, which also proceeds, albeit sluggishly, in cyclohexane (which has nearly the same boiling point as benzene). This has interesting theoretical implications and seems to rule out hydrogen transfer between steroid and benzene leading to cyclohexene (and thence to cyclohexane) as mechanism for oxidation, an attractive hypothesis[12] in view of the fact that the reverse *viz.* disproportionation of cyclohexene into benzene with Raney nickel has been demonstrated.[13]

Biological Activity.—Since the completion of this work, Dr. D. K. Fukushima kindly informed us (private communication, May 5, 1960) that 17α-methylandrostane-3α,17β-diol had been tested at the Sloan-Kettering Institute for Cancer Research and found to have no hypocholesteremic activity. We thank Dr. Fukushima for this information.

Experimental[14]

17α-Methylandrostane-3β,17β-diol Monohydrate (II).—A solution of 17α-methyl-Δ⁵-androstene-3β,17β-diol (50 g.) in ethanol (300 ml.) and glacial acetic acid (200 ml.) was stirred with hydrogen at 50 p.s.i. (3.51 kg./cm.²) in the presence of Adams' catalyst (5 g.) until uptake of hydrogen ceased. The mixture was then filtered, the filtrate was evaporated to dryness *in vacuo* at 50°, and the residue was triturated with hexane (250 ml.) at room temperature for 30 min., to give II as a monohydrate (47.91 g., 90%), m.p. 209–210°, $[\alpha]^{28}D$ −12.72 (*c* 0.979) (lit.[15] m.p. 211–212°). This material, which gave no color with tetranitromethane, was used for subsequent experiments, without further purification. An analytical sample obtained by crystallization from ethyl acetate had m.p. 209–210°; $[\alpha]^{31}D$ −12.61 (*c* 0.62); infrared bands: 3480, 3400, 3210, 1077, and 1037 cm.⁻¹.

Anal. Calcd. for $C_{20}H_{34}O_2 \cdot H_2O$: C, 74.07; H, 11.11; O, 14.81. Found: C, 73.93; H, 11.22; O, 14.85.

17α-Methyl-3β-tosyloxyandrostan-17β-ol.—*p*-Toluenesulfonyl chloride (31 g., 2.5 molar proportions) was added in small portions to a solution of the diol II (20 g.) in anhydrous pyridine (200 ml.), cooled to 0°. The mixture was maintained at that temperature for 24 hr. and the excess tosyl chloride decomposed by gradual addition of water. Isolation of the product by pouring the whole mixture into ice water gave 27.64 g. (97.3%), m.p. 121–129° (prior sintering), λ_{max} 225 mμ ($E^{1\%}_{1cm}$ 274, indicating a purity of 97%). An analytical sample obtained by crystallizations from ether–hexane had m.p. 137–137.5°, $[\alpha]^{28}D$ −2.00 (*c* 1.0). The melting point varied with the rate of heating in the range 137–141°; λ_{max} 225 mμ ($E^{1\%}_{1cm}$ 282, ε 13,900); infrared bands (CS_2): 3610, 1370, 1190, 1180, and 937 cm.⁻¹.

Anal. Calcd. for $C_{27}H_{40}O_4S$: C, 70.40; H, 8.75; O, 13.89; S, 6.96. Found: C, 70.17; H, 8.67; O, 13.98; S, 6.82.

17α-Methylandrostane-3α,17β-diol (III). A.—A solution of the preceding unpurified (97% pure) tosylate (27.6 g.) in

(6) *Inter alia* (a) R. Mozingo, C. Spencer, and K. Folkers, *J. Am. Chem. Soc.*, **66**, 1850 (1944), and references cited therein; (b) H. Hauptmann and B. Wladislaw, *ibid.*, **72**, 707, 710 (1950); (c) W. A. Bonner, *ibid.*, **74**, 1033 (1952); (d) L. F. Fieser, *ibid.*, **76**, 1945 (1954); (e) L. F. Fieser, C. Yuan, and T. Goto, *ibid.*, **82**, 1996 (1960).

(7) R. J. Kokes and P. H. Emmett, *ibid.*, **81**, 5032 (1959).

(8) (a) M. L. Wolfrom and J. V. Karabinos, *ibid.*, **66**, 909 (1944); (b) C. Djerassi, A. J. Manson, and M. Gorman, *ibid.*, **77**, 4925 (1955); (c) E. C. Kleiderer and E. C. Kornfeld, *J. Org. Chem.*, **13**, 455 (1948).

(9) (a) R. Schröter in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 70; (b) M. M. Korotaeva and M. P. Kocheneva, *J. Chem. Ind. (USSR)*, 52 (1933); *Chem. Abstr.*, **28**, 138 (1934); (c) R. Paul, *Compt. rend.*, **208**, 1319 (1939); (d) L. Palfray and S. Sabetay, *ibid.*, **208**, 109 (1939); (e) L. Palfray, S. Sabetay, and A. Halasz, *ibid.*, **209**, 1000 (1939); (f) A. Halasz, *Ann. chim.* (Paris), **14**, 318 (1940).

(10) (a) M. Ehrenstein, A. R. Johnson, P. C. Olmsted, V. I. Vivian, and M. A. Wagner, *J. Org. Chem.*, **15**, 264 (1950); (b) J. Romo, *Bol. inst. quim. univ. nacl. auton Mex.*, **4**, 91 (1952); (c) P. N. Rao and H. R. Gollberg, *Tetrahedron*, **18**, 1251 (1962); (d) J. Fishman, *Chem. Ind.* (London), 1467 (1962).

(11) Since the conclusion of this work in 1959, an inspection of the literature revealed two isolated examples of oxidation with Raney nickel under comparable conditions: (a) C. Djerassi, M. Gorman, and J. A. Henry, *J. Am. Chem. Soc.*, **77**, 4647 (1955); (b) J. A. Berson and W. M. Jones, *J. Org. Chem.*, **21**, 1325 (1956).

(12) See footnote 4a in ref. 11b.

(13) B. B. Carson and V. N. Ipatieff, *J. Am. Chem. Soc.*, **61**, 1056 (1939).

(14) Unless otherwise stated, optical rotations were measured in alcohol-free chloroform, ultraviolet spectra in ethanol on a Beckman DK-2 recording spectrophotometer, and infrared spectra as mulls in Nujol on Beckman IR 4 double-beam spectrophotometer with sodium chloride optics. Only the prominent and/or characteristic bands in the infrared are reported. Microanalyses were carried out by Mr. E. Thommen, Basel, Switzerland.

(15) (a) L. Ruzicka, M. W. Goldberg, and H. R. Rosenberg, *Helv. Chim. Acta*, **18**, 1487 (1935); (b) L. Ruzicka, P. Meister, and V. Prelog, *ibid.*, **30**, 867 (1947). In the first publication, Ruzicka, *et al.*, give analytical results for the diol agreeing for the free compound, while in the subsequent publication, the figures quoted are for the diol hydrate. No explanation is given for this apparent discrepancy. Present findings confirm the composition of the diol as a monohydrate.

commercial dimethylformamide (1100 ml.) was heated (N_2 atmosphere) at 78° for 45 hr. Evaporation of the solvent *in vacuo* at 60–70° (bath temp.) left an amber gum (36.3 g.), which was dissolved in methanol (500 ml.) and refluxed for 30 min. with potassium carbonate (10 g.) in water (100 ml.). After removal of bulk of solvent *in vacuo*, the residue was diluted with water and chilled to 0° for 24 hr. Filtration gave a colorless solid (18.0 g.), which was dissolved in a mixture of benzene (200 ml.) and ethyl acetate (100 ml.) and adsorbed on a column of alumina (450 g.). Elution with benzene–ethyl acetate (2:1) gave a colorless waxy solid (5.76 g.), m.p. 107–111° (sintering at 103°), which could not be crystallized satisfactorily, the material having a great tendency to separate out as a gel. It gave a positive tetranitromethane test and is probably impure 17α-methyl-Δ²-androsten-17β-ol[16]; infrared bands (CS_2): 3620, 3018, 1656, 776, and 667 cm.$^{-1}$. Elution with benzene–ethyl acetate (1:1, 1600 ml.) and evaporation gave a colorless solid (9.65 g.), m.p. 172–181°, which was crystallized from ethyl acetate at 0° to afford 7.5 g., m.p. 182–184° (sintering at 179°). Further recrystallizations from the same solvent at 0° did not improve the melting point. However, when the material was crystallized from ethyl acetate at room temp. for 2 hr., pure III (5 g.), m.p. 184–185°, $[\alpha]^{31}D$ −12.33 (*c* 0.940), was obtained (lit.[17] m.p. 184–185°); infrared bands: 3350–3330, 1267, 1172, 1087, 1074, 1017, and 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44. Found: C, 78.21; H, 11.28; O, 10.56.

B.—A solution of the crude tosylate (28.8 g.) and potassium acetate (43.2 g.) in dimethylformamide (230 ml.) and water (23 ml.) was heated (N_2 atmosphere) at 110–115° (bath temp.) for 5 hr. After concentration *in vacuo* at 60–65° (bath temp.), the product was isolated, by pouring into water, as a colorless solid (26.28 g.) which was shown by its infrared spectrum to be a mixture of acetate and hydroxy compounds. A portion (25.78 g.) of the solid in methanol (500 ml.) was heated under reflux with potassium carbonate (10 g.) in water (100 ml.) for 1 hr. Infrared spectrum of the product (19.2 g.) indicated incomplete hydrolysis. Resaponification for 2 hr. afforded a colorless solid (19.0 g.), free from acetate. This was dissolved in benzene (200 ml.) and ethyl acetate (100 ml.) and adsorbed on a column of alumina (400 g.). Elution with benzene–ethyl acetate (2:1, 500 ml.) gave a colorless solid (3.43 g.), which was crude 17α-methyl-Δ²-androsten-17β-ol (infrared spectrum). Further elution (400 ml.) with the same mixture of solvents afforded a colorless solid (2.10 g.), identified by its infrared spectrum to be a mixture of the olefin and the desired 3α-hydroxy compound. Separation was achieved by leaching with boiling hexane (50 ml.), whereby the 3α,17β-diol (1.08 g.), m.p. 182–185° (sintering at 178°), was obtained as the insoluble portion. Crystallization from ethyl acetate afforded 0.93 g., m.p. 182–184° (sintering at 180°).

The eluent from benzene–ethyl acetate (1:1) was collected in three fractions of 500 ml. each, and on evaporation gave 6.16 g., m.p. 178–185° (sintering at 175°); 4.15 g., m.p. 177–185° (sintering at 174°); and 1.05 g. Crystallizations from ethyl acetate at 0° yielded 5.37 g., m.p. 183–185° (sintering at 181°); 3.61 g., m.p. 182–184.5° (180° at sintering); and 0.81 g., m.p. 182–183.5° (180° at sintering), respectively. The three crops were combined with the crude diol (0.93 g.) from the above benzene–ethyl acetate (2:1) eluate and crystallized from ethyl acetate at room temperature for 2 hr. to give pure 17α-methylandrostane-3α,17β-diol (8.03 g.), m.p. and m.m.p. 184–185°, $[\alpha]^{23}D$ −12.84 (*c* 1.277). The infrared spectrum was identical with that of the sample prepared as in **A**.

Raney Nickel Oxidations.—Raney nickel was an old sample (at least 4 months old) supplied as a suspension in water, by Raney Catalyst Co., Chattanooga, Tenn. The catalyst was filtered and washed under suction with distilled water until the washings were almost neutral. It was dried as rapidly as possible between folds of filter paper and the damp material was weighed, washed first with absolute ethanol and then three times with benzene, by decantation. The remaining traces of ethanol and water were finally removed by azeotropic distillation with benzene, immediately prior to use.

(16) This compound has recently been obtained crystalline, m.p. 155–157°, by A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 160 (1963).

(17) L. Ruzicka, M. W. Goldberg, and J. Meyer, *Helv. Chim. Acta*, **18**, 994 (1935).

A. Oxidation of 17α-Methyl-Δ⁵-androstene-3β,17β-diol with Raney Nickel.—A mixture of 17α-methyl-Δ⁵-androstene-3β,17β-diol (3 g.), Raney nickel catalyst (30 g.) prepared as above, and benzene (150 ml.) was heated under reflux with exclusion of moisture for 3 hr. The nickel was removed by filtration and the extremely pyrophoric filter cake was washed well with benzene. Evaporation *in vacuo* yielded a colorless solid (2.6 g.) giving a positive Zimmerman test and showing no high-intensity absorption in the ultraviolet region. Chromatography on neutral alumina (270 g.) and elution with benzene–ethyl acetate (1:1, 250 ml.) gave a pale yellow solid (2.1 g.), which crystallized from ethyl acetate to afford colorless needles (0.97 g.) of 17α-methylandrostan-17β-ol-3-one, m.p. 190–193°, raised to 192–193° on recrystallization from the same solvent (lit[15a] m.p. 192–193°).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.94; H, 10.52; O, 10.52. Found: C, 78.80; H, 10.32; O, 10.95.

A mixture melting point with an authentic sample was not depressed. Infrared spectrum in $CHCl_3$ (bands at 3610, 3460, 1705, and 1084 cm.$^{-1}$) was identical with that of the authentic ketone. Evaporation of the mother liquors after removal of crystals gave a gum (1.2 g.), which was still ketonic, but could not be induced to crystallize. Elution with further 500 ml. of benzene–ethyl acetate (1:1) gave a colorless semisolid (0.35 g.) from which no pure material could be isolated by crystallizations. Its infrared spectrum indicated a mixture of Δ⁵-unsaturated and saturated diols contaminated with traces of ketonic impurity. Elution with benzene–ethyl acetate (1:2) and crystallization of the resultant product (0.05 g.) from ethyl acetate gave 0.034 g. of 17α-methylandrostane-3β,17β-diol, m.p. and m.m.p. 207–209°. Identity was also established by their infrared spectra. When the amount of Raney nickel was curtailed to 6 g., other experimental conditions remaining the same, the crude product (2.92 g.), m.p. 162–173° (sintering at 155°), showed positive Zimmerman reaction and had $E^{1\%}_{1\,cm}$ 50 at 242 mμ, indicating the presence of *ca.* 10% of methyltestosterone.

B. Treatment of 17α-Methyl-Δ⁵-androstene-3β,17β-diol with "Hydrogen-Free" Raney Nickel.—The Raney nickel catalyst, after filtration and washing with water, was rendered essentially hydrogen free by heating *in vacuo* at 200–210° (bath temp.) for 2.25 hr. according to the procedure of Hauptmann and Wladislaw.[6b] On cooling, dry benzene (150 ml.) was run in through a dropping funnel to cover the catalyst (30 g.) completely, before breaking vacuum, thus avoiding contact with air. Methylandrostenediol (3 g.) was added, and the mixture was heated under reflux, with exclusion of moisture, for 3 hr. Filtration, washing with chloroform, and evaporation gave a colorless solid (2.86 g.), m.p. 156–165°, $E^{1\%}_{1\,cm}$ 117 at 241 mμ, indicating *ca.* 20% of methyltestosterone. Chromatography on neutral alumina (270 g.), elution with benzene–ethyl acetate (2:1; 500 ml.), and fractional crystallizations of the residue (1 g.), $E^{1\%}_{1\,cm}$ 243 at 241 mμ, from ethyl acetate and ethyl acetate–isooctane furnished 17α-methyltestosterone (0.25 g.), m.p. and m.m.p. 163–166°, $E^{1\%}_{1\,cm}$ 515 at 241 mμ. Further elution (500 ml.) with the same mixture of solvents gave a colorless oil (0.3 g.), $E^{1\%}_{1\,cm}$ 224 at 241 mμ, showing positive Zimmerman reaction. Elution with benzene–ethyl acetate (1:1), evaporation, and crystallization of the residue (1.41 g.) from ethyl acetate furnished starting diol (1.27 g.), m.p. and m.m.p. 202–204°.

C. Treatment of 17α-Methyltestosterone with Raney Nickel.—When 17α-methyltestosterone (3 g.) was substituted for methylandrostenediol in **A** above, the crude product (2.8 g.) showed $E^{1\%}_{1\,cm}$ 212 at 242 mμ, indicating *ca.* 40% of starting material. Chromatography on neutral alumina (275 g.), elution with benzene–ethyl acetate (4:1, 500 ml.), and evaporation gave a pale yellow semisolid (1.0 g.), showing no significant absorption in the ultraviolet region. Crystallizations from ethyl acetate and acetone furnished pure 17α-methylandrostan-17β-ol-3-one (0.21 g.), m.p. and m.m.p. 191–193°. The infrared spectrum was identical with that of an authentic sample. Further elution (500 ml.) with benzene–ethyl acetate (4:1) gave a colorless solid (0.8 g.), $E^{1\%}_{1\,cm}$ 140 at 240–243 mμ, which could not be resolved satisfactorily by crystallizations. The infrared spectrum indicated a mixture of saturated 3-keto and 3-keto-Δ⁴ compounds. Elution with benzene–ethyl acetate (3:1) and crystallization of the residue (0.85 g.), m.p. 163–166°, $E^{1\%}_{1\,cm}$ 525 at 242 mμ, from ethyl acetate–isooctane furnished pure methyltestosterone (0.76 g.), m.p. 165–167°. A mixture melting point with starting material was not depressed.

D. Oxidation of 17α-Methyl-Δ⁵-androstene-3β,17β-diol with Raney Nickel in Cyclohexane.—This experiment was carried out

exactly as described in A above, with the only difference that cyclohexane was used in place of benzene. The crude oxidation product (2.3 g.), showing no absorption maximum in the ultraviolet, was dissolved in benzene and adsorbed on a column of neutral alumina (200 g.). Elution with benzene–ethyl acetate (1:1, 300 ml.) and two crystallizations of the residue (1.1 g.) from ethyl acetate gave 17α-methylandrostan-17β-ol-3-one (0.33 g.), m.p. and m.m.p. 190–193°. Identity was also confirmed by their infrared spectra. The column was eluted further with benzene–ethyl acetate (1:1), and the eluates were collected in 200-ml. portions. Evaporation gave a colorless oil (0.35 g.) and colorless solids (0.4 g., 0.25 g., and 0.1 g.) in that order. The last three solids were mixtures of diols containing some 17α-methylandrostane-3β,17β-diol, detected by its characteristic triple peaks at 3480, 3400, and 3210 cm.$^{-1}$ in the O–H stretching region of the infrared spectrum.

Benzo[*b*]thiophene Derivatives. V. Mannich Bases With Antimicrobial Activity[1]

E. CAMPAIGNE, E. D. WEINBERG, G. CARLSON,[2a] AND E. S. NEISS[2b]

Departments of Chemistry and Bacteriology, Indiana University, Bloomington, Indiana 47405

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In a continuation of our studies[3] of benzo[*b*]thiophene as a source of compounds of potential biological activity, a series of β-amino ketone hydrochlorides of this heterocycle have been prepared and tested for antimicrobial activity. A wide variety of ketonic bases are reported in the literature and many of these compounds have been found to exhibit analgesic, local anesthetic, antispasmodic, and chemotherapeutic activity.[4–10]

The Mannich reaction has been reviewed by Blicke[11] and more recently by Hellmann and Opitz.[12] Only one Mannich base of 3-acetylbenzo[*b*]thiophene (I) has been reported,[13] but no biological activity evaluation was included in this report. This compound, 3-(β-dimethylaminopropionyl)benzo[*b*]thiophene hydrochloride (II), has been included in this work for comparison of its antimicrobial properties with the other members of the series described in Table I. Com-

TABLE I
MANNICH BASE HYDROCHLORIDES OF 3-ACETYLBENZO[*b*]THIOPHENE[a]

No.	Amine	M.p., °C.	Purified yield, %	Formula	Carbon, %, Calcd.	Carbon, %, Found	Hydrogen, %, Calcd.	Hydrogen, %, Found	Nitrogen, %, Calcd.	Nitrogen, %, Found	MIC[b] S. aureus	MIC[b] E. coli	S. epidermidis
II	Dimethyl	173–174	65	$C_{13}H_{16}CINOS$	57.85	57.56	5.99	6.20	5.19	5.35	10–33	>100	>100
III	Diethyl	136–137	53	$C_{15}H_{20}CINOS$	60.05	60.24	6.77	6.91	4.70	4.87	10–33	>100	>100
IV	Dibenzyl	213–214	44	$C_{25}H_{24}CINOS$	71.25	71.48	5.73	6.05	3.32	3.64	>100	>100	>100
V	Pyrrolidine	198–199	67	$C_{15}H_{18}CINOS$	61.40	61.03	6.14	6.11	4.74	4.75	33–100	33–100	>100
VI	Piperidine	228–229	71	$C_{16}H_{20}CINOS$	61.95	61.86	6.46	6.62	4.53	4.82	33–100	>100	>100
VII	Morpholine	205–206	55	$C_{15}H_{18}CINO_2S$	57.75	58.10	5.82	5.93	4.49	4.51	3.3–10	10–33	10–33
VIII	Hexamethyleneimine	194–195	70	$C_{17}H_{22}CINOS$	63.10	63.10	6.84	7.04	4.32	4.21	10–33	33–100	10–33
IX	3-Azabicyclo[3,2,2]nonane	189–190	54	$C_{18}H_{22}CINOS$	65.25	64.93	6.62	7.14	4.03	4.27	10–33	>100	10–33
	Penicillin G										0.33–1.0	33–100	>100
	Tetracycline										0.33–1.0	1.0–3.3	>100
	Streptomycin										1.0–3.3	1.0–3.3	>100
	Chloramphenicol										3.3–10	3.3–10	>100

[a] Compounds are all white solids. Melting points are corrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. [b] Expressed in γ/ml. of agar for 100% inhibitory concentration. [c] Reported previously by F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.*, **71**, 2856 (1949).

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